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Intrathecal Baclofen Therapy for Spasticity: Experience of 48 Cases

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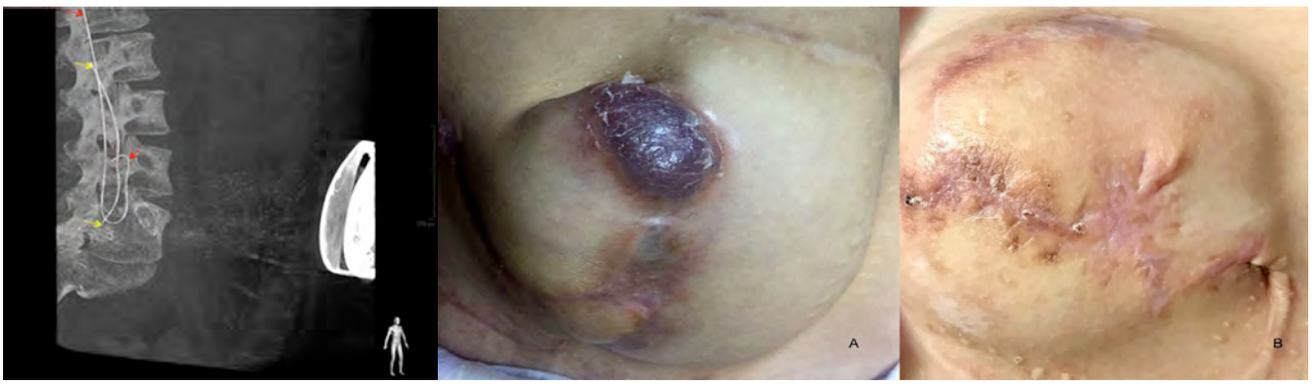

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National Editorial Board

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A. Original Research

ATTITUDES OF NURSES WORKING EMERGENCY AND INTENSIVE CARE UNITS TOWARD GOOD DEATH AND DEATH ANXIETY

ACİL SERVİS VE YOĞUN BAKIMDA ÇALIŞAN HEMŞİRELERİN İYİ ÖLÜM KAVRAMI VE ÖLÜM KAYGISI

GOOD DEATH AND DEATH ANXIETY

Deniz Say Şahin[1], Özgür Önal[2], Betül Battaloğlu İnanç[3]
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Öz

Amaç: Çalışmamız, acil servis ve yoğun bakım hemşirelerinde, iyi ölüm kavramı ve ölüm kaygısını belirlemek amacıyla planlandı. Gereç ve Yöntem: Araştırmanın evrenini, Burdur ilinde bulunan İl Sağlık Müdürlüğüne bağlı kamu hastanelerinde ve üniversite hastanesinde, acil servis ve yoğun bakım ünitelerinde çalışan hemşireler oluşturmaktadır (N=168). Örneklem seçilmemiş, araştırmaya katılmaya gönüllü 140 hemşireye anket formları uygulanmıştır. Araştırmanın verileri, hemşirelerin tanıtıcı özelliklerini içeren sosyodemografik veri formu, Templer's ölüm anksiyete ölçeği ve İyi Ölüm Ölçeği kullanılarak elde edildi. Sonuçlar % 95'lik güven aralığında, anlamlılık p<0.05 düzeyinde değerlendirildi. Bulgular: Çalışmaya Acil Servisten 65(%46,4) Yoğun Bakımdan 75 kişi(%53,6) olmak üzere 140 kişi katıldı. Toplam ölüm kaygısı puanı 8,24±3,05'dir. İyi ölüm ölçeği alt gruplarının, korelasyonları istatistiksel olarak anlamlı bulundu (Personalcontrol r=0.65, p=0,0001; Clinical criteria r=0.72, p=0,0001; and Personal control and Clinical criteria r=0.63 p=0,0001) ve alt grupların ölüm kaygısıyla aralarında düşük düzeyli anlamlı ilişki saptandı. (death anxiety r =0.23, p=0,006; personal control r=0.18, p=0,037; clinicalcriteria r=0.23 p=0,006). Meslekte çalışma yılı, şu an bulunduğu kurumda çalışma yılı, yaş ve aylık çalışma saati ile ölüm kaygısı ve iyi ölüm ölçeği alt ölçekleri arasında korelasyon saptanmadı. Tartışma: Sonuç olarak; Ülkemizde, henüz, iyi ölüm kavramı netleşmemiş olup, çalışanlar bu stresli durumu, kendi becerileriyle karşılamaya çalışmaktadır. Oysa, bu durumun, kavramlaşarak, bilgi, deneyim ve davranış oluşturularak, karşılanırlığı olan bir sağlık politikasıyla desteklenmesi gerekmektedir.

Anahtar Kelimeler

Ölüm Kaygısı; Ölüm Öncesi Hemşirelik Bakımı; İyi Ölüm

Abstract

Aim: Our study aimed to define and measure attitudes toward good death and death anxiety in nurses working at emergency service and intensive care. Material and Method:The scope of this research involved the nurses working at emergency service and intensive care units in public hospitals and university hospitals associated with the Local Health Authority in Burdur (N=168). The sample not selected; the questionnaire forms were applied to 140 volunteers nurses who agreed to participate in this study. The research data included collecting sociodemographic data of the nurses, and from administering the Templer Death Anxiety Scale and the Good Death Scale. The results were evaluated at 95% confidence interval and at p<.05 significance level. Results: The study included 140 nurses working either at emergency services (46.4%) or intensive care units (53.6%) of the hospital. The total Death Anxiety score was 8.24±3.05. The inter-subscale correlations of Good Death scale subgroups were found to be statistically significant (Personal control r=0.65,p<.001; Clinical criteria r=.72, p<.001; Personal control and Clinical criteria r=0.63 p=.001); a significant relationship (but at a low level) was determined between subgroups and Death Anxiety (Death Anxiety r=0.23, p=0.006, Personal control r =0.18, p=0.037; Clinical criteria r =0.23 p=0.006). No correlation was found between the number of working years in the profession, working years in the current institution, age, monthly working hours and the sub-scales of the Death Anxiety and the Good Death scale. Discussion: In Turkey, the concept of "good death" has not yet been clarified and yet professionals have had to approach this stressful condition and topic on their own. We believe that these professionals should be supported through guidance, mentoring, and education programs to deal with both the clinical and the humanitarian aspects of death, an inevitable constant in life.

Keywords

Death Anxiety; Hospice Care; Good Death

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Introduction

What constitutes a "good death"? The Institute of Medicine's definition is: "Decent or good death is one that is: free from avoidable distress and suffering for patients, families, and caregivers; in general accord with patients' and families' wishes; and reasonably consistent with clinical, cultural, and ethical standards" [1]. Recent research has led to determining some criteria related to the concept of good death. Some of these criteria are as follows: death largely without pain, determination of treatment choices in the terminal period, conformity to religious and moral beliefs of the individual, having a life quality, believing that her/his life has come to an end, and cooperation and harmony with healthcare providers [2]. Death inevitably affects all people so it is quite important to support people in the way they desire. In Turkey in 2014, 390,121 people died and "bad" death or mortality occurred at a rate of approximately 5.1 per thousand [3]. The definitions of "good death" were categorized into core themes and subthemes, and the frequency of each theme was determined by the perspectives of the stakeholder, patient, family, and health care providers (HCPs) [2]. Good death which the palliative care workers have adopted is a kind of death in which the physical symptoms and pain of the patient is under control while preparing him/her psychologically. If these conditions are not provided for the patient, then we cannot talk about the term "good death" [4]. Many current studies have indicated that patients most prefer the treatments that focus on communication and that are compatible with their values, while doctors most prefer biomedical treatment options aligned with their values [5]. We think that making contact with the patients approaching death and giving them the support they need might help the nurses examine their own feelings related to life, illness, death, and loss and thus provide patients with better physical and psychological care; in this way the quality of behaviour and care toward patients approaching death can be improved. Working in intensive care is described as hard as it includes providing support to the patient, relieving patients from pain, relieving patients from anxiety, communicating, touching, facing death, comforting family and friends, and supporting other nursing staff [6]. In addition, doctors and nurses working in critical care frequently feel that they are powerless to alter some situations [7]. Also, clinical factors reflect the more biomedical aspects of a good death. Critical care nurses reported that they had more occupational stress, sustained greater burnout, and experienced more death anxiety than hospice nurses [8]. Therefore, in Burdur, Turkey, we aimed to determine the approach of health professionals to the concept of "good death" and the factors affecting death anxiety, defined using scales.

Material and Method

Our study is a descriptive and cross-sectional study which was planned to determine the death concept and death anxiety of nurses working at emergency service and intensive care units. The scope of the research included nurses working at emergency service and intensive care units in public hospitals and university hospitals associated with the Local Health Authority in Burdur, Turkey (N=168). Volunteers were composed of 140 nurses who agreed to participate in this study. The research was evaluated through a sociodemographic data form composed of 10 questions including personal features (gender, age, marital status, number of children, family type, education status, smoking and/or alcohol use, chronic disease condition, the work unit and number of years working, etc.) and the Templer Death Anxiety and Good Death scales. All participants met with a survey taker in a face-to-face interview. Each face-to-face interview required 25-35 minutes of the nurse's time. The study was approved by the ethics committee of Mehmet Akif Ersoy University (dated 28.03.2014, no: 79325306-020-10818) and the required institutional permissions for the research were obtained.

Templer Death Anxiety Scale

Death anxiety was evaluated by using the Templer Death Anxiety Scale. This scale was developed by Templer in 1970 and is composed of a total of 15 questions aiming at determining death anxiety level [9]. The original form includes true/false questions. In their study, Akça and Köse adapted it into Turkish and transformed it into a seven-point Likert type scale by utilizing other studies in the literature as examples, believing this would result in more effective measurement [10]. Also, the response spaces for the Likert type scale were reversed in negatively-worded questions to prevent the possibility of repeating the same answers and because of the tendency of the attendants to reply to questions positively. Templer identified the reliability coefficient of the scale (Kuder Richardson Formula 20) as 0.76 and product-moment correlation coefficient as 0.83. In the Turkish version, the internal consistency was Cronbach's alpha = 0.72, test-retest was $r=0.80$, $p<0.01$ ($n=127$). In a better selected and better standardized sample group, an analysis of 326 persons reported a Cronbach alpha of 0.74. These data are close to both the original Templer DAS test-retest and the McMordie Likert test-retest results. In his adaptation to Polish, Donovan identified the half segmentation correlation as $r=0.77$ and defined that result as "a rate with a strong reliability" [11].

Good Death Scale

The evaluation was made by using the Good Death Scale which was developed in 2003 by Schwartz et al. to determine the concept and features of good death [12]. The scale includes 17 questions in total and 3 sub-dimensions. The first sub-dimension, the psycho-social spiritual sub-dimension, consists of 9 questions (4., 6., 7., 8., 9., 10., 11., 12., 13.) and describes the psycho-social and spiritual sides of death. The second sub-dimension, the personal control sub-dimension, consists of three questions (15., 16., 17.) and describes mental concentration, communication ability, and physical functions. The third sub-dimension, the clinical sub-dimension, consists of five questions (1., 2., 3., 5., 14.) and describes the medical and clinical sides of death. Each statement in the scale were evaluated by a quartet Likert type grading system as none (1), some (2), mild (3), much (4). There were no inversely-stated expressions. The total scoring ranged between 17 and 68 [12].

The data from the research were analysed by using SPSS 17.0 for Windows. The scale values, arithmetic mean, standard deviation, and the values defined by counting were calculated as a number percent. Due to the importance of the differences be-

tween the mean scores of the groups, a 2-independent sample T test was used for double-measurement values; the one-way ANOVA test was used to compare more variables in measurable life quality, and the post-hoc Tukey test was used to determine the factor causing significance. Cronbach alpha method was used to determine the consistency of scales and Pearson correlation method was used to determine the relationship between them. The results were evaluated at 95% confidence interval and at $p<0.05$ significance level.

Results

The study involved 140 nurses working at emergency services 65 (46.4%) and intensive care 75(53.6%) units of the hospitals. Of the participants, 121(86.4%) were women, 97(69.3%) were married, and their mean age was 32.82±7.35 (min-max=18-45). It was found that 10 (7.1%) of the nurses were working as unit responsible nurses. The nurses were working 168.74±24.05 hours per month on average. Their average number of years working in the profession was 12.33±7.56 year, and the average working years in their current institution was 6.02±5.35 year. Of the nurses 24(17.1%) had chronic diseases, 51(36.4%) were active smokers, and 19(13.6%) used alcohol. It was determined that of the 24(17.1%) of the nurses had chronic diseases, 6(25%) had respiratory track diseases (chronic obstructive lung disease, asthma, or bronchitis), 7(29.2%) had cardiovascular diseases (hypertension, coronary failure, or valvular heart problems), 2(8.4%) had diabetes, 2(8.4%) had thyroid disease and 2 (8.4%) had central nerve system disease (Meniere disease, migraine).

The total death anxiety of nurses was measured at 8.24±3.05. The death anxiety conditions are shown in Table 1. The Cronbach alpha value of death anxiety was 0.706. In our study, the sub-group consistency of the good death scales used to determine which dimensions of death were given importance, as follows: Cronbach alpha values 0.877, Personal Control 0.909, Clinical 0.820. The opinions of nurses on good death concept and the factors increasing death anxiety have been evaluated in Table 2, while the factors affecting multiple analysis results have been evaluated in Table 3. It was observed that female nurses had more death anxiety than male nurses and those female nurses gave more importance to the closure and personal control side. It was found that smoking status increased the importance given to closure and the clinical sides of death, and education and number of children correlated with an increase in the importance given to the personal control side of death. The inter-subscale correlations were found

Table 1. Death anxiety conditions of nurses working at emergency services and intensive care units (Death Anxiety Scale)

	Yes
	n (%)
1. I am terrified of death.	49 (35.0)
2. It mostly bothers me that time passes so quickly.	58 (41.4)
3. I am very afraid when I think of having a medical operation.	59 (42.1)
4. I frequently think how short life actually is.	99 (70.7)
5. Life after death makes me highly anxious.	80 (57.1)
6. I am really afraid of having a heart attack.	62 (44.3)
7. A corpse image terrifies me.	17 (12.1)
8. Rumours about a probable world war makes me scared.	73 (52.1)
9. I am afraid of dying in pain.	116 (82.9)
10. I am not afraid of death at all.	36 (25.7)
11. I feel there is nothing for me to be scared of in the future.	30 (21.4)
12. I do not have a specific fear of suffering from cancer.	57 (40.7)
13. People's talks about death does not bother me.	88 (62.9)
14. The idea of death never makes me anxious.	63 (45.0)
15. The idea of death occasionally comes to my mind.	115 (82.1)

Table 2. Factors affecting the concept of good death and death anxiety (univariate analysis)

			Concept of good death	Death anxiety		
			Closure	Personal Control	Clinical	
		n (%)	Mean±SD (p)	Mean±SD	Mean±SD	Mean±SD
The unit	Emergency S.	65(46.4)	3.26±0.67	3.23±0.87	3.04±0.72	7.52±2.85
	Intensive care	75(53.6)	3.41±0.45	3.46±0.63	3.37±0.56	8.87±3.09
	(p)	(0.131)	(0.070)	(0.003)**	(0.009)**	
Gender	Male	19 (13.6)	3.07±0.74	2.98±1.01	3.01±0.73	6.79±2.59
	Female	121 (86.4)	3.38±0.52	3.41±0.69	3.24±0.64	8.47±3.06
	(p)		(0.025)*	(0.020)*	(0.143)	(0.025)*
Age	At and under age 35	76 (54.3)	3.31±0.56	3.27±0.78	3.18±0.67	8.12±2.59
	Over age 35	64 (45.7)	3.38±0.57	3.45±0.71	3.26±0.64	8.39±3.03
	(p)		(0.489)	(0.157)	(0.472)	(0.600)
Marital Status	Married	97 (69.3)	3.34±0.59	3.38±0.77	3.22±0.69	8.34±2.96
	Single	36 (25.7)	3.29±0.51	3.29±0.74	3.19±0.60	7.92±3.25
	Divorced/Widowed	7 (5.0)	3.51±0.56	3.29±0.71	3.31±0.41	8.57±3.41
	(p)		(0.638)	(0.780)	(0.908)	(0.746)
Child	Yes	94 (67.1)	3.39±0.57	3.46±0.71	3.27±0.66	8.59±2.88
	No	46 (32.9)	3.22±0.53	3.14±0.79	3.10±0.65	7.52±3.27
	(p)		(0.093)	(0.017)*	(0.145)	(0.050)*
Family Type	Nuclear	134 (95.7)	3.35±0.56	3.34±0.76	3.21±0.67	8.12±3.05
	Extended	6 (4.3)	3.09±0.68	3.56±0.46	3.33±0.43	9.33±2.94
	(p)		(0.275)	(0.507)	(0.655)	(0.372)
Educational Status	High school	25 (17.9)	3.31±0.55	3.09±0.88	3.26±0.63	7.64±2.50
	Associate degree	64 (45.7)	3.34±0.65	3.35±0.76	3.17±0.74	8.50±3.03
	Undergraduate	47 (33.6)	3.35±0.46	3.48±0.68	3.26±0.57	8.30±3.30
	Graduate	4 (2.9)	3.33±0.45	3.50±0.43	3.05±0.10	7.25±3.86
	(p)		(0.992)	(0.213)	(0.822)	(0.603)
Smoking	No	74 (52.9)	3.21±0.61	3.27±0.79	3.04±0.70	8.00±3.29
	Quit	15 (10.7)	3.50±0.42	3.36±0.58	3.44±0.45	8.60±2.87
	Yes	51 (36.4)	3.48±0.49	3.48±0.74	3.40±0.57	8.49±2.73
	(p)		(0.011)*	(0.285)	(0.003)**	(0.606)
Alcohol use	No	121 (86.4)	3.34±0.57	3.34±0.78	3.21±0.68	8.28±3.11
	Yes	19 (13.6)	3.30±0.54	3.43±0.53	3.27±0.50	8.00±2.69
	(p)		(0.773)	(0.604)	(0.680)	(0.710)
Chronic disease condition	Yes	24 (17.1)	3.35±0.49	3.51±0.61	3.23±0.66	7.66±3.03
	No	116 (82.9)	3.34±0.58	3.32±0.78	3.21±0.66	8.36±3.05
	(p)		(0.937)	(0.257)	(0.940)	(0.310)
	Total	140 (100.0)	3.34±0.56	3.35±0.75	3.32±0.66	8.24±3.05

*: $p<0.05$; **: $p<0.001$

Table 3. Factors affecting the concept of good death and death anxiety (multivariety analysis)

Concept of good death			
Closure B (%95GA) p	Personal control B (%95GA) p	Clinical B (%95GA) p	Death anxiety B (%95GA) p
Gender: 0.350 (0.086-0.613) 0.010* Smoking condition: 0.154 (0.057-0.251) 0.002**	Gender : 0.433(0.079-0.786) 0.017* Number of children: 0.127(0.014-0.240) 0.028 Educational status: 0.171(0.012-0.330) 0.035*	Unit worked in : 0.315 (0.108-0.522) 0.003** Smoking condition: 0.186 (0.075-0.297) 0.001**	Unit worked in: 1.147 (0.132-2.163) 0.027*
Linear regression (backward regression): df:14; R:0.43; R2:0.18 Dubin Watson: 0.897. ANOVA; p=0.23	Linear regression (backward regression): df:14; R:0.47; R2:0.23 Dubin Watson: 0.948. ANOVA; p=0.015*	Linear regression (backward regression): df:14; R:0.41; R2:0.17 Dubin Watson: 0.823. ANOVA; p=0.023*	Linear regression (backward regression): df:14; R:0.51; R2:0.26 Dubin Watson: 1.972. ANOVA; p=0.011*

*: p<0.05; **: p<0.001

statistically significant (Personal control r=0.65, p<0.001; Clinical criteria r=0.72, p<0.001; and Personal control and Clinical criteria r=0.63 p<0.001) and a significant relationship with subgroups was determined on a low level (death anxiety r=0.23, p=0.006, personal control r=0.18, p=0.037; clinical criteria r=0.23, p=0.006). It was determined that there was no correlation between the factors of the number of working years in the profession, working years at the current institution, age, or monthly working hours and the concepts of death anxiety and good death inter-subscales.

Discussion

Our total Templer Death Anxiety score was 8.24±3.05. In another study in Turkey, the nursing students' Templer Death Anxiety score was 6.71±2.28. These anxiety scores named mild anxiety, likely another studies support and found this result as mild. For instance, in nurse and midwifery students Death Anxiety score was 59.15±14.94, and others was found to be 54.27±11.30. So these results show us fear of death is an experience for humans. But, it is an important concept to life threatening illness. Death anxiety have been associated with many factors and these factors always affects every to some degree, even though they work as health professionals [13]. It is concluded in our study that being a female nurse, having children, and smoking increase death anxiety and fear of death. High levels of death anxiety were found among Egyptian female nursing students and American cancer nurses. From the same study, it was found that the less work experience the more likely it was to have higher death fears [14]. The same frame also implied that younger nurses consistently reported stronger fear of death and more negative attitudes toward caring at the end of life [14, 15]. We can infer that this increased anxiety level is due to the fact that, in general, nurses are relatively young and mostly female. Besides, the fact that the nurses participating in the study have been working in units with a higher stress load is also effective in this condition. In our study, working at intensive care unit was considered as the factor increasing death anxiety. In Acehan's study, death anxiety was found to be higher in women [11]. Similarly, in studies conducted with other groups in the literature, death anxiety scores for women was found to be higher than that of men [16, 17]. In addition, some studies found out that emergency nurses experienced post-traumatic stress disorder more often than their colleagues working in other departments did. The reason for this was that emergency nurses encountered sudden death of an adolescent, little child or infant quite frequently, resulting in feeling distress [18]. Actually, we are of the opinion that the departments dealing with death are frequently very stressful departments. Here in this stage, it is possible to understand the death anxiety of nurses having a child, as they are affected by stress and they feel the trauma of young and infant deaths by identifying with them, as presented in the literature. The age of nurses (higher age) and length of work experience (longer time) have always been found to be significantly positive in relation to less anxiety about death [15]. Also, training and education are important in HCPs. For example renal nurses with more experience and training in palliative care have lower death fear and more positive attitudes toward caring for dying patients [14]. And these results support our study as well. Because, the second domain, personal control, focuses on the more physical aspects of the dying experience, such as being female, increasing age, and level of education. However, contrary to the literature, it was found in our study that working time had no effect on death anxiety. Therefore, we can explain this case with the idea that personal features of those working in traumatic departments affect their responses to trauma. In fact, some research indicated that the perception of death on the part of nurses can vary depending on the department they are working for or their personal characteristics [14]. Furthermore, considering that nurses belong to a profession where frequent deaths are possible, further studies are essential in order to better understand their perception of inadequacy, and their reactions to unexpected conditions and deaths [14].

Conclusions

Thus, for those working in hospital departments with high mortality incidence we propose that self-consciousness against death phenomenon should be enhanced and supportive education programmes should be prepared related to dealing with death and its aftermath. Moreover, we believe that the nurses of units with high mortality incidence should be assisted through guidance and should be trained about proper ways of communicating with family and patients through the use of motivational teaching methods.

Even though the staffs had enough equipment, knowledge, and skills, providing care for dying patients and fulfilling their needs, respecting their beliefs, giving information, and supporting their families remain the inevitable factors of a difficult process. Being of service during this process, it is very important for health professionals to know what issues must be coped with and how to overcome them. Personal experiences inform the approach of professionals to the dying, having both scientific and humanitarian features [19].

Competing interests

The authors declare that they have no competing interests.

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PATIENTS WITH SPONTANEOUS INTRAMURAL HEMATOMA AND OUR CLINICAL APPROACH

SPONTAN İNTRAMURAL HEMATOMLU HASTALAR VE KLİNİK YAKLAŞIMIMIZ

INTRAMURAL HEMATOMA

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Öz

Amaç: Travma sonucu olmayan, spontan ince barsak hematomları oldukça nadir görülen klinik tablolar olup klinik tanıları da zor konulabilmektedir.İleri görüntüleme yöntemleri sayesinde tanı konan bu durumlarda genellikle antikoagulan kullanımı suçlanılmakta ve dikkatli anamnez önerilmektedir.Retrosepektif olarak taradığımız spontan intestinal hematom vakalarımızı incelemeyi planladık. Gereç ve Method: Üç merkezli olan bu çalışmada Ocak 2010-Temmuz 2016 tarihleri arasında spontan intestinal hematom tanısı konan hastalar çalışmaya dahil edilmiş ve demografik verileri ile tedavi ve radyolojik yöntemleri kaydedilmiştir.Sağlıklı bilgilere ulaşılamayan hastalar çalışma dışı bırakılmıştır. Bulgular: Toplam 11 hastaya tanı konmuş olup bunların 6(%54.5)'sı kadın,5(%45.5)'i erkektir. Ortalama yaşı 67.4(58-78) olup hastalarımızın şikayetlerinin başlaması ile tanı alması arasında geçen süre 5.9(1-15) gündür. Hastaların tamamı (%100) antikoagulan tedavisi almaktaydı ve. başvuru sırasında ortalama INR değerleri: 5.8(3.2-8.4) idi.6(%54.5)'sında tutulan segment jejunum iken, 5(%45.5) hastada tutulan segment ileumdu.Tamamı(%100) konservatif tedavi ile taburcu edildi. Tartışma: Spontan intramural hematomlar nadir görülen bir durum olup antikoagulan kullanan hastalarda mutlaka akılda tutulmalıdırlar.Genellikle konservatif tedavi bu tür vakalarda yüz güldürücü sonuçlar vermektedir.

Anahtar Kelimeler

Spontan; Barsak; Hematom

Abstract

Aim: Non-traumatic, spontaneous small intestinal hematomas are very rare clinical conditions, diagnoses of which are difficult. These cases, in whom the diagnosis is made by the help of advanced visualization techniques, are usually attributed to anticoagulant therapy and obtaining a careful medical historyis suggested. We planned a retrospective study on our cases with spontaneous intestinal hematoma. Material and Method: In thismulti-center study involving three medical facilities, patients diagnosed with spontaneous intestinal hematoma between January 2010 and July 2016 were included in the study and their demographic data was recorded along with their treatments and radiological methods. Patients whose accurate data could not be acquired were excluded from the study. Results: A total number of 11 patients were diagnosed, 6 (54.5%) of which were women and 5 (45.5%) of them were men. The average age of the study group was 67.4 (58-78) years and the duration between the initiation of their complaints and the time of diagnosis was 5.9 (1-15) days. All patients were under anticoagulant therapy and their average INR value was 5.8 (3.2-8.4) when they were first admitted. The affected segment was jejunum in 6 patients (54.5%) whereas the ileum was involved in 5 patients (45.5%). All (100%) patients were discharged from the hospital as the result of conservative treatment. Discussion: Spontaneous intramural hematoma is a rare condition that has to be kept in mind when treating patients with anticoagulant therapy. Conservative treatment generally gives pleasing results in this condition.

Keywords

Spontaneous; Intestine; Hematoma

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Introduction

Spontaneous small intestinal hematoma that is not secondary to trauma isa rare condition. Extensive use of anticoagulants being in the first place, hemophilia, idiopathic thrombocytopenic purpura,von Willebrand disease, leukemia, lymphoma, multiple myeloma, chemotherapy, vasculitis and pancreatitis are among other causes [1-5]. Intramural intestinal hematoma was first identified by McLouchlan in 1838 during the autopsy of a 49 years old male patient who died from dehydration and intestinal obstruction. In this published case of his, the localization was at the duodenum and it was diagnosed as a pseudoaneurysm tumor. Radiological identification of spontaneous intestinal hematoma was made by Liverud 100 years later [6,7]. Berman and Mainellareported the first anticoagulant-induced spontaneous intramural small intestinal hematoma in 1952 [8]. In 1968,Herbert published the first extensive investigation on this subject by adding his own two cases to the six former cases existing in the literature [9]. Anticoagulant therapy-related spontaneous intramural gastrointestinal tract hematomas are mostly located in the duodenum and small intestine, whereasthe involvements of the colon and rectum are rare [10-13]. Since our patient group was admitted to our clinics with delayed diagnosis, the physical and radiological examination are enough for a diagnosis when they are considered together with the patient's medical history, and the conservative treatment results in remission of the hematoma in most of the patients [14], we felt the need to write this article with the aim of retrospectively investigating our patients who were treated for anticoagulant-induced spontaneous intramural small intestinal hematoma together with the review of the literature.

Material and Method

Patients with spontaneous anticoagulant-induced intramural intestinal hematoma who were diagnosed and treated inAdnan Medneres University Department of General Surgery, Bozyaka Training and Research Hospital Division of General Surgery, and Inonu University Department of General Surgery between the dates of January 2010 and July 2016 were investigated with respect to their demographic structures, medical histories, radiological appearances and treatment methods; their data were recorded and compared. Patients whose accurate data could not be acquired from their chartswere excluded from the study.

Statistical Analysis

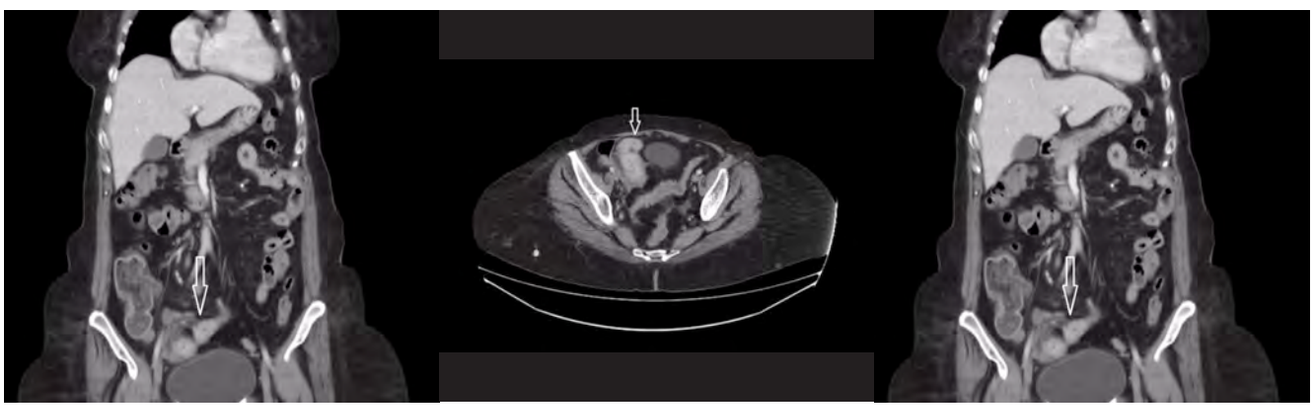
The statistical analysis of the data was performed using SPSS 21.0 software package (SPSS 21.0 software IL-Chicago-US). The statistical results were obtained for descriptive analysis, demographical information and clinical features. The average values ± standard deviation values and percentages of the results were calculated.

Results

There were a total of 11 patients who were diagnosed and treated for spontaneous anticoagulant- induced intramural intestinal hematoma between the dates of January 2010 and July 2016. Six (54.5%) of our patients were female and 5 (45.5%) of them were male. The average age of our patients was 67.4 (58-78) years. Four (36.3%) of our patients were diagnosed by presenting to the emergency service, while the remaining seven (63.7%) were diagnosed following their admission to the clinic.The duration between their initial complaints and the diagnosis was 5.9 (1-15) days. The number of hospital admissions during this period was 2.1 (1-4). Anticoagulant therapy was administered in four (36.3%) of our patients due to coronary artery disease, in three (27.3%) due to valve replacement, in three (27.3%) due to chronic atrial fibrillation, and in one (9.1%) patient due to deep venous thrombosis. All of our patients were hospitalized for treatment. The average INR value was 5.8 (3.2-8.4) during the first admission. When their complaints during their admission were analyzed, eleven (100%) patientsmanifested tenderness, three (27.3%) had mild distention, and four (36.3%) had nausea and vomiting. None of the patients manifested rebound-defense in their first physical examination. No findings of hematochezia or melenawere present during their rectal examinations.None of the patients showed non-gastrointestinal bleeding (epistaxis, hematuria, hemoptysis etc.). Two (18.2%) of the patients had moderate leukocytosis (13.600-14.200 K/mm3) while the remaining nine (82.8%) patients did not have leukocytosis. One (9.1%) patient had electrolyte imbalance (Na:151mEq/L, K: 2.78mEq/L) and elevation of creatinine caused by pre-renal acute renal failure (creatinin:3.1) due to reduced oral intake, recurrent nausea-vomiting and late diagnosis. The remaining ten (90.9%) patients had normal biochemical values.Abdominal ultrasonography and abdominal computed tomography were performed in all patients. Ultrasonography enabled the diagnosis in only six (54.6%) of the patients whereas computed tomography showed that all (100%) patients had long-segment mural thickening (the segment length,scanned with computed tomography, was reported to be approximately 15-25 cm) and was diagnostic by showing the free fluid between the surrounding bowel loops (PICTURES 1,2 and 3). Theinvolved intestinal loops were at jejunal and ileal levels in all (100%) patients. While the involved intestinal loops were jejunal in six (54.5%) of the patients,the ileal segments were affected in five (45.5%). The involved intestinal loop was solitary in all of our patients; no multi-involvement of the loops was observed. No extension of the lesion to the colonic loop was present in the patients with ileal involvement. All of our patients responded to conservative treatment (intravenous hydration, discontinuation of oral intake, parenteral nutrition, correction of coagulopathy with plasma and vitamin K, low molecular weight heparin treatment administered following the decline in INR value, frequent mobilization, and initiation of oral intake gradually following the regression of symptoms); no surgical need emerged. The average duration of hospitalization was 8.4 (5-12) days. (Table:1) All patients were discharged from the hospital following the fullrecovery of clinical symptoms (cessation of abdominal pain, improvement of distention, toleration of oral feeding), without taking radiological complete hematoma resolution into consideration in abdominal tomography. In all of our patients, the abdominal tomography, performed during the outpatient follow-up two weeks after the hospital discharge, revealed complete hematoma resolution, disappearance of intra-abdominal fluid and the dilatation of the intestinal loops proximal to the hematoma.We discharged all our patients with prescription of subcutaneous low molecular weight heparin. We

Table 1. General features of the patients

Sex	Age (years)	The site of admission	Time passed prior to diagnosis (days)	Number of institutions admitted before	Comorbid disease	INR value	Leucocytosis	Abdominal USG	Abdominal CT	Involved GIS site	Hospitalization (days)	Treatment method
F	65	Outpat.	5	2	Coronary artery disease	6.2	normal	-	+	ileum	6	conservative
F	69	Outpat.	3	1	Valve replacement	3.2	normal	+	+	jejunum	7	conservative
M	69	Emerg.	1	1	Valve replacement	5.8	normal	+	+	ileum	8	conservative
F	71	Outpat.	4	2	Coronary artery disease	7.4	normal	+	+	jejunum	9	conservative
M	73	Emerg.	9	3	Chronic atrial fibrillation	8.4	14.200	_	+	ileum	12	conservative
M	59	Outpat..	6	2	Deep venous thrombosis	6.4	Normal	+	+	jejunum	8	conservative
F	60	Outpat.	5	3	Chronic atrial fibrillation	5.2	normal	+	+	jejunum	7	conservative
F	69	Outpat.	4	1	Valve replacement	4.8	Normal	+	+	ileum	10	conservative
M	68	Emerg.	6	2	Chronic atrial fibrillation	7.2	Normal	-	+	ileum	8	conservative
F	78	Outpat.	7	2	Coronary artery disease	3.5	Normal	-	+	jejunum	9	conservative
M	61	Emerg.	15	4	Coronary artery disease	5.7	13600	_	+	jejunum	9	conservative
	67.4 (59-78)		5.9(1-15)	2.1(1-4)		5.8(3.2-8.4)		54.6%	100%		8.4(5-12)	



Figures 1,2,3. 69 years old female patient, intestinal intramural hematoma, long segment wall thickening at ileum, minimal free fluid around the loop and minimal dilatation at proximal intestinal loop are visible.

resumed the anticoagulant therapyafter the abdominal tomographic images obtained during the outpatient follow-up admission revealed complete resolution of hematoma.

Discussion

Anticoagulant-induced intramural hematoma of the gastrointestinal is one of the rare complications of drug utilization. Its annual incidence is 1/2500 [15]. It is usually not life-threatening and is responsive to medical treatment [16]. 36% of all gastrointestinal intramural hematomas are secondary to anticoagulant therapy [17].

Its probable pathophysiology is the rupture of the terminal artery of themesentery and the blood dissecting the site between the muscularis mucosa and the muscular layer following the penetration of the muscular layer of the intestinal wall [18].

Even though the hematoma involving the intestinal wall was solitary in our patient group, it has beenreportedin the medical literature that 15% of spontaneous intestinal hematomas are multiple and 85% are single. The most frequently involved siteswere reported to be the jejunum with a rate of 69% and the ileum with a rate of 38%. Although the dilatation of the ileal intramural hematoma into the colonic segment is probable, the incidence of isolated spontaneous colonic and rectal intramural hematoma is rare and there are only few patients reported in the literature [2, 19, 20]. While duodenal intramural hematomas are mostly secondary to endoscopy and pancreatitis, spontaneous duodenal intramural hematoma is also reported in the literature [3].

In coherence with our study, there is no difference between the ratios of affected males and females in the literature. The average age of the affected patient group is 6-7 decades [2, 16, 18]. This can be explained by the fact that the structure of the mesenteric terminal artery, which penetrates the intestinal wall, deteriorates with age and the prescriptions of anticoagulant

therapy due to comorbid diseasesat this age period are more frequent.

Sorbello MP et al. reported in their analysis of 21 clinical studies and case reports that during the initial diagnosis, 97.5% of the patients had abdominal pain, 50% had nausea, 45% had vomiting complaints and only 20% of the patients stated that the only complaint was abdominal pain during their first admission to the hospital [21]. The small intestinal obstructions are mostly incomplete and the findings in physical examination are generally vague [22, 23]. Hence, in our clinical study also, only four (36.3%) of our patients were diagnosed through emergency service admission and the remaining seven (63.7%) were diagnosed through their outpatient admissions.Various authorshave determined the period between the initiation of complaints and the time of diagnosis as 2.5-5 days[14, 16, 21] whereas we found theaverage duration to be 5.9 [1-15) days in our study. However, we also found that the number of hospital admissions during this period was 2.1 [1-4]. In our opinion, this means that patients are diagnosed with delay due to the fact that they present late to the medical facilities since their symptoms are vague, and also because anticoagulant use is ignored in the clinics and emergency services, investigations that will help detecting the coagulopathy are not being done, physical examination findings are vague and intravenous contrast enhanced abdominal computed tomography is not being used liberally. The average INR value of the patients in the initial hospital admission is 6.2-11.6 according to the literature [2, 16, 21]. Intestinal wall thickening and presence of intraabdominal free fluid in these patients can only be identified through ultrasonography (USG) and IV contrast-enhanced abdominal tomography (CT). However, these symptoms do not specifically suggest small intestinal intramural hematoma; they can also suggest infectious small intestinal disorders, inflammatory intestinal diseases, and small intestinal ischemia [24]. In the literature, there is a consensus on the fact that abdominal tomography is the most valuable diagnostic method in intestinal intramural hematoma [16, 21]. In our patient group, USG was diagnostic in six (54.6%) of our patients whereas computed tomography was diagnostic for all (100%) of them.

In the literature, there are nonoperatively followed-up cases in whom diagnosis was made through diagnostic laparotomy and the operation wasterminated without performing a resection [18]. Usually, the clinical findings resolvewithin five to seven days when conservative treatment methods are chosen and no surgical intervention is required. The complete radiological resolution occurs in a few weeks. If the case remains radiologically the same after two months, a different underlying clinical cause should be considered [15, 14]. Late complications such as recurrent bleeding or stenosis are rare [21].

Conclusion

Spontaneous intramural hematoma of the gastrointestinal system is a rare condition. Coagulopathy due to anticoagulant therapy is its most common cause.Nonspecific abdominal pain, mild distension, nausea and vomiting are its clinical symptoms. Leukocytosis and the symptoms of acute abdomen are rare. Electrolyte imbalance may be present due to limited oral intake, recurrent nausea and vomiting, together with delayed diagnosis. The most frequently involved gastrointestinal sites are the jejunum and ileum. The handicap for this clinical condition which usually does not require surgery and responds very well to conservative treatment is the delayed diagnosis. For the diagnosis of patients who have medical histories of anticoagulant usage due to their comorbid disorders and who are admitted to the emergency services or outpatient clinics with thecomplaint of nonspecific abdominal pain, it will be sufficient to conduct investigations which will reveal their coagulopathies and to obtainabdominal tomography with intravenous contrast enhancement. Early response to conservative treatment and complete resolution in the control abdominal tomography, performed 2-3 weeks after hospital discharge are sufficient for differential diagnosis. Late complications such as recurrent bleeding and stenosis have not been reported in the literature.

Competing interests

The authors declare that they have no competing interests.

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IMPACT OF PRE-STENT IMPLANTATION PLAQUE BURDEN ON THE DEVELOPMENT OF STENT RESTENOSIS

STENT İMPLANTASYONU ÖNCESİNDEKİ PLAK YÜKÜNÜN STENT RESTENOZUNA OLAN ETKİSİ

PRE-STENT IMPLANTATION PLAQUE BURDEN AND RESTENOSIS

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Öz

Amaç: Biz bu çalışmamızda stent implantasyonu öncesinde kantitatif koroner anjiografi (QCA) ve Imaj J programını kullanarak hesapladığımız plak alanının stent restenozu gelişimi üzerine olan etkisini araştırmayı amaçladık. Gereç ve Yöntem: Mart 2008 ve Temmuz 2011 arasında uygulanan 5180 adet koroner anjiografi prosedürü çalışmada incelendi, 227 adet in-stent restenoz mevcut idi. Dışlama kriterlerinin ardından, yüz altmış dört adet stent implantasyonunun yapıldığı 121 hasta retrospektif olarak incelendi. Stentler hastaların klinik durumlarına göre; a) in-stent restenosis gelişen grup (n:77, 47%) ve b) in-stent restenosis gelişmeyen grup (n:87, 53%) olmak üzere iki gruba ayrıldı. Stent implantasyonundan en az 6 ay sonra koroner anjiografi ile 50% veya daha fazla daralmanın saptandığı durumlar in-stent restenoz oluşumu için pozitif olarak değerlendirildi. Plak alanı ölçümleri kantitatif koroner anjiografi (QCA) ve İmaj J programı kullanılarak yapıldı. Bulgular: Kantitatif olarak ölçülen plak alanlarında gruplar arasında istatistiksel olarak anlamlı farklılık saptanmadı (p>0.05). Ancak İmaj J ile ölçülen alanlarda gruplar arasında anlamlı düzeyde farklılık gözlendi (p<0.05). Gruplar arasında hipertansiyon, hiperlipidemi öyküsü, statin kullanımı, HDL değerleri ve lezyon tipleri (p<0.05) istatistiksel olarak anlamlı farklılık gösterirken, diyabet varlığı ve sigara kullanımı anlamlı düzeyde farklı saptanmadı (p>0.05). Stent restenoz gelişimi ile hipertansiyon, statin tedavisi kullanmama, HDL değerleri, kötü lezyon tipi ve İmaj J ile ölçülen plak alanı arasında ilişki mevcut idi. Tartışma: Hipertansiyon, statin tedavisi kullanmama, düşük HDL seviyeleri, kötü lezyon tipi ve İmaj J ile ölçülen geniş plak alanları in-stent restenoz gelişimi için önemli birer belirteçlerdir.

Anahtar Kelimeler

İmaj J; Plak Alanı; İn-Stent Restenoz

Abstract

Aim: In this study we have used quantitative coronary angiography (QCA) and the Image J program in order to investigate the influence of plaque area, as identified prior to stent implantation, on the development of stent restenosis. Material and Method: 5180 coronary angiography procedures were performed between March 2008 and July 2011. Of these, 227 presented with in-stent restenosis. After application of the exclusion criteria, 164 intracoronary stents implanted in 121 patients were retrospectively investigated. These stents were divided into two groups depending upon the clinical status of the patient: (a) those who developed in-stent restenosis (n: 77, 47%), and (b) those who failed to develop in-stent restenosis (n: 87, 53%). Narrowing by 50% or more, as identified during coronary angiography performed at least six months after the stent implantation, was considered as positive for development of in-stent restenosis. Plaque area measurement in the patients was performed using quantitative coronary angiography (QCA) and the Image J program. Results: Plaque area measurement when performed quantitatively revealed no statistically significant difference between the groups (p>0.05). However, significant difference in area was observed when Image J was used (p<0.05). Statistically significant differences were observed between groups in terms of history of hypertension and hyperlipidemia, use of statins, HDL values, and lesion type (p<0.05); the difference in terms of presence of diabetes or smoking status (p>0.05) was not significant. There was a relationship among the development of restenosis and hypertension, non-usage of statin therapy, HDL level, poor lesion type, and plaque area as measured with Image J. Discussion: Hypertension, non-usage statin therapy, low levels of HDL, poor lesion type, and larger plaque areas as measured with the Image J program were identified as important indicators for development of in-stent restenosis.

Keywords

Image J; Plaque Area; In-Stent Restenosis.

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Introduction

Intracoronary stenting has emerged as one of the most commonly used therapeutic modalities for the treatment of coronary artery disease. However, one of the most serious problems encountered during the follow-up of patients who have received this treatment is the development of in-stent restenosis. It is difficult to determine the exact rate of restenosis because it depends on a number of different factors and variables. In the pre-stent era it ranged between 32-55% of all angioplasties, dropping to 17-41% [1-4] in the BMS era [5-7]. A further step to reduce restenosis was undertaken with the advent of DES, with a reduction to numbers <10% [8-9]. However, in one study, within a time frame of six months nearly 20-35% of patients with bare-metal stents and 5-10% of those with drug-eluting stents developed this complication [10].

Reports in the literature have pinpointed several factors suspected to be active in the development of restenosis [11-14]. These include advanced age, history of diabetes, long lesion, small vessel diameter, and poor lesion type. Some studies have suggested that monitoring the plaque area prior to the last stent implantation could help in predicting restenosis via using intravascular ultrasound (IVUS) [15-16]. As a result of this, interventions aimed at decreasing the plaque material are popularly considered to reduce restenosis as well; however, the expected results have not been obtained [17].

In this study we have used quantitative coronary angiography (QCA) and the Image J program to investigate the influence of plaque area, as measured prior to stent implantation, on the development of restenosis. We have also monitored and analyzed several clinical, biochemical, and angiography-related factors.

Material and Method

Study Population

The study included patients who had undergone coronary angiography at the Cardiology Department Coronary Angiography Unit between March 2008 and July 2011. This inclusion was irrespective of the presence or absence of in-stent restenosis. Of the 5180 coronary angiography procedures, 227 presented with in-stent restenosis whereas 383 did not develop the same. Medical records and prior history of these patients, as present in the database, were analyzed retrospectively. Only those patients who had undergone the stent implantation procedure at our clinic were enrolled in the study. Patients whose stent implantation procedure was performed elsewhere, patients whose files could not be accessed, and patients who presented with stent thrombosis were excluded from the study group. In total, 164 intracoronary stents implanted in 121 patients were found to match the inclusion criteria and hence were investigated retrospectively as part of the analysis procedure. These stents were divided into two groups depending upon the clinical status of the patient: (a) those who presented with in-stent restenosis (n: 77, 47%), and (b) those who failed to develop in-stent restenosis (n: 87, 53%).

Narrowing by 50% or more, as identified during coronary angiography performed at least six months after the stent implantation, was considered as positive for development of in-stent restenosis.

All characteristics of the patients that could potentially be related to the development of restenosis, including basic demographic characteristics such as age and gender, smoking status, hypertension, hyperlipidemia, diabetes, currently used drugs, and biochemical parameters, were meticulously recorded.

Angiographic Examination and Evaluation of the Plaque Burden

Records pertaining to the coronary angiography procedure performed during the stent implantation were obtained for each patient.

The plaque area present prior to the stent implantation was investigated semi-quantitatively using coronary angiography (QCA) and the Image J program.

The plaque area was calculated semi-quantitatively using the Siemens Axiom (Germany) coronary angiography instrument. Our analysis was based on the best possible view of the lesion-containing segment of the coronary artery into which the stent was implanted. Using the QCA method, calibration was performed based on the catheter diameter and the segment with stenosis was marked on the coronary angiography instrument. The margins of the lesion were adjusted manually and the plaque area was optimally calculated using the instrument (Figure 1). Plaque area calculations were done by two separate observers and the average of the results was used.

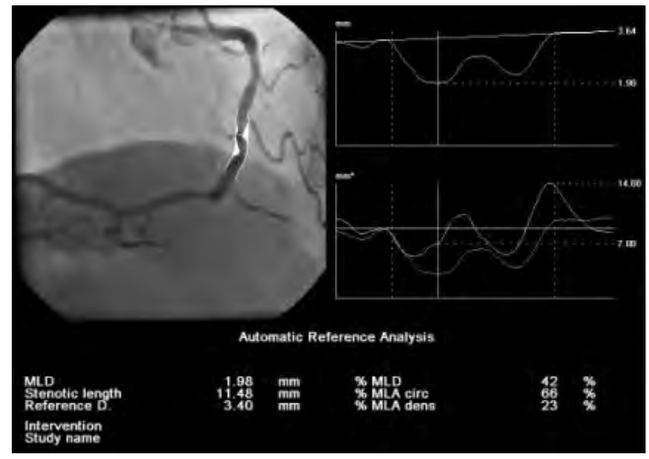

Figure 1. Plaque area calculation with QCA method

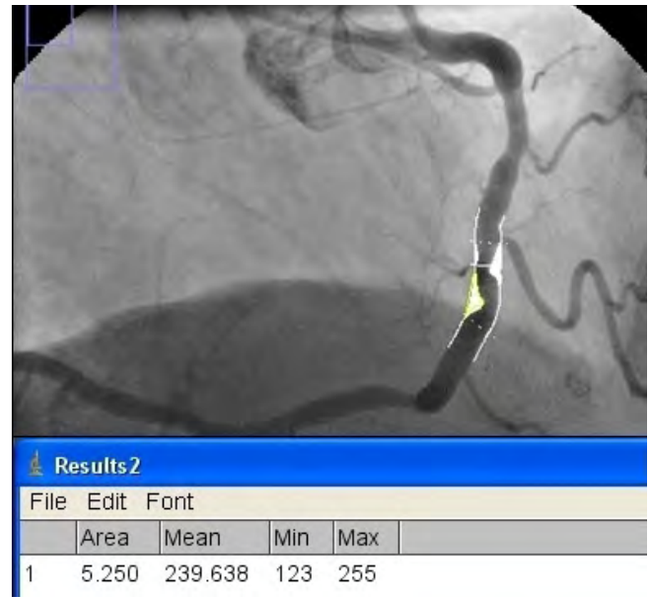

Figure 2. Plaque area calculation with Image J method

Plaque area calculation with both the methods was performed using the same image. An image of the plaque area, as calculated by the QCA method, was recorded in JPEG format and the plaque area was calculated using Image J.

The Image J program is easily accessed via the internet (http://rsbweb.nih.gov) and can be used to perform two-dimensional area calculation. Calibration is performed prior to area calculation. Then the area that needs be calculated is marked manually (Figure 2). In this study, we accepted the catheter diameter as a reference value with which the calibration was performed. ACC/AHA lesion classification was used for coronary lesion type [18]. The reproducibility of two-dimensional area calculation was assessed by coefficients of variation (standard deviation of differences between the repeated measurements divided by the mean value and expressed as a percentage) between measurements. The intra-observer variability was calculated in 34 randomly selected study participants (18 patients who presented with in-stent restenosis and 16 control patients who did not develop in-stent restenosis) by repeating the measurements under the same basal conditions. Intra-observer and inter-observer variation was found to be <5%.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for all statistical analyses. The results obtained are presented as mean ±SD and frequency. Student's t test, Pearson's correlation analysis, chi-square test, and logistic regression analysis were performed for evaluation of data. A p-value less than 0.05 was considered statistically significant.

Results

A total of 164 stents were included as part of the study. Of these, 77 were found to have developed in-stent restenosis whereas 87 failed to do so. No significant differences were observed between the two groups with respect to age, gender, presence of diabetes mellitus, and smoking status (p> 0.05). However, the prevalence of hypertension and hyperlipidemia was statistically significantly higher in patients with in-stent restenosis (p<0.05).

When the current drug regimen was taken into account, a significant difference in the development of in-stent restenosis was observed for the use of statins (p< 0.05). It was observed that the risk for development of in-stent restenosis was lower in patients undergoing statin therapy as compared to those who were prescribed other medication. The development of in-stent restenosis was not found to be associated with the use of aspirin, clopidogrel, ticlopidine, or beta-blocker (p> 0.05, Table 1). When basic laboratory parameters for all the patients were analyzed, no single factor was seen to make a statistically significant difference between the two groups except for HDL, whose levels were lower in the patient group diagnosed with in-stent restenosis (p<0.05, Table 1).

The patients with and without in-stent restenosis were investigated with respect to the type of percutaneous coronary intervention (PCI) associated with the stent implantation procedure. Of the 77 stents that were diagnosed with in-stent restenosis, 66 (85.7%) were implanted using elective PCI, nine (11.7%) using primary PCI, and two (2.6%) with rescue PCI. Of the 87

Table 1. Baseline characteristics and laboratory parameters of the study population

Variables	Without Restenosis (n=87)	With Restenosis (n=77)	P value
Age	58,6 ± 11	57,5 ± 11	0,890
Gender, male	71 (%81,6)	58 (%75,3)	0,669
Hypertension	63 (%75)	69 (%89,6)	0,022
Diabetes mellitus	29 (%33,3)	26 (%33,8)	0,557
Dyslipidemia	21 (%24,1)	34 (%44,2)	0,028
Smoking	24 (%27,6)	31 (%40,3)	0,129
Acetylsalicylic acid	70 (%86,4)	66 (%89,2)	0,883
Klopidogrel	20 (%26)	11 (%15,9)	0,065
B-blocker	66 (%82,5)	62 (%82,7)	0,560
Statin	53 (%67,9)	33 (%45,8)	0,036
Glucose (mg/dL)	123,7 ± 52,7	126,6 ± 51,5	0,850
Creatine (mg/dL)	0,98 ± 0,35	1,08 ± 0,69	0,450
Total cholesterol (mg/dL)	183,1 ± 47,9	180,6 ± 50,3	0,850
Triglyceride (mg/dL)	166,9 ± 112,6	179,1 ± 83,3	0,450
HDL (mg/dL)	39,8 ± 10,0	36,4 ± 10,1	0,045
LDL (mg/dL)	109,2 ± 39,7	106,4 ± 40,4	0,750
Hemoglobin (g/dL)	13,7 ± 1,9	13,5 ± 1,9	0,850
Platelet (thousand/uL)	235 ± 54	255 ± 79	0,095
MPV (fL)	8,6 ± 1,0	8,5 ± 0,9	0,910

Abbrevations: HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; MPV, mean platelet volume

Table 2. Evaluation and Measurement of Coronary Angiograpy Image

Variables	Without Restenosis (n=87)	With Restenosis (n=77)	P value
PCI Type			
Elective PCI	81 (%93,1)	66 (%85,7)	0,075
Primer PCI	4 (%4,6)	9 (%11,7)	
Rescue PCI	2 (%2,3)	2 (%2,6)	
Lesion type			
A	10 (%11,5)	1 (%1,3)	0,001
B1	47 (%54)	24 (%31,2)	
B2	23 (%26,5)	33 (%42,8)	
C	7 (%8)	19 (%24,7)	
Stent Localization			
LAD	41 (%47,2)	39 (%50,6)	0,890
D1	2 (%2,3)	2 (%2,6)	
LCX	15 (%17,2)	14 (%18,2)	
RCA	29 (%33,3)	22 (%28,6)	
Stent Type			
BMS	67 (%73)	68 (%88,3)	0,910
DES	20 (%27)	9 (%11,7)	
Plaque Area Quantitative	4,22 ± 2,61	4,67 ± 2,39	0,664
Plaque Area İMAGE J	7,68 ± 4,45	11,03 ± 6,17	0,025

Abbrevations: PCI, percutaneous coronary interventions; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex coronary artery; D1, first diagonal coronary artery; BMS, Bare metal coronary stent; DES, drug-eluting coronary stent

Table 3. Logistic regression analysis associated with the risk for development of in-stent restenosis

Variables	BETA (ß)	O.R.	%95 CI	P value
Hypertension	1,50	4,49	1,26-15,93	0.035
Hyperlypidemia	0,82	2,28	0,89-5,80	0.861
Non usage Statin	1,51	4,52	1,75-11,67	0.028
HDL	-0,47	0,95	0,91-0,99	0.042
Stent length	-0,11	0,89	0,76-1,04	0.783
Plaque areaμ	0,10	1,11	1,02-1,21	0.025
Type -B1 Lesion	2,36	10,62*	0,90-124,39	0.036
Type -B2 Lesion	3,60	36,91*	2,83-480,15	0.042
Type –C Lesion	5,40	222,26*	5,79-8528,71	0.037

Abbrevations: HDL, high density lipoprotein cholesterol.
μ Plaque area calculation with Image J method
* Risk increase with respect to Type-A Lesion

stents that did not present with in-stent restenosis, 81 (93.1%) were implanted with elective PCI, four (4.6%) with primary PCI and two (2.3%) with rescue PCI. There was no significant difference between the two groups in terms of the type of percutaneous coronary intervention (p>0.05, Table 2).

The two groups were also compared with respect to the type of lesion into which the stent implantation were performed. Of the 77 stents with in-stent restenosis, one (1.3%) was implanted into a type A lesion, 24 (31.2%) into type B1 lesion, 33 (42.9%) into type B2 lesion, and 19 (24.7%) into type C lesion. Of the 87 stents without in-stent restenosis, 10 (11.5%) were implanted into type A lesion, 47 (54.0%) into type B1 lesion, 23 (26.4%) into type B2 lesion, and seven (8.0%) into type C lesion. The type of lesion differed significantly between the two groups (p<0.01). It was observed that the risk for in-stent restenosis increased as the type of lesion progressed from A to C (Table 2). It was identified that, of the 77 stents that presented with in-stent restenosis, 39 (50.6) were implanted in the left anterior descending (LAD), two (2.6%) in the diagonal, 14 (18.2%) in the circumflex, and 22 (28.6%) in the right coronary artery (RCA). For the 87 stents that did not develop in-stent restenosis, 41 (47.2) were implanted in the LAD, two (2.3%) in the diagonal, 15 (17.2%) in the circumflex, and 29 (33.3%) in the RCA. When the patients with open and stenotic stents were compared, no statistically significant difference with respect to the artery into which the PCI had been performed was noticed (p>0.05, Table 2).

Amongst the 77 stents with in-stent restenosis, it was observed that 68 (88.3%) were bare-metal stents (BMS) and nine (11.7%) were drug-eluting stents (DES). Of the 87 stents without in-stent restenosis, 67 (77.0%) were BMS and 20 (23.0%) were DES. When the correlation between type of implanted stent and development of restenosis was evaluated, a statistically non-significant difference was determined (p=0.091). However, it can be stated that the use of drug-eluting stents was more frequent in the group that failed to develop in stent restenosis (Table 2).

The performance of percutaneous transluminal coronary angioplasty (PTCA) prior to the stent implantation was also compared for the two groups. Of the 77 stents that presented with in-stent restenosis, 38 (49.4%) were observed to have undergone PTCA whereas 39 (50.6%) did not due to decisions related to coronary by-pass operation and medical treatment. In the 87 stents that did not develop in-stent restenosis, 40 (46.0%) were noted to have undergone PTCA because of thrombus burden of the lesion whereas 47 (54.0%) did not. Upon comparison, groups with and without in-stent restenosis did not demonstrate any statistically significant difference with respect to the performance of the PTCA (p>0.05).

The two groups were compared with respect to the performance of post-dilatation after stent implantation. Of the 77 stents with in-stent restenosis, ten (13.0%) underwent post-dilatation and 67 (87.0%) did not. Of the 87 stents that did not develop in-stent restenosis, ten (11.5%) underwent post-dilatation and 77 (88.5%) did not. Statistically there was no significant difference between the two groups (p>0.05).

The stents implanted in the two groups were compared in terms of stent size and diameter. Statistically significant difference was observed for difference in stent size (p<0.05) but not for stent diameter (p>0.05).

There was no statistically significant difference between the two groups with respect to the quantitative plaque area determined during follow-up coronary angiography (p>0.05); importantly, the plaque area as examined with Image J displayed no difference between the groups (p<0.05).

There was a moderately positive correlation between the quantitative measurement of the plaque area and the measurement of plaque area done with Image J ($r = 0.60$, $p < 0.001$).

Considering the aforementioned evaluations, the factors that were found to make a difference between stents that did and did not develop restenosis included the presence of hypertension, presence of hyperlipidemia, non-usage statin therapy, lower HDL levels, longer stent size, type of lesion, and plaque area as calculated by Image J. Logistic regression analysis was performed with factors associated with the risk for development of in-stent restenosis (Table 3).

Although a significant difference was observed between the groups with and without in-stent restenosis in terms of hyperlipidemia and stent size, logistic regression analysis revealed that these variables were not influential for the development of in-stent restenosis (p>0.05).

Discussion

Detailed analysis performed during the course of our study revealed no significant difference between patients with and without in-stent restenosis with respect to the plaque area calculated through QCA, whereas plaque area as measured with Image J was larger in those with restenosis. Correlation analysis revealed a significant correlation between QCA and the plaque area as measured through Image J. Regression analysis determined that the plaque area measured with Image J was a significant determinant for the development of in-stent restenosis. Every 1 mm2 increase in the plaque area as measured with Image J was found to cause a 1.11-fold increase in the development of restenosis. Although popularly used in the research arena, QCA is unable to replace visual assessment in clinical practice because it is both time-consuming as well as technologically intensive. Another disadvantage is that finalizing the square and segment for which measurement will be performed is a subjective matter and hence is known to vary among people

who perform this measurement using the QCA method. Therefore, Image J is a more practical and serviceable alternative method.

Intracoronary stent implantation, an invasive revascularization method, has become the therapy of choice for coronary artery disease and its popularity is increasing on a daily basis. Unfortunately, in spite of advancements in the materials used and an increase in the rate of procedural success, no concordant improvement in terms of in-stent restenosis, the main problem affecting percutaneous coronary interventions, has yet been achieved. A meta-analysis of 11 studies that included a total of 5103 patients showed that the prevalence of angiographic in-stent restenosis was 5-10% in case of DES and 20-35% in case of BMS [10].

Some previously published studies have identified pre-procedural plaque burden as a predictor of restenosis. Although the mechanism underlying the relationship between plaque burden and restenosis are not clear, plaque burden has emerged as a potential indicator. A high pre-procedural plaque burden could hinder optimal dilatation of the stent. To overcome this problem, balloon angioplasty with higher pressure could be performed but doing so would increase the trauma effect on the vascular walls which in turn would increase the risk of restenosis. Another study advanced the explanation that atherosclerotic plaque burden could be the source for cells involved in the intimal hyperplasia process [15]. Hoffman et al. investigated various predictors for development of restenosis following stent implantation and also tried to address the question of whether plaque burden was influential in the process. In their study they examined the plaque burden before stent implantation using intravascular ultrasound (IVUS) and found that the plaque burden was correlated with development of restenosis [15]. Similarly, a study by Shiran et al. showed that the pre-procedural plaque area as measured using IVUS was a strong predictor for restenosis [16]. Considering that the real-life data show that IVUS is not commonly used by interventional cardiologists, Image J can be developed as a useful and convenient process to assess the plaque burden. Subsequent comparative studies with IVUS would give better information about the usefulness of this method.

Previous studies have suggested that factors such as gender and age can function as predictors of in-stent restenosis development, but their impact still needs to be conclusively assessed. A study by Gupta et al. revealed that female gender is a risk factor for restenosis [19]. A study by Bainey et al. reached the same conclusion [20]. Other sources have defined gender and advanced age as predictors of restenosis [21]. In our study, no significant difference could be uncovered between the two groups with respect to gender and age.

When the two groups were compared, hypertension emerged as a clinical factor that was capable of influencing the development of in-stent restenosis; patients with hypertension were at a 4.5-fold greater risk for developing the complication. Similar to our study results, a report by Kastrati et al. also definitively identified hypertension as a risk factor for restenosis [22].

In our study, the prevalence of diabetes was 33.8% in the group with restenosis and 33.3% in the group without stenosis. There was no significant difference between the groups and the presence of diabetes did not appear to increase the risk for in-stent restenosis. Our results are in direct contradiction to several previously published studies that have reported contrary results [23-26]. One factor that can account for the lower incidence of restenosis in the diabetic pool of our study could be the more frequent use of DES and the relatively limited number of patients.

Study Limitations

The number of enrolled patients and the study design were entirely based on the retrospective analysis of patient files; therefore the database can be presented as a major limitation of our study. The data of the patients who underwent second coronary angiography in another clinic or who did not require coronary angiography were unavailable.

Conclusions

No correlation was observed between QCA measured plaque area and the development of restenosis. However, a significant link was observed between plaque area measured with Image J and the development of restenosis. The presence of a correlation between the two methods indicates that the latter methodology can potentially prove useful in cardiology practice, furnishing clinicians with sensitive and significant findings. Intra-procedural techniques aimed at reducing the plaque burden could prove effective for decreasing restenosis development but more extensive research on this subject needs to be conducted and better methodology needs to be developed for the purpose.

Competing interests

The authors declare that they have no competing interests.

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CERVICAL SHORTENING MEASUREMENT FOR PREDICTION OF SUCCESSFUL LABOR INDUCTION

BAŞARILI DOĞUM İNDÜKSİYONUNU BELİRLEMEDE SERVİKAL KISALMANIN ÖLÇÜMÜ

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Öz

Amaç: Bu çalışmada asıl amacımız doğumun başlangıcında ve indüksiyon sırasında periyodik servikal uzunluk ölçümünün doğum indüksiyon sonuçlarını öngörmedeki etkinliğini belirlemeyi hedefledik. Gereç ve Yöntem: Çalışma Bursa Yüksek İtisas Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde 2013 yılı ağustos ile aralık ayları arasında gerçekleştirilmiştir. Dinoproston doğum indüksiyonu için kulllanılmıştır. 137 hasta vajinal doğum grubunu, 64 gebe kadın ise sezaryen doğum grubunu olşturmuştur. Bulgular: Çalışma popülasyonunda indüksiyonun başlangıcında servikal durum değerlendirilmiş(n=201) ve ortalama servikal efasman % 26.5 ± 17.9 ve ortalama servikal dilatasyon 1.5 ± 3.6 cm olarak bulunmuştur. Ortalama Bishop skoru 2.9 ± 2.5 olarak hesaplanmıştır. İndüksiyonun başlagıcından 4. Saatine(I), indüksiyonun 4. Saatinden 8. Saatine(II) ve indüksiyonun başlangıcından 8. Saatine(III) kadar olan gruplarda servikal kısalma vajinal doğum gerçekleşen grupta hüksek derecede anlamalı bulundu.(I: 26.8 ± 19.5 karşın 16.9 ± 15.1, II: 31.4 ± 23.9 karşın 19.2 ± 18.5 ve III: 44.2 ± 24.1 karşın 30.5 ± 21.2). Tartışma: Çalışmamızda servikal uzunluğun başlangıçtaki değeri ile aktif faz dönemindeki uzunluğu arasında anlamlı korelasyon belirledik. Benzer olarak, 4. Ve 8 saat servikal uzunluk ölçümleri arasında aktif faz döneminde anlamlı korelasyon belirledik. Bishop skoru ve aktif faz dönemi arasında negative korelasyon mevcuttu. Sonuç olarak servikal uzunluk ölçümünün karşılaştırmalı analizi doğum sırasında indüksiyon başarısını belirlemede yardımcı olabilir ve yeni bir teknik olarak uygulanabilir.

Anahtar Kelimeler

Dinoproston; Servikal Uzunluk; İndüksiyon

Abstract

Aim: In this study, main goal is to evaluate the efficiency of periodical cervical length measurements, at the beginning and during the induction, in predicting the outcome of labor induction. Material and Method: This prospective study was performed in Bursa Yuksek Ihtisas Research and Training Hospital Gynecology and Obstetrics clinic between August and December 2013. Dinoprostone was used for inducing labors. 137 cases in vaginal delivery group, 64 pregnant women in cesarean delivery group. Results: In study population, cervical conditions at the initiation of induction was evaluated (n=201) and mean cervical effacement was 26.5 ± 17.9 percent and mean cervical dilatation was 1.5 ± 3.6 cm. Average Bishop score was 2.9 ± 2.5. Cervical shortening from beginning to 4th hour of induction, 4th hour to 8th hour of induction and from beginning to 8th hour of induction were significantly higher in vaginal delivery group 26.8 ± 19.5 to 16.9 ± 15.1, 31.4 ± 23.9 to 19.2 ± 18.5 and 44.2 ± 24.1 to 30.5 ± 21.2 respectively. Discussion: We determined a significant correlation between cervical length at the start with the duration of active phase. Similarly, 4-hour and 8-hour cervical length measurements significantly correlated with the duration of active phase. Bishop score and the duration of active phase had a negative correlation. Finally comparative analysis of cervical length measurements may be useful to predict the success of induction during labor and contribute the precision of current techniques.

Keywords

Dinoprostone; Cervical Length; Induction

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Introduction

Induction of labor is the artificial stimulation of uterine contractions before its spontaneous onset for the purpose of vaginal delivery. Vaginal delivery is the main goal of the labor induction. 20 percent of pregnancies needs to induction of labor because of various obstetric and non-obstetric reasons [1]. The rate of labor induction is increasing in modern obstetrics [2].

Labor induction performed by medical reason is associated with increased rates of cesarean section, mainly in nulliparous patients [3]. Bishop score has been widely used for to determine the success of labor induction. But the subjective nature and limitations of this scoring system can reduce the predictive power for the success of labor induction [4,5].

Studies have demonstrated the benefits of transvaginal ultrasonographic evaluation of the cervix to predict the success of labor induction over the clinical examination [6-8]. Because transvaginal ultrasonography provides better measurement of the cervix.

Many studies evaluated only the cervical length at the time of induction, but not the dynamic changes of the cervix during labor. The present study aimed to measure the dynamic changes of the cervix during labor for the prediction of success of labor induction. In addition, the present study also determined the cut-off values of cervical shortening at 4th and 8th hour of induction of labor.

Material and Method

This is a prospective observational study. From August 2013 to December 2013, 201 women were prospectively recruited for the study at Bursa Yuksek Ihtisas Research and Training Hospital, Department of Gynecology and Obstetrics. Study was approved by the Institutional Ethics Committee. All patients gave written consent to participate inthe present study.

During the study period, 6441 women delivered at our center and 1281 (19.8%) consecutive women underwent labor induction. 1080 of these women were excluded because they did not meet the inclusion criteria (n = 827) or they declined to participate (n = 253). 201 patients included in the study.

The inclusion criteria were as follows: singleton pregnancy; alive fetus; cephalic presentation; gestational age between 37 and 41 weeks (determined by the date of the last period and confirmed by first-/second-trimester ultrasound); absence of premature rupture of the membranes; normal fetal well-being on cardiotography (before and during labor); absence of contractions and/or onset of labor; absence of previous uterine scars (cesarean, metroplasty, myomectomy). For all participants, data on age, gravidity, parity, gestational week at delivery, systemic disorders, body mass index (BMI) at the time of delivery and indications for induction were recorded.

The patients first underwent a standard complete evaluation. Bishop score assessed by an expert obstetrician who were blinded to the results of the ultrasound. All women underwent cervical assessment by transvaginal ultrasound by one of the authors (EA) using an ESAOTE My Lab Six (ESAOTE, Genoa, Italy) equipped witha 5 MHz transvaginal probe. First the patient empty her bladder. An endovaginal probe was placed in the anterior vaginal fornix. Ultrasound measurement of cervical length was made in the sagittal plane along the length of the endocervical canal with simultaneous visualization of theinternal and external cervical os.

For those with Bishop score 6 or more (favorable cervix for labor induction) for labor induction, intravenous oxytocin (5 IU of oxytocin diluted in 500 mL of ringer lactate solution, starting with 2 mIU/min) was used to obtain labor's active phase according our routinely clinical protocol. Oxytocin dose was regularly increased every 15 minutes by 2 mU/min until 3-5 contractions per 10 minutes were achieved. Maximum dosage was 32mU/min.

If the Bishop score less than 6 (unfavorable cervix for labor induction) preinduction cervical ripening was performed using 10 mg of controlled-release dinoprostone inserted as a single dose(Propess 10 mg, Controlled Therapeutics, East Kilbride, Scotland) until the Bishop score became 6 or more. Then dinoprostone vaginal insert removed and complementary oxytocin was used when adequate. If the Bishop score remained unfavorable after 24 hours of dinoprostone insertion then vaginal insert removed and patient underwent cesarean section.

Continuous electronic fetal heart rate monitoring was employed to all patients. Artificial amniotomy was performed when a cervical dilatation of 5–7 cm was achieved. Artificial amniotomy was not performed until the cervix was dilated to at least 5 cm and the vertex was engaged.

For the purpose of the study, we defined an induction a ssuccessful only if vaginal delivery was achieved. Ultrasound measurement of cervical shortening was calculated at 4th and 8th hours of induction.

Data processed by statistics programme for social scientists for Windows 21.0 (SPSS, Chicago, IL, USA). Normal data distributionwas analyzed via the Kolmogorov–Smirnov test. Results were presented as the mean±SD. Demographic characteristics of the patients were analyzed using the t test, x2 test, and the Fisher's exact test, where appropriate. In order to deal with uncertainty in estimation, we generated 95% confidence intervals for posttest probabilities around the point estimate. Overall logistic regression analysis was used to examine the relationship between the degree of cervical length shortening and successful labor induction. Receiver operating characteristic (ROC) curves and area under the curve (AUC) values were used to determine the cut-off values of cervical shortening for successful labor induction. $P<0.05$ was considered statistically significant.

Results

The characteristics of the study group are listed in Table 1(Table 1). Maternal age, gestational age and body mass index did not differ between the vaginal delivery and cesarean section groups. Oligohydroamnios (n:70, 34.8%) was the most common indication for labor induction. Postmaturity (n:67), intra-uterine growth restiriction (n:28), non-reassuring NST (n:21) and hypertension (n:15) were the other indications for induction (Table 2).The method of induction was administration of: both dinoprostone and oxytocin(n=103), oxytocin only (n=98).

One hundred thirty seven (68.2%) women had a vaginal delivery. Cesarean delivery was performed in the other (n:64, 31.8%) women for the following indications: failure to progress (n = 43) and induction failure(n = 21). Mean preinduction cervical length in the vaginal delivery group was 29.6 ± 7.4 mm and in

Table 1. Characteristics of vaginal delivery group and cesarean section group

	Vaginal Delivery n: 137	Cesarean Section n: 64	p Value
Maternal Age	26.5 ± 5.5	27 ± 4.7	0.514
Gestational Age	39.4 ± 1.9	39.5 ± 1.9	0.756
Body Mass Index	28.1 ± 4.2	28.3 ± 4.5	0.723
Nulliparity	42 (65.6%)	74 (54%)	
Bishop Score	3.4 ± 2.5	1.9 ± 2.1	<0.001
Preinduction Cervical Length (mm)	29.6 ± 7.4	31.5 ± 7.4	0.09

#Values given as mean ± SD. Chi-Square test.

Table 2. Indications for labor induction#

Indication	Vaginal delivery (n = 137)	Cesarean (n=64)	p Value
Postmaturity	50 (36.5%)	17 (26.6%)	0.493
Oligohydramnios	46 (33.6%)	24 (37.5%)	0.164
IUGR	16 (11.6%)	12 (18.7%)	0.200
Non-reassuring NST	14 (10.4%)	7 (10.9%)	0.349
Hypertension	11 (7.9%)	4 (6.3%)	0.932

Values are given as n(%). Univariate regresion

the cesarean section group was 31.5 ± 7.4 mm (p:0.09, Table 1). Mean Bishop score in the vaginal delivery group was significantly higher than in the cesarean group (P<0.001).

Cervical shortening from beginning to 4th hour of induction, 4th hour to 8th hour of induction and from beginning to 8th hour of induction were significantly higher in vaginal delivery group 26.8 ± 19.5 to 16.9 ± 15.1, 31.4 ± 23.9 to 19.2 ± 18.5 and 44.2 ± 24.1 to 30.5 ± 21.2 respectively (Table 3). Receiver operating characteristic (ROC) curves analysis showed that optimal cervical shortening cut-off values for successful labor induction were 10 mm (beginning to 4th hour) with 66% sensitivity, 44% specificity(95% CI, AUC: 0.580); 14 mm (4th hour to 8th hour) with 73% sensitivity, 52% specificity(95% CI, AUC: 0.657) and

Table 3. Decrease in cervicallength in vaginal delivery and cesarean section groups#

	Vaginal delivery	Cesarean section	P value
Cervical Shortening – From beginnig to 4th hour	26.8 ± 19.5	16.9 ± 15.1	0.001
Cervical Shortening – From 4th hour to 8th hour	31.4 ± 23.9	19.2 ± 18.5	0.006
Cervical Shortening – From beginning to 8th hour	44.2 ± 24.1	30.5 ± 21.2	0.003

#Values given as mean ± SD. Chi-Square Test.

Table 4. Relationship of cervical length and Bishop score with mode of delivery in patients with a Bishop's score 5 or less#

	Vaginal Delivery	Cesarean Section	P value
Cervical Lenght at the beginning (mm)	31.2 ± 6.9	32.1 ± 7.1	0.418
Cervical Shortening – From beginning to 4th hour	25.8 ± 19.7	15.1 ± 12.9	<0.001
CervicalShortening – from 4th hourto 8th hour	30.4 ± 23.6	16.7 ± 15.5	<0.001
Cervical Shortening – From beginning to 8th hour	43.2 ± 27.7	27.7 ± 17.7	<0.001

#Valuesaregiven as mean ± SD. Chi-Square Test.

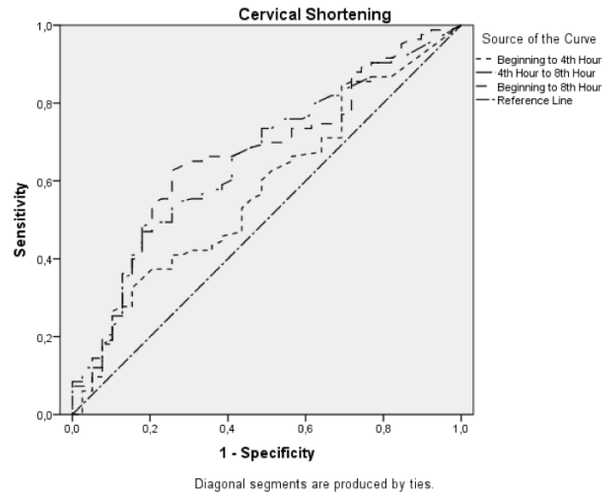

Figure 1. Receiver–operating characteristics curves for cervical length shortening beginning to 4th hour, 4th to 8th hour and beginning to 8th hour in predicting successful labor induction (95% CI, AUC: 0.580, AUC: 0.657 and AUC: 0.667 respectively)

30 mm (beginning to 8th hour) with 66% sensitivity, 62% specificity (95% CI, AUC: 0.667) respectively (Figure 1). When the Bishop's score 5 or less, vaginal delivery group still have significantly higher cervical shortening degree (Table 4).

Discussion

The exact process of cervical ripening is not clearly established [9]. Cervical ripening and cervical shortening are dynamic processes. However, evaluation of the preinduction cervical length and assessment of Bishop score are not enough to predict successful induction of labor, also cervical shortening should be included.

Our results support that cervical shortening and Bishop score may predict vaginal delivery with reasonable accuracy. In vaginal delivery group, preinduction mean cervical length was lower, mean Bishop score and cervical shortening degree was higher compared with cesarean section group. Assessment of cervical shortening at 4th and 8th hour of labor may be useful for predict the success of labor induction with moderate sensitivity and specificity. Our data shows that, cut-off values for 4th and 8th hour cervical shortening were 10 mm and 30 mm respectively. Cervical shortening degree at 4th and 8th hour are useful too even if cervix is unfavorable (bishop score 5 or less).

The performance of the Bishop score has been evaluated in various studies [10-12]. However, Bishop score has limitations [7,11,13]. Bishop Score is more favorable for multiparous women. It demonstrates intra- and inter-observer variability [14]. A potential advantage of transvaginal ultrasound assessment compared with Bishop score is that ultrasound measurement may provide a more objective assessment. Eggebo et al. suggested that TVUS is superior to digital examination in the prediction successful labor induction [15].

This study demonstrated that measurement of cervical length during labor is useful for prediction of successful labor induction, but it can be prompt to fault if:

-Performing measurement of cervical length during uterine contraction by ultrasound

-Insufficient experience of using transvaginal ultrasound prob for measuring cervical length

-performing the measurement with low-quality ultrasound devices.

All these handicaps may cause incorrect results and assumed as drawbacks of our study.

Cervical dilatation and effacement are dynamic processes during labor. Bishop score and preinduction cervical length measurement provides moderate prediction for successful labor induction. Assessment of cervical shortening combined with Bishop score during labor may provide a better prediction.

Authors' contributions:

This work was carried out in collaboration by all authors. Authors EA,TC and EK wrote the first drafts of the manuscript. Author BB,MT managed the literature search. Author EU revised and edited the manuscript. All authors read and approved the final manuscript.

Consent:

The authors declare that 'written informed consent' was obtained from the patient for
publication of this case report with accompanying images.

Ethical approval:

The authors hereby also declare that all examinations and interventions have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards.

Competing interests

The authors declare that they have no competing interests.

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EVALUATION OF EPIDEMIOLOGICAL DATA OF THE PATIENTS UNDERGOING DXA: CROSS-SECTIONAL STUDY IN SUBURBS

DXA YAPILAN OLGULARIN EPİDEMİYOLOJİK VERİLERİNİN DEĞERLENDİRİLMESİ: BANLİYÖLERDE KESİTSEL ÇALIŞMA

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This study was presented at 9th Turkish National Radiotechnology Congress, October 7–9, 2011 in İzmir, Turkey.

Öz

Amaç: Mersin ilinde banliyö bölgelerinde kemik mineral dansitometri (KMD) tetkiki yapılan olguların epidemiyolojik verilerini elde etmeyi ve değerlendirmeyi amaçladık. Gereç ve Yöntem: KMD tetkiki yapılan 370 olgudan elde edilen epidemiyolojik veriler oransal olarak değerlendirilmiştir. Veriler yüzde olarak ve n=n1/Toplam sayı olarak belirtilmiştir. Bulgular: Olguların yaş ortalaması 54.71 yıl (yaş aralığı, 6–82 yıl); kadın sayısı %97.6 (n=361/370); erkek sayısı %2.4 (n=9/370) olarak saptandı. Olguların çoğunluğu 40–60 yaş aralığında (%65.7, n=243/370) idi. İlkokul düzeyinde veya altında eğitim alanlar %78.9 (n=292/370), ortaokul mezunu olanlar %7.3 (n=27/370), lise ve üniversite mezunu olanlar %13.8 (n=51/370) oranında bulundu. Hastalarımızın ana yakınma nedeni kas-iskelet sistemi ağrısı idi (%47.6, n=176/370). KMD tetkikini düzenli aralıklarla yaptıranlar %20.8 (n=77/370) oranında bulunmuştur. Olgular arasında sigara kullanmayanlar %83 (n=307/370), düzenli sigara kullananlar %17 (n=63/370) oranında saptanmıştır. Olgular arasında hiç egzersiz yapmayanların veya düzensiz yapanların oranı %73 (n=270/370) idi. Tartışma: Çalışmamızda, eğitim düzeyinin artışı ile düzenli KMD tetkiki yaptırma oranının artabileceği öngörülmüştür. KMD tetkiki yapılacak hastalarda ölçüm değerlerini etkileyebilecek epidemiyolojik verilerin elde edilmesi, hasta eğitimi ve gelecekte yapılacak KMD tetkiklerinin planlanması açısından yarar sağlayacaktır.

Anahtar Kelimeler

Kemik Mineral Dansitesi; Epidemiyoloji; Osteoporoz

Abstract

Aim: We aimed to obtain and evaluate epidemiological data of the patients who underwent bone mineral densitometry (BMD) examination with dual x-ray absorptiometry (DXA) in suburbs of Mersin City. Material and Method: We evaluated the data obtained from a prepared questionnaire administered to 370 patients who underwent BMD examination. The data obtained were given in terms of percentages and as n=n1/whole population. Results: The mean age of the patients was 54.71 years (range, 6–82 years). The percentages and the numbers of females and males were 97.6% (n=361/370) and 2.4% (n=9/370), respectively. The majority of the patients were between 40–60 years of age (65.7%, n=243/370). The percentages and the numbers of patients who had education at or below primary school level were 78.9% (n=292/370). The percentages and the numbers of patients who graduated from secondary school and who had high school or an upper degree education were 7.3% (n=27/370) and 13.8% (n=51/370), respectively. The major complaint of our patients was musculoskeletal pain (47.6%, n=176/370). Only 20.8% (n=77/370) of the patients mentioned regular previous BMD measurements. The majority of patients (83%, n=307/370) gave no history of cigarette smoking, whereas 17% (n=63/370) of our patients were smoking regularly. 73% (n=270/370) of the patients did not perform regular exercise. Discussion: With a higher level of education, the patient's complicance in undergoing regular BMD measurements can increase. Obtaining epidemiological data of patients at the time of BMD measurements and evaluation of these data were considered useful and recommended for patient education and future planning of BMD measurements.

Keywords

Bone Mineral Density; Epidemiology; Osteoporosis

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Introduction

Decrease in bone density increases the risk of bone fracture. In adults, advanced age is accompanied by decreased bone density. Since bone density affects the fracture resistance of bone, bone mineral density (BMD) measurement is extremely important for determination of the fracture risk. Because, as a systemic bone disease, it leads to fractures, osteoporosis causes serious health problems and economic losses. It is estimated to be present in 10% of the world population [1]. BMD measurement methods such as dual x-ray absorptiometry (DXA), were developed for the diagnosis and follow-up of osteoporosis and for predicting the fracture risk [2]. With the aid of DXA, osteopenia and osteoporosis can accurately be diagnosed in geriatric and non-geriatric adult males [3]. DXA has also been defined as the best densitometric technique for the evaluation of BMD in postmenopausal women, for diagnosing osteopenia and osteoporosis, and for their follow-up [4]. Today, DXA is the reference method because of its acceptable accuracy, better sensitivity, repeatability, and reproducibility [4,5]. During BMD measurements with DXA there is minimal exposure to ionizing radiation and the measurements can be completed within minutes [4]. The patients' awareness of the importance of osteoporosis and BMD measurements with DXA can help prevent this worldwide health problem. In our study we aimed to obtain and evaluate epidemiological data of the patients who underwent DXA in suburbs of Mersin City.

Material and Method

In this cross-sectional study which was performed between May 2011 and December 2011 in accordance with the World Medical Association Declaration of Helsinki (revised in 2000, Edinburgh), we included 370 consecutive patients from suburbs of Mersin City who were to undergo BMD measurements with DXA. All the patients were informed about DXA procedures and gave their consent. The data were obtained through face-to-face interviews using a prepared questionnaire. The age, gender, complaints, education level, the intervals of BMD measurements (whether regular or not), smoking habits of the patients, and their frequency of exercise were recorded. The epidemiological data of these patients were given in terms of percentages and as n=n1/whole population.

Results

The mean age of the patients was 54.71 years (range, 6–82 years). The percentages and the numbers of females and males were 97.6% (n=361/370) and 2.4% (n=9/370), respectively. Of the whole study population, 1.9% (n=7/370) were between 6–14 years, 2.2% (n=8/370) were between 30–40 years, 31.1% (n=115/370) were between 40–50 years, 34.6% (n=128/370) were between 50–60 years, 19.5% (n=72/370) were between 60–70 years, and 10.8% (n=40/370) were between 70–82 years of age. The percentages and the numbers of the patients who had education at or below primary school level were 78.9% (n=292/370). The percentages and the numbers of the patients who graduated from secondary school and who had high school or an upper degree education were 7.3% (n=27/370) and 13.8% (n=51/370), respectively. The major complaint of our patients was musculoskeletal pain (47.6%, n=176/370). Only 20.8% (n=77/370) of the patients mentioned regular previous BMD measurements. The majority of the patients (83%, n=307/370) gave no history of cigarette smoking, whereas 17% (n=63/370) of our patients were smoking regularly. 73% (n=270/370) of the patients did not perform regular exercise. The main epidemiological data of the patients are given in Table 1.

Table 1. Main epidemiological data of the patients.

Epidemiological parameter	Percentage
Complaints/the reasons of referral for DXA	
Musculoskeletal pain	47.6%
Routine control	44%
Other complaints	8.4%
Smoking habit	
No smoking	83%
Regular smoking	17%
The intervals/regularity of BMD measurements	
First referral	46.2%
Not regular	33%
Regular (annual)	20.8%
The frequency of exercise	
Not regular/no exercise	73%
Regular (twice or more a week)	27%

Discussion

Today, the gold standard for the diagnosis of osteoporosis is DXA. Major risk factors related with decreased bone density are advanced age, lower body mass index, weight loss, decreased physical activity, prolonged use of corticosteroids, androgen suppression treatment in men, and history of fracture due to osteoporosis [6, 7]. Performing BMD measurements before starting treatments such as corticosteroid administration is important to predict the high risk of osteoporosis and to take the necessary measures [8].

Osteoporosis is a systemic disease characterized by low bone density and microarchitectural deterioration which leads to increased risk of bone fracture [1]. For this reason the main goals of osteoporosis treatment are to prevent or decrease bone loss, to increase bone mineral density and bone strength, and to prevent fracture formation [9]. An ideal anti-osteoporosis agent should serve the above-mentioned goals, be well-tolerated by the patients, and suitable for long-term use. Anti-osteoporotic effects of statins have been demonstrated after at least six months period of treatment [10]. Osteoporosis treatment is appropriate for patients with moderate to high risk of fracture; however in the low-risk group, the balance between the beneficial vs. adverse effects, and the costs of pharmacological prevention, should be taken into consideration [11]. In our study, which gathered the fundemental epidemiological data of the patients who were referred for BMD measurements, we detected that the majority (65.7%) of our patients were between 40–60 years of age. Musculoskeletal pain was the major complaint of our patients. We considered that their lifestyle without regular exercise was related to these complaints in most of these patients, because sedentary living lacking adequate physical activities leads to a decrease in bone mass [12]. Lifting light weights and isotonic exercises like brisk walking are

important in the prevention and treatment of osteoporosis [12–14]. In a study that evaluated the relationship between smoking and BMD using biochemical parameters such as calcitropic hormones, it was reported that smoking caused a decrease in BMD [15]. A considerable portion of our patients (17%) in our study were smoking regularly.

In a multicenter study, the educational status of the osteoporotic patients was found to have a great impact on their level of knowledge about osteoporosis [16]. The main goals of educating people about osteoporosis are to increase their awareness about this disease and to encourage them to take precautions such as performing regular exercise and maintaining anti-osteoporosis treatment. Most of the patients in our study were undereducated (78.9%), which was considered to be related to the low rates of regular exercise (27%) and regular BMD measurements (20.8%). In one study, significant differences were found between female patients from different places or regions with regard to their consciousness about osteoporosis, level of education, level of physical activities, dressing style, and smoking habits [16]. More studies such as ours from different regions of Turkey can be performed in order to investigate diversities in the epidemiological data of patients undergoing DXA. With the guidance of these data, it can be possible to increase the awareness of patients about ostoporosis and to provide access to preventive measures through the whole country.

Our cross-sectional study had some limitations. Firstly, the patients were not followed up, which could be useful to observe the changes in their attitudes to undergoing regular DXA measurements and exercising regularly. Secondly, detailed epidemiological parameters such as dietary habits and family history of fracture could not be obtained in our busy public hospital. Thirdly, we could not gather all of the necessary information for fracture risk assessment tool (FRAX®) [17], which could help assess the probability of major osteoporotic fractures in our region. However, we consider that our sample size was large enough to reflect the status of the people living in suburban areas of Mersin.

Conclusion

With a higher level of education, the patient's compliance in undergoing regular BMD measurements can increase. In each DXA unit of the country, obtaining epidemiological data of the patients at the time of BMD measurements via face-to-face interviews using prepared questionnaire, and evaluation of these data can be useful for patient education and future planning of BMD measurements. Aggregation of all these epidemiological data in a single national center can help develop more efficient health policies to prevent osteoporosis and its complications.

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Competing interests

The authors declare that they have no competing interests.

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A COMPARISON OF 4 DIFFERENT PATIENT GROUPS IN THE TREATMENT OF TRIGGER FINGER: IS TREATMENT ACCORDING TO GRADE IMPORTANT?

TETİK PARMAK TEDAVİSİNDE 4 FARKLI HASTA GRUBUNUN KARŞILAŞTIRILMASI: EVREYE GÖRE TEDAVİ ÖNEMLİ Mİ?

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Öz

Amaç: Stenozan tenosinovit olarak da adlandırılan tetik parmak elde ağrı ve fonksiyon bozukluğuna sebep olan ve en sık görülen el patolojileri arasındadır. Çalışmamızda hastalar, uygulanan tedavi açısından 4 farklı gruba ayrılmış ve bu tedavi seçeneklerinin farklı evreler üzerindeki etkinliği değerlendirilmiştir. Gereç ve Yöntem: 2011-ocak 2015 arasında A1 pulleyi etkileyen 543 tetik parmak tanılı hasta retrospektif olarak değerlendirildi. Hasta verilerine hastane kayıtları ve klinik kayıt dosyalarından ulaşıldı. 301 hasta kadın 242 hasta erkek idi. Hastaların evrelenmesinde Quinnell evreleme sistemi kullanıldı. Bulgular: Hastaların uygulanan tedaviler ve evrelerine göre work modülleri değerlenderildiğinde ;tüm evreler için preoperatif değerlere göre work modulu oral ve lokal NSİİ grubu hariç; lokal kortikosteroid, perkutan release ve açık cerrahi gevşetme tedavilerinde istatiksel olarak anlamlı düzeyde düzelmiş idi ($p<0.005$). Oral NSİİ grubunda ise tedavi sonrası değerler preoperatif değerlere yakın ve anlamlı bir farklılık yok idi. Tartışma: Çalışmamızda elde ettiğimiz veriler ışığında tetik parmak patolojisinde evre artıkça, fonksiyonel performans ve kinematik üzerinde meydana gelen olumsuz etkilerin giderilmesi için daha invazif tedavi seçeneklerinin daha tatminkar sonuçlar sağladığı kanısındayız.

Anahtar Kelimeler

Tetik Parmak; Perkutan Gevşetme; Kortikosteroid

Abstract

Aim: Stenosing tenosynovitis, known as trigger finger, is one of the most commonly seen hand pathologies, causing pain and impaired function in the hand. In this study, the patients were separated into 4 groups according to the treatment applied and an evaluation was made of the efficacy of these treatment options on different grades. Material and Method: A retrospective evaluation was made of 543 patients, 301 females and 242 males, diagnosed with trigger finger affecting the A1 pulley between February 2011 and January 2015. Patient data were obtained from hospital records and the patient clinical records. The Quinnell grading system was used to grade the trigger fingers. Results: When the work modules were evaluated according to the grades and the treatments applied to the patients, with the exception of the oral NSAID group, a statistically significant improvement was determined in the work module for all grades compared to the preoperative values of the local corticosteroid, percutaneous release, and open release treatments ($p<0.05$). In the oral NSAID group, the post-treatment values were similar to the pre-treatment values and there was no significant difference. Discussion: In light of the data obtained in this study, it was seen that as the grade increased in trigger finger, more satisfactory results were provided by more invasive treatment options to remove the negative effects on functional performance and kinematics.

Keywords

Trigger Finger; Percutaneous Release; Corticosteroid

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Introduction

Stenosing tenosynovitis, known as trigger finger, is one of the most commonly seen hand pathologies, causing pain and impaired function in the hand. The pathology, which starts with pain and sensitivity at the level of the tendon related to the palmar region of the hand, gradually progresses to sticking during flexion and extension movements of the finger, popping, and finally may result in locking in a specific position. Incompatibility between the dimensions of the retinacular pulley and the flexor tendon is known to cause this pathology. Although trigger finger is defined as a mild hand pathology, it is becoming more emphasized because of the increasingly negative effect on hand functions and daily activities [1].

The treatment protocol for trigger finger continues to be a controversial topic. In contrast to the very good results reported from open and percutaneous surgery on trigger finger [2-3], there are also studies which have reported undesired outcomes in open surgery, such as infection, scar formation, and delayed return to work [4-5] and incomplete release and iatrogenic nerve damage in percutaneous surgery [6]. In recent years, the negative effect on rehabilitation of adhesions which have formed postoperatively has been better demonstrated, thereby strengthening the view that trigger finger treatment should be planned according to the clinical stage and unnecessary surgery should be avoided [7]. In this study, the patients were separated into 4 groups according to the treatment applied and an evaluation was made of the efficacy of these treatment options on different grades.

Material and Method

A retrospective evaluation was made of 543 patients diagnosed with trigger finger affecting the 1st finger A1 pulley between February 2011 and January 2015. Patient data were obtained from hospital records and the patient clinical records. The patients were 301 females and 242 males. The Quinnell grading system was used to grade the trigger fingers (Figure 1). Accordingly, 122 patients were evaluated as Grade 1, 173 patients were Grade 2, 144 were Grade 3, and 104 were Grade 4. Patients at Grade 1 and any patients with diabetes were excluded from the study. Thus the evaluations were made on a total of 402 patients, 231 females and 171 males. Three groups were formed in accordance with the Quinnell grading system as Grade 2, Grade 3, and Grade 4. All patients were treated with oral non-steroid anti-inflammatory drugs (NSAID) of 50mg diclofenac potassium x 2/day (100mg/day) (Dicloflam, Santa Farma, Istanbul) for a total of 6 weeks for the analgesic and anti-inflammatory effects.

Grade 0	Mild crepitus in the non-triggering finger
Grade 1	No triggering, but uneven finger movements
Grade 2	Triggering is actively correctable
Grade 3	Usually correctable by the other hand
Grade 4	The digit is locked

Figure 1. Quinnell classification of trigger finger

In each grade, the patients were then divided into 4 different subgroups treated with:

only NSAID, local corticosteroid injection to the A1 pulley (Diprospan, Schering Plough, Istanbul: single dose Betamethasone diproprionate 6.43mg+Betamethasone sodium phosphate 2.63mg), percutaneous A1 pulley loosening under local anaesthesia, and mini open A1 pulley loosening under local anaesthesia.

In all the grades, patients who refused surgical treatment or the application of local corticosteroid injection were included in the NSAID protocol. For each patient, a record was made before and after treatment of the DASH values (Disabilities of the Arm, Shoulder and Hand), work module, complication rates, time of return to work, and recurrence rates.

Results

In the Grade 2 group, a statistically significant improvement was determined in the postoperative DASH evaluations of all the treatment options compared to the preoperative values ($p<0.005$). In the comparison of the postoperative DASH values of the sub groups of Grade 2, a statistically significant improvement was determined in the local corticosteroid, percutaneous release, and open release groups compared to the NSAID group ($p<0.05$). The results obtained in the local corticosteroid, percutaneous release, and open release groups were seen to be similar ($p>0.05$) (Figure 2). In the interpretation of the clinical results for Grade 2, it can be said that although an improvement was obtained with the administration of NSAID, this was not as effective as local corticosteroid, percutaneous release, and open release. Patient dissatisfaction was determined at the rate of 76% in the NSAID group. Recurrence was determined in 1.46% of the local corticosteroid patients, in 2.2% of the percutaneous release group, and in 2.6% of the open release group.

In the Grade 3 patients, in the comparison of the clinical results, the pre-treatment and post-treatment DASH values were seen

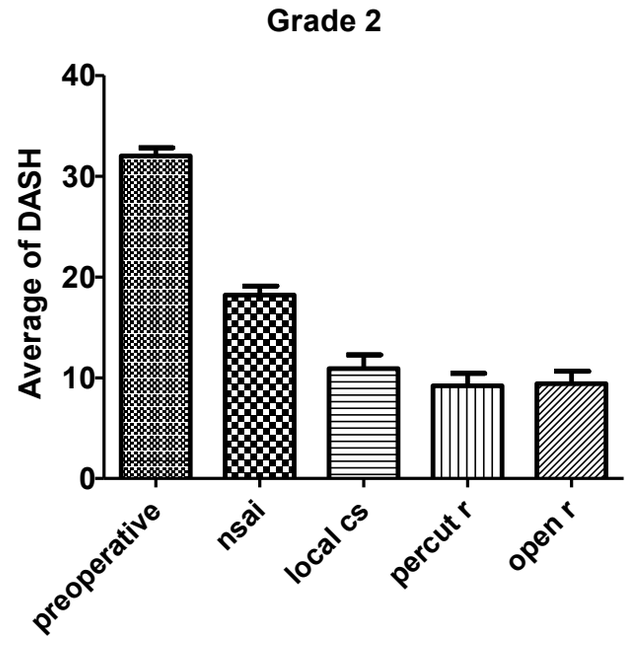

Figure 2. Evaluation of the treatment types of Grade 2 patients

to be similar in the patients who received NSAID only (p>0.05). This suggests that NSAID is not an effective treatment for Grade 3 trigger finger (Figure 3). Clinically similar results were obtained from the local corticosteroid, percutaneous release, and open release techniques and no statistically significant difference was determined in the DASH values (p>0.05). At the final follow-up examination, patient dissatisfaction was determined at the rate of 88% in the NSAID group. Recurrence was determined in 4.4% of the local corticosteroid patients, in 2.2% of the percutaneous release group, and in 2.7% of the open release group.

In the Grade 4 patients, in the comparison of the clinical results of the applied treatments, no significant improvement was determined in the post-treatment DASH values of the patients administered with NSAID only compared to the pre-treatment values (p>0.05). This indicates that instead of using NSAID as a curative treatment for Grades 3 and 4, it would be more correct to consider NSAID as an adjuvant to the main treatments. A statistically significant improvement was determined in the postoperative period of all the patient groups applied with local corticosteroid, percutaneous release, and open release compared to the preoperative DASH values (p<0.05).

In the comparison of the local corticosteroid, percutaneous release, and open release applications for Grade 4, similar clinical results were determined in the local corticosteroid and percutaneous release groups (p>0.05). In the open release group, statistically significant better clinical results were obtained than in the other two treatment options (p<0.05) (Figure 4). These results demonstrate that the application of local corticosteroid and percutaneous release significantly improved the clinical results, but open release can be said to be clinically more effective at a statistically significant level compared to the other two techniques. In this group of Grade 4 trigger finger, patient dissatisfaction was determined at the rate of 100% in the NSAID group. Recurrence was determined to be 7.4% of the local corticosteroid patients, in 2.2% of the percutaneous release group, and in 2.4% of the open release group.

When the work modules were evaluated according to the grades

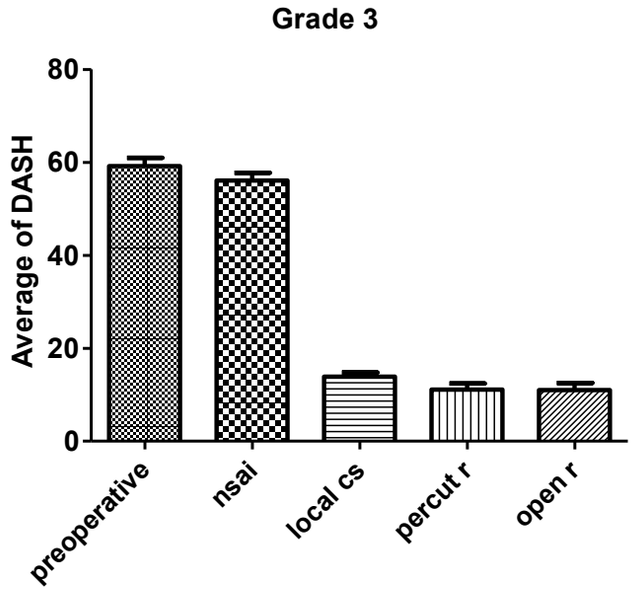

Figure 3. Evaluation of the treatment types of Grade 3 patients

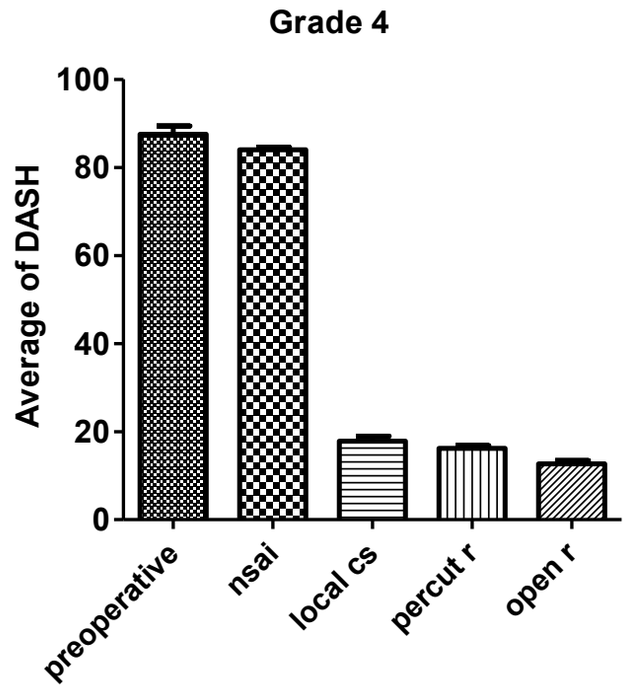

Figure 4. Evaluation of the treatment types of Grade 4 patients

and the treatments applied to the patients, with the exception of the oral NSAID group, a statistically significant improvement was determined in the work module for all grades compared to the preoperative values of the local corticosteroid, percutaneous release, and open release treatments (p<0.05). The values between the groups were similar (p>0.005). In the oral NSAID group, the post-treatment values were similar to the pre-treatment values and there was no significant difference (Table 1).

Statistical Analysis

The statistical analyses of the study were applied using SPSS v.22.0 software. The descriptive statistics of categorical variables were stated as number (n) and percentage (%). In the 2x2 cross-check tables, the Pearson's Chi-square test was used for categorical variables and the Fisher's Exact Chi-square test was used for values that were expected to be <5.

The conformity to normal distribution of the measured variables of both categories was assessed with the Shapiro-Wilk test. In the comparison of data not showing normal distribution, the non-parametric Mann Whitney U-test was used. For data with normal distribution, the t-test was used and the test statistic was selected according to the variance homogeneity examined with the Levene test.

In the comparison of variables with a ratio measurement level of more than two categories, first the normality hypothesis was examined with the Shapiro-Wilk test. If all the categories of the variables had normal distribution at the same time, the non-parametric Kruskal Wallis test was used for those parameters, and if the categories of the variables did not have normal distribution, ANOVA was applied. However, if the result obtained from ANOVA did not have variance homogeneity according to the results of the Levene test, the Kruskal Wallis test was applied in place of ANOVA. Unless otherwise specified, a value of p<0.05 was considered statistically significant.

Table 1. Preoperative and postoperative DASH and Work Modules

	Preop DASH and WM	Postop DASH and Work Module (WM)			
		Oral NSAID	LOCAL CORTICOSTEROİD	PERCUTANEOUS RELEASE	OPEN RELEASE
Grade-2	DASH:31.8 4.8 WM: 25 5.3	DASH:18.2 4.6 WM: 18.8 6.3	DASH:11.4 8.2 WM:6.3 6.3	DASH:9.1 7.2 WM:6.3 6.3	DASH:9.2 6.3 WM:6.3 6.3
Grade-3	DASH:59.1 7.8 WM:50 6.2	DASH:56.8 8.2 WM: 43.8 6.2	DASH:13.6 4.2 WM:6.3 6.3	DASH:11.4 6.2 WM:6.3 6.3	DASH:11.4 8.2 WB:6.3 6.3
Grade-4	DASH:88.6 9.3 WM:81.3 5.4	DASH:84.1 2.3 WM: 75 6.3	DASH:18.2 6.3 WM:12.5 6.3	DASH:15.9 2.3 WB:6.3 6.3	DASH:13.6 3.2 WB:6.3 6.3

Discussion

In the classification of trigger finger, functional performance and kinematics are significantly affected in different grades and this shows correlation with histopathological finding [8, 9]. These data suggest that in cases of trigger finger determined in different grades, the choice of the conservative and surgical treatments applied could affect clinical and functional results and the rates of recurrence. There is evidence that different results are obtained at each grade with different treatment options such as oral NSAID, local corticosteroid injection, percutaneous release, and mini open surgical release. In the literature, while results have been reported of comparative studies related to different invasive treatment protocols in patients at an advanced grade, to the best of our knowledge, there has been no previous study which has compared the treatment results of the whole spectrum from conservative to invasive surgery in patients at the same grade. In this study, by presenting the results of different treatment protocols applied to patients at the same grade, it has been attempted to define a basic algorithm of which treatment would be most appropriate at which grade in the treatment of trigger finger.

In patients diagnosed with Grade 2-4 trigger finger, and treated with local corticosteroid injection, percutaneous release, or open surgical release without any differentiation based on grade, it has been reported that surgical techniques are superior to conservative corticosteroid injection with respect to clinical satisfaction and recurrence rates [10-11].

Many previous studies have compared the application of percutaneous release and open surgical treatment options. It has been reported that percutaneous release carries a greater risk of postoperative complications, particularly related to iatrogenic digital nerve damage [12].

In many large series studies, the use of NSAID as a treatment option for trigger finger has not been evaluated [13, 14]. In the current study, patients who did not accept the recommended invasive and semi-invasive treatments were treated conservatively with oral NSAID, but it was determined from the patient records that dissatisfaction was reported by 76% of Grade 2 patients, by 88% of Grade 3 patients, and by 100% of the Grade 4 patients. This indicates that NSAID treatment was not effective in Grade 2, 3, and 4 patients and treatment with NSAID should be considered as a non-curative symptomatic application with the aim of reducing pain and inflammation.

The application of local corticosteroid injection to Grade 2 patients has been made in many studies and good results have been reported [15-16]. In the current study, satisfactory results were obtained with the application of single dose corticosteroid in 41 (88%) of 46 patients, results supported by similar studies in the literature [17-18]. Good results at a similar rate were obtained in patients at the grade treated with mini open surgery and percutaneous release. Single dose corticosteroid injection could be considered as the first treatment option as it is less invasive and expensive. In 5 patients who did not benefit from the steroid injection in the current study, percutaneous release was then applied. No diagnosis of spontaneous tendon rupture was encountered in any case in the current study population.

Although there are publications reporting very good results in open and percutaneous surgical treatment of trigger finger, there are also studies that have reported infection, scar formation, and delayed return to work in open surgery and incomplete release and iatrogenic digital nerve injury in percutaneous treatment [4, 5, 6].

In a study, Diab applied percutaneous release to 43 patients diagnosed with Grades 2 and 3 trigger finger. While complete release was obtained in 40 patients, incomplete release was reported in 3 patients. No vascular nerve complications or flexor tendon damage that would cause functional loss were encountered [19]. In the current study, following percutaneous release in patients with Grade 3 trigger finger, unwanted side effects were observed of temporary joint stiffness in 3 of 41 patients and temporary hyperalgesia in 4. No digital nerve injury was observed in any case. Of the 41 patients, 38 were pleased with the result. Following the application of mini open surgery to 43 patients with Grade 3 trigger finger, temporary joint stiffness was observed in 8 cases, bowstring in the flexor tendon in 2, and temporary digital nerve damage in 1. In the Grade 3 steroid application group, 16 (24.7%) of the 38 patients were not satisfied with the result. Based on the results of this study, percutaneous release can be considered to be a preferable treatment option for patients with Grade 3 trigger finger as this technique had higher rates of patient satisfaction, it is less invasive than mini open surgical release, and fewer postoperative complications were seen.

In a study by Lepegue et al. of 60 patients, corticosteroid injection was applied to 10 patients with persistent symptoms after percutaneous A1 pulley release. Of these patients, 7 benefitted from the injection and symptoms were reported to have continued in only 3 patients [20]. In the same study, percutaneous A1 pulley release was performed on 10 cadavers before the application was performed on patients and it was observed that none of the A1 pulleys was completely released. From this study it can be considered that when including symptoms that could be eliminated following percutaneous release, in patients where there is partial persistence of symptoms, the application of corticosteroid injection could completely eliminate symptoms. In the current study, when patients did not sufficiently benefit from percutaneous release and recurrence developed, rather than steroid injection, A1 pulley release was applied with a mini open incision. In the study by Lepegue et al., as 70% success was achieved with the application of corticosteroid to patients who had not seen benefit from percutaneous release and

for whom recurrence had occurred, this suggests that the less invasive method of corticosteroid injection could be considered as an alternative before mini open surgery.

In a study by Shinomiya et al., the efficacy of steroid injection was compared in cases of trigger finger with and without contracture and it was shown that the efficacy of the steroid injection was significantly low in advanced stage patients with contracture [13]. In the current study, the results of steroid injection to Grade 4 cases were not satisfactory. The application of percutaneous release and mini open surgical release in Grade 4 patients was determined to be more effective than the application of corticosteroid injection (Figure 4). In a comparison of surgical techniques, more satisfactory clinical results were seen to have been achieved with the mini open release technique. However, a noticeable disadvantage of this technique is a delayed return to work.

In the light of the data obtained in this study, it was seen that as the grade increased in the pathology of trigger finger, more satisfactory results were provided by more invasive treatment options to eliminate the negative effects on functional performance and kinematics. While local corticosteroid injection provided sufficient and satisfactory clinical results in Grade 2 cases, it was observed that in Grade 4, the most satisfactory results were obtained from the application of the mini open release technique. These results strengthen the view that it is necessary to use different treatment options according to grade in the treatment of trigger finger.

Conclusion

In Grade 2 or higher pathology of trigger finger, oral NSAIDs show no curative effect in the treatment of trigger finger. Although satisfactory results were obtained with local corticosteroid injection at all grades, as the grade increases, the efficacy is reduced and recurrence rates may increase. At all grades, percutaneous release and mini open release were similar in respect to the clinical results and were seen to be the most effective treatment options. For Grade 3 patients, percutaneous release can be preferred as the treatment option because of low complication rates.

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TYPES OF ANASTOMOSIS IN FEMOROFEMORAL BYPASS SURGERY

FEMOROFEMORAL BYPASS CERRAHİSİNDE ANASTOMOZ TÜRLERİ

TYPES OF ANASTOMOSIS

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Öz

Amaç: Bu çalışmanın amacı, femorofemoral anastomoz için farklı cerrahi tekniklerdeki enerji kayıplarını deneysel olarak değerlendirmektir. Gereç ve Yöntem: Femorofemoral anastomoz, S 450, S 900, ters U, U ve right-angled olmak üzere beş farklı konfigürasyonda yapıldı. Anastomoz konfigürasyonları aynı uzunlukta tüp setleri ve politetrafluoroetilen (PTFE) sentetik tüp greftler kullanılarak oluşturuldu. Flow sağlamak için Kardiyopulmoner bypass makinası kullanıldı. Basınç ölçümleri,anastomoz bölgesinin öncesi ve sonrasında sabit ve eş zamanlı basınç takibi ile sağlandı. Bulgular: Bu deneysel çalışmada S tipi anastomozun avantajlı olduğu belirlendi. S anastomoz tipinde, minimum enerji kaybı ve en düşük basınç gradient ölçümleri saptandı. Minimum enerji kaybı ve basınç gradient farkı S 450 anastomoz tipinde gözlenmiştir. Tartışma: S tipi femorofemoral anastomoz tipi hemodinamik olarak diğer anastomoz tiplerinden daha etkili bir seçenektir.

Anahtar Kelimeler

Femorofemoral Bypass; Greft Açısı; Akım Gradienti

Abstract

Aim: The aim of this study was to experimentally determine the energy loss in different techniques of femorofemoral anastomosis. Material and Method: Femorofemoral anastomoses were performed in five different configurations including the S 45°, S 90°, inverted - U, U, and right-angled. Femorofemoral anastomosis configurations were created by using tubing sets and polytetrafluoroethylene (PTFE) synthetic ringed grafts of the same length. The flow was provided by a cardiopulmonary bypass pump. The pressure measurements were taken with constant, real-time pressure monitoring of the lines before and after the femorofemoral anastomosis sites. Results: This experimental study revealed the advantage of type S anastomosis. In the S anastomosis type, minimum energy loss and the lowest gradient recordings were determined. The minimum energy loss and gradient difference were observed in the S 45°. Discussion: Type S femorofemoral anastomosis is a hemodynamically more effective choice than the other techniques.

Keywords

Femorofemoral Bypass; Graft Angulation; Flow Gradient.

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Introduction

Femorofemoral crossover bypass is an extra-anatomical arterial bypass. It is usually performed on patients with unilateral iliac artery occlusion and endovascular abdominal aortic aneurysm repair (EVAR) using an aortouniiliac endoprosthesis. Femorofemoral bypass is a simple, safe, and acceptable alternative to aortobifemoral, aorto-unifemoral, and iliofemoral bypass in older patients and in patients with high-risk profiles, particularly those with limb-threatening ischemia [1].

In terms of performing bypasses and anastomoses, the hemodynamic effects of the geometrical configurations of the grafts are very important from a surgical point of view. Inadequate inflow is considered the most likely cause of poor femorofemoral bypass function [1].

Flow disturbances and loss of energy due to anastomosis models are important problems with regard to perfusion pressure. Therefore, the aim of this experimental study is to describe the pressure-energy loss in different techniques of femorofemoral anastomosis.

Material and Method

Five different femorofemoral anastomosis models were studied (Fig. 1). Different types of femorofemoral anastomoses were created using the same length tubing sets and polytetrafluoroethylene (PTFE) synthetic ringed grafts. The bypass length and anatomical positions were standardized for every type of anastomosis. The proximal and distal ends of the PTFE graft were connected to a cardiopulmonary pump (COBE) for every anastomosis type. In each experiment, we used a set of normothermic cardiopulmonary bypass (CPB) circuits with a standard 3/8 inch tubing set, a reservoir, and a pump; the prime of the CPB circuit consisted of 800 mL blood (Hct 30%). We used the traditional method to set occlusion, and a drop speed of 2.5 cm/min to calibrate roller pumps for use in CPB. The blood flow was circulated in the circuit at a flow rate of 5 L/min. The experimental period was 30 minutes. The pressure sensors were placed at the femorofemoral anastomosis right inlet and left outlet point. The distances between the pressure lines were equal. The pressure on both sides of the femorofemoral anastomosis was monitored continuously with flow on throughout the experiments and the data were recorded separately for every experiment every 5 minutes over 30 minutes. Pressure monitoring was achieved with PETAS MKA 900. The pressure transducer was calibrated to accurately process the data after every experiment.

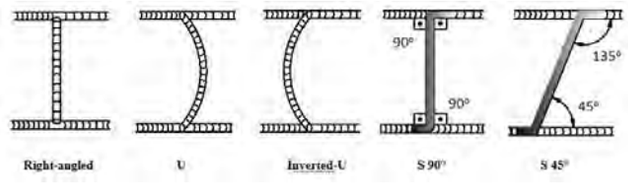

Figure 1. Femorofemoral anastomosis: Right-angled, U, inverted - U, S 90°, S 45°

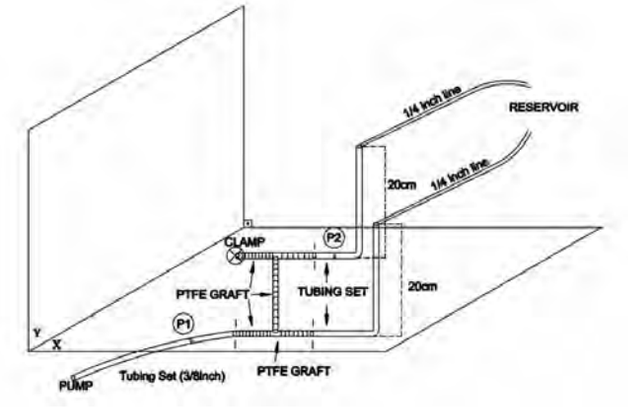

Figure 2. Experimental model of femorofemoral anastomosis.

To reproduce arterial resistance because the flow was nonpulsatile in our study, the free sides of the lines were raised 20 cm on the X-axis (perpendicularly to the Y-axis). These heights were bilaterally equalized. In addition, at a point distant from the pressure sensor, ¼ inch lines were used to reproduce arterial resistance after this 20th cm of these raised lines (Fig. 1).

A 5 L/min flow was chosen because the flow was continuous in our study. In normal subjects, volumetric mean arterial blood flow is, on average, 500-750 ml/min for one lower extremity and 1000-1500 ml/min for two lower extremities. In normal cardiac physiology, however, the diastolic component of the cardiac cycle is twice the systole. Therefore, when we divided the continuous 5 L/min cardiopulmonary pump flow by 3, this would match the normal cardiac systolic flow for lower extremities, which is 1.66 L/min.

The mean and median values "were equal" in all groups. The Kruskal-Wallis Test (post-hoc test using Mann-Whitney tests with Bonferroni correction) was used to compare the types of anastomosis. Statistical significance was defined as a p-value of 0.05 or less. SPSS for Windows (SPSS Version 15.0. SPSS Inc., Chicago, IL) was employed for statistical analyses.

Results

Table 1 shows the distribution of the pressure gradient of five anastomosis models with five values and comparison of variances. The mean pressure values after anastomosis among the types of anastomosis were statistically significantly different ($p < 0.001$).

To determine the technique that causes the lowest loss of energy and pressure gradient is one of the most important components of surgical competency. In the present study, especially, inverted - U, U, and right - angled anastomosis models were found to cause greater flow disturbances and decreased energy. The median pressure gradient was significantly lower in S (S 45° and S 90°) anastomosis models than in the right - angled, U, and inverted - U anastomosis models (18, 29, 48, 53, and 58 mmHg respectively, Table 1). The lowest gradient (18 mmHg) was found in the S 45° anastomosis.

Table 1. Pressure gradients of femorofemoral anastomosis (mmHg).

Type of anastomosis	Mean ± SD	Med (Min - Max)	p
Inverted-U	58.4 ± 2.71	58 (55 - 62)	0.001*
U	53.8 ± 2.77	53 (51 - 58)	
Right-angled	48 ± 2.12	48 (45 - 50)	
S 90o	28.8 ± 2.59	29 (25 - 32)	
S 45o	18.2 ± 2.39	18 (15 - 21)	

* Kruskal-Wallis H-test; Med, median; Min, minimum; Max, maximum

Discussion

The mode of graft failure appears to be closely related to the problems of inflow rather than the runoff. This relationship shows the importance of anatomically correct femorofemoral modeling. Vascular anastomosis is a complex task that has multiple requisite skills, which include manual dexterity and visual-spatial ability [2].

Although the type of anastomosis is one of the most important components of surgical competency, patency after femorofemoral bypass is affected by a variety of factors [3]. Factors affecting long-term patency include the amount of suture material used; the anatomic level of arterial disease and the outflow target artery; the degree of calcification of the vessels; more effective medication regimens consisting of a statin, an antiplatelet agent, and -blocker; and intraoperative care and postoperative management [3,4].

Improvements in preoperative medical optimization, vascular characteristics of patients, and postoperative medical therapy have all contributed to improvements in the patency rate of vascular grafts [4,5]. Even so, the type of anastomosis continues to play a significant role in the optimal strategy and long-term patency for revascularization.

In vitro fluid dynamic studies have revealed that geometry plays a key role in determining local flow fields [6]. According to in vitro fluid dynamic studies, the flow fields vary with the angle of anastomosis, and different types and degrees of flow disturbances are present at different locations within the same anastomosis [7-9]. To determine the technique with the lowest loss of energy and pressure gradient is one of the most important components of surgical competency. In particular, inverted - U, U, and right-angled anastomosis models were found to cause more flow disturbances and decreased energy.

It is widely accepted that local flow dynamics and mechanical conditions play a major role in the development of subsequent graft failure in vascular graft anastomosis [10]. Flow characteristics and vascular resistance are strongly influenced by the angulation of the graft in femorofemoral tunnel and the type of anastomosis. The postoperative perfusion pressure in lower extremities is important in the clinical application of femorofemoral bypass configurations. The pressure gradients and perfusion pressures are strongly influenced by the type of femorofemoral anastomosis in our experimental study.

The graft angulation and types of anastomosis can create significant differences in terms of graft patency regarding energy loss and turbulent flow. Accordingly, decrease of energy loss leads to increased distal perfusion pressures. Comparing these five anastomosis techniques, the S 90° and the S 45° femorofemoral anastomoses had better results than the other techniques. The 45-degree tilt in femorofemoral tunnel leads to the most significant minimum loss of energy in comparison with the other two S configurations.

In conclusion, femorofemoral bypass with S-type anastomosis is a hemodynamically more effective choice. The S 45° anastomosis is superior to the S 90° anastomosis. In this aspect, this experimental study concluded that the S 45° type of anastomosis is preferable from a hemodynamic perspective. In light of this data, we suggest it would be wise to reduce the use of the other techniques in femorofemoral crossover bypass procedures.

Competing interests

The authors declare that they have no competing interests.

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EVALUATION OF THE ANTI HEPATITIS C VIRUS SEROPOSITIVITY AND SERUM TRANSAMINASES IN OUR HOSPITALS

HASTANEMİZ ANTİ HEPATİTİS C VİRUS SEROPOZİTİLİKLİĞİNİN VE SERUM TRANSAMİNAZLARININ DEĞERLENDİRİLMESİ

HEPATIT C VIRUS

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Öz

Amaç: Hepatit C Virus (HCV) , kronik karaciğer hastalığı, siroz ve hepatoselluler karsinomaya yol açabilen önemli bir enfeksiyon hastalığı etkenidir. HCV' ye bağlı karaciğer hastalıklarının toplumu ne derece etkileyeceğinin belirlenebilmesi için HCV prevalansındaki değişimlerin bilinmesi ve izlenmesi gerekir. Çalışmamızda, hastanemize başvuran hastaların anti HCV seropozitifliğinin belirlenmesi ve serum transaminazları ile birlikte değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Ocak 2012-Haziran 2015 tarihleri arasında hastanemize başvuran, çeşitli kliniklerden gelen 131851 hastaya ait kan örnekleri Anti-HCV pozitifliği kemiluminesans mikropartikül immunoassay tekniği ile , Serum transaminazları spektrofotometrik enzimatik yöntemleri ile çalışılmıştır. Sonuçlar anti HCV≥1 S/CO değerlerine sahip örnekler pozitif olarak değerlendirilmiştir. Veriler retrospektif olarak incelenmiştir. İstatistiksel analizler için IBM SPSS statistics 22 (IBM SPSS, Türkiye) programı kullanılmıştır. Mükerrer örnekler değerlendirme dışı bırakılmıştır. Bulgular: Çalışma da131851 olguda Anti HCV pozitif liği 868 (%0.65) olarak saptanmıştır. Anti HCV, ALT, AST eş zamanlı değerlendirilen 80507 olgunun 655(%0,8)'inde anti HCV pozitif tespit edilmiştir. Hastaların cinsiyet dağılımı 45293 (%56.3)'ü kadın, 35214(%43.7)'si erkek olmak üzere, yaşları 0-115 arasında değişmekte olup, ortalaması 43,23±19,58 yıldır. AST düzeyi yüksek olan olgularda Anti HCV pozitifliği görülme oranı (%2), ALT düzeyi yüksek olan olgularda Anti HCV pozitifliği görülme oranı (%2.2) normal olan olgulara göre, istatistiksel olarak anlamlı düzeyde yüksektir (p:0.001; p0.05). Anti HCV pozitif 655 hastanın 138(%21,06)' inde AST yüksekliği, 242(%36,94)'inde ALT yüksekliği görülmüştür. Yaş dağılımına göre Anti HCV pozitifliği 5, 6 ve 7. dekatta daha yüksek tespit edilmiştir. Tartışma: Dünyada HCV infeksiyonu prevalansının yaklaşık %2.8, Türkiye de HCV sıklığı %1-2.4 arasında değişmektedir. Hastanemize başvuran hastalarda, Türkiye geneline göre %0.65 tespit edilerek düşük bulunmuştur. Anti HCV pozitif 655 hastanın 138(%21,06)' inde AST yüksekliği, 242(%36,94)'inde ALT yüksekliği görülmüştür. AST yüksekliğinde Anti HCV prevalansı %2, ALT yüksekliğinde Anti HCV prevalansı %2.2 tespit edilmiştir.

Anahtar Kelimeler

Hepatit C Virus; Alanin Aminotrasferaz; Aspartat Aminotransferaz

Abstract

Aim: Hepatitis C Virus (HCV) is an important infectious disease agent that can cause chronic liver disease, cirrhosis, and hepatocellular carcinoma. It is necessary to follow the changes in incidence of HCV in order to determine the extent to which liver diseases caused by HCV will affect the population. Our study aimed to determine the anti-HCV seropositivity in the patients presenting to our hospital and to evaluate this in conjunction with serum transaminase levels. Material and Method: The anti-HCV seropositivity of blood samples of a total 131,851 patients presenting to various departments in our hospital between January 2012 and June 2015 was studied with spectrophotometric enzymatic methods by using chemiluminescence microparticle immunoassay technique. The samples with anti-HCV S/CO values %u22651 were considered to be positive. Data were analyzed retrospectively. The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. Repeat specimens were excluded from the analysis. Results: Anti-HCV seropositivity was determined in 868 (0.65%) of the 131,851 patients in the study. Anti-HCV seropositivity was determined in 655 (0.8%) of 80,507 patients in whom anti-HCV, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were examined together. The mean age of the patients was 43.23±19.58 years (range: 0-115 years), of whom 45,293 (56.3%) were female and 35,214 (43.7%) were male. The prevalence rate of anti-HCV seropositivity was statistically significantly higher in the patients with higher levels of AST (2.0%) and in the cases with higher levels of ALT (2.2%) compared to the healthy individuals (p: 0.001; p<0.01). There was no statistically significant difference between incidence rates of anti-HCV seropositivity in the patients according to AST/ALT distributions (p>0.05). Higher levels of AST and ALT were observed in 138 (21.06%) and 242 (36.94%) of 655 patients with anti-HCV seropositivity, respectively. The anti-HCV seropositivity was determined to be higher in patients in their 5th, 6th, and 7th decades. Discussion: The prevalence of HCV infection is approximately 2.8% worldwide, while the prevalence of HCV infection in Turkey varies between 1% and 2.4%. The prevalence of HCV infection was determined to be 0.65% in the patients presenting to our hospital, which is lower than the overall prevalaence inTurkey. Elevated levels of AST and ALT were observed in 138 (21.06%) and 242 (36.94%) of 655 patients with anti-HCV seropositivity, respectively. Anti-HCV prevalence was determined to be 2% in those with elevated AST levels and 2.2% in those with elevated ALT levels.

Keywords

Hepatit C Virus; Alanine Aminotransferase; Aspartate Aminotransferase

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Introduction

Hepatitis C virus (HCV) infection is an important public health problem that causes mortality and morbidity throughout the world [1]. It is estimated that, worldwide, approximately 185 million people (2.8% of the global population) are infected with hepatitis C [2]. Chronic HCV infection is the leading indication for liver transplantations [3]. The primary transmission route of HCV is transfusion of blood and blood products. A marked decrease has occurred in this route of transmission with the introduction of routine screening of HCV antibodies in the blood banks [4,5]. The diagnosis of chronic viral hepatitis is made during the investigation of elevated liver enzymes, which is determined incidentally in approximately half of the patients [6]. Fatty liver disease is the cause of elevated ALT (alanine aminotransferase) levels in more than half of the cases. The result is considered to be chronic viral hepatitis in approximately 5% of the patients with elevated ALT levels [7]. Enzymes are found to be within normal limits in one-third of the patients with chronic hepatitis C infection. Anti-HCV antibody is investigated serologically for the diagnosis of the infection and HCV RNA levels are examined using a molecular method for the detection of viremia. HCV RNA viral load is monitored with liver transaminases during treatment and follow-up, while the severity of inflammation and fibrosis in the liver is determined through biopsy. Although the serum level of liver transaminases is not specific for the disease, it may contribute to the diagnosis and follow-up of the infection. The ratio of AST (aspartate transaminase)/ALT (alanine transaminase), called the De Ritis ratio, is used to discriminate between acute and chronic forms of hepatocellular injury [8]. Our study aimed to contribute to the relevant literature on this subject by evaluating the incidence of anti-HCV seropositivity in our region together with elevated ALT, AST levels, and the AST/ALT ratio.

Material and Method

The blood samples of 131,851 patients (age range: 0-115 years) sent from various departments of our hospital between January 2012 and June 2015 were studied using the chemiluminescence immunoassay method (Advia Centaur CP Bayer-Siemens (Germany), Architect i1000 Abbott ABD autoanalyzer). According to the manufacturer's instructions, specimens with an S/CO value of <1 were considered to be negative and specimens with an S/CO value of ≥1 were considered to be positive. ALT level of 0-34 U/mL, AST level of 0-40, and AST/ALT ratio of <1 were considered to be normal values. Data were evaluated regarding anti-HCV seropositivity, ALT, AST, AST/ALT ratio, and mean age. Statistical analysis was performed using the IBM SPSS Statistics 22 (IBM SPSS, Turkey) program. The Chi-Square test was used for comparison of qualitative data, in addition to descriptive statistical methods (mean, standard deviation, and frequency). Significance was evaluated at a level of $p<0.05$.

Results

Blood specimens of 131,851 patients were sent to the microbiology laboratory of our hospital. Of these, 868 (0.65%) were determined to be anti-HCV positive. Six hundred and fifty-five (0.8%) of 80,507 blood specimens examined simultaneously for anti-HCV, ALT, and AST were determined to be anti-HCV positive. There was no statistically significant difference between prevalence rates of anti-HCV seropositivity in the patients by gender ($p>0.05$) (Table I).

Prevalence rates of anti-HCV seropositivity were higher in patients in their 5th, 6th, and 7th decades (Table II). Elevated levels of AST and ALT were observed in 138 (21.06%) and 242 (36.94%) of 655 patients with anti-HCV seropositivity, respectively.

The prevalence rate of anti-HCV seropositivity was statistically significantly higher in the patients with elevated levels of AST (2%) compared to the patients with normal levels of AST (0.7%) (p: 0.001; $p<0.01$). The risk for anti-HCV seropositivity was 0.340-fold greater in the patients with elevated levels of AST (OR: 0.340; 95% CI: 0.281-0.411).

The prevalence rate of anti-HCV seropositivity was statistically significantly higher in the patients with elevated levels of ALT (2.2%) compared to the patients with normal levels of ALT (0.6%) (p: 0.001; $p<0.01$). The risk for anti-HCV seropositivity was 0.267-fold greater in the patients with higher levels of ALT (OR: 0.267; 95% CI: 0.228-0.313).

Table I. Evaluation of Anti-HCV seropositivity according to gender distributions

	Gender		p
Anti-HCV	Female	Men	
	n (%)	n (%)	
Positive	356 (%0,8)	299 (%0,8)	0,323
Negative	44937 (%99,2)	34915 (%99,2)	

Chi-Square Test

Table II. Distribution of Anti-HCV according to the age groups

Age Groups	Anti-HCV	
	Positive	Negative
	n (%)	n (%)
0-9 years	5 (0,2%)	2639 (99,8%)
10-19 years	12 (0,3%)	3982 (99,7%)
20-29 years	47 (0,3%)	14947 (99,7%)
30-39 years	67 (0,4%)	18076 (99,6%)
40-49 years	80 (0,7%)	11599 (99,3%)
50-59 years	127 (1,2%)	10845 (98,8%)
60-69 years	158 (1,8%)	8510 (98,2%)
70-79 years	101 (1,8%)	5562 (98,2%)
80-89 years	51 (1,6%)	3173 (98,4%)
90-99 years	6 (1,2%)	503 (98,8%)
100 years and over	1 (5,9%)	16 (94,1%)

Table III. Evaluation of Anti-HCV seropositivity according to distributions of ALT, AST, AST/ALT

		Anti-HCV		p
		Positive	Negative	
		n (%)	n (%)	
AST	Normal	517 (0,7%)	73213 (99,3%)	0,001**
	High	138 (2%)	6639 (98%)	
ALT	Normal	413 (0,6%)	69048 (99,4%)	0,001**
	High	242 (2,2) %	10804 (97,8%)	
AST/ALT	Normal	602 (0,8%)	72829 (99,2%)	0,527
	High	53 (0,7%)	7023 (99,3%)	

Chi-Square Test **p<0.01

There was no statistically significant difference between prevalence rates of anti-HCV seropositivity in the patients according to AST/ALT distributions (p>0.05). Anti-HCV seropositivity was observed in 602 (0.8%) of the patients with lower AST/ALT ratio and in 53 (0.7%) of the patients with higher AST/ALT ratio (Table III).

Discussion

The prevalence of HCV varies according to the geographical region and age. The prevalence of HCV infection is estimated to be 2.8% worldwide. It is estimated that approximately 185 million people are infected with hepatitis C throughout the world [2]. The regional prevalence of HCV in Africa, America, Asia, Australia and Oceania, Europe, and the Middle East are as follows: 3.2%, 1.5%, 2.1%, 1.2%, 2.3%, and 4.7% [9]. Japan, Taiwan, and Italy are among the countries with a higher prevalence of HCV infection. The prevalence of HCV infection is the lowest in North Europe, at less than 1% [10]. The prevalence of HCV infection is as high as 15-20% of the general population in Egypt [10,11]. Estimated the prevalence of HCV antibodies and HCV RNA, among the 15–59 year age group, to be 14.7 and 9.8% respectively in Egypt [11]. HCV prevalence rates are as follows in developed countries with lower prevalence rates but higher population: Germany 0.6%, Canada 0.8%, France 1.1%, and Australia 1.1%. HCV prevalence rates have been reported as follows in developed countries with larger populations and slightly lower prevalence rates: United States of America (USA) 1.8%, Japan 1.5-2.3%, and Italy 2.2% [10]. In the meta-analysis performed by Hanafiah et al., higher prevalence rates (>3.5%) were observed in North Africa/Middle East, Central and East Asia; moderate prevalence rates (1.5-3.5%) in sub-Saharan Africa, Andean, South and Southeast Asia, Central and Southern Latin America, Caribbean, Oceania, Australasia, and Central, Eastern, and Western Europe; and lower prevalence rates (<1.5%) in Asia Pacific, Tropical Latin America, and North America [12]. HCV prevalence rates in Turkey vary between 1% and 2.4%. In our study, the HCV prevalence rate was found to be 0.65% in the general hospital population, which is lower than the overall HCV prevalence rate of Turkey. Although countries like the USA, Australia, Spain, Italy, Japan, and Turkey have similar mean HCV prevalence rates (1-1.9%), the age-specific HCV prevalence patterns of these countries are very different. The highest HCV prevalence in USA is between 30-49 years of age. The prevalence is lower under 20 years of age and after 50 years of age. Similar to Australia, HCV transmission during the past 2-4 decades has occurred predominantly in young adults [10]. There are large variations in prevalence between groups with different risk factors in countries with the epidemiological characteristics of the USA, Australia, and North and Western European countries. IV drug use has been the leading transmission route of HCV in the USA over the past 40 years and also accounts for most of the newly acquired infections in the west, north, and south European regions [10]. Most of the anti-HCV positive patients in Turkey are over 50 years of age, which shows us that risk of HCV infection was higher about 40-60 years ago. Age-specific prevalence gradually increases with population age increases in countries such as Turkey, Spain, Italy, Japan, and China [10]. Studies investigating age-specific prevalence in Turkey have determined that the prevalence increases after 50 years of age [5,13]. Also in our study, anti-HCV seropositivity was observed to occur more frequently in the 5th, 6th, and 7th decades (Table II), consistent with the other studies performed in Turkey. HCV is most commonly transmitted with a percutaneous exposure to infected blood. The predominant route for transmission of HCV differs from country to country. Although blood transfusions are the most frequent route of transmission, intravenous drug use is also significant in developed countries. Transmission through sexual contact and vertical transmission are less commonly seen transmission routes [4,10,14]. Data from the blood center of the Turkish Red Crescent between 2008 and 2012 found that the rate of anti-HCV seropositivity in donors was between 0.02% and 0.004% [15,16]. The rate of anti-HCV seropositivity among hemodialysis patients and peritoneal dialysis patients in our country was reported as 9.8% and 4.7%, respectively [17]. Twenty-seven percent of cirrhosis and 25% of hepatocellular carcinoma (HCC) in the world is associated with HCV [10]. In the study performed by Okten [18], while hepatitis B virus (HBV) infection still maintains its importance in the etiology, the contribution of HCV has risen from 23% to 38.1% during the last decade. Similarly, while the contribution of HBV in the etiology of cirrhosis decreased from 56.6% to 45.9%, the contribution of HCV rose from 25.2% to 45.9% [10]. Certainly, it is critically important to develop diagnostic tests for hepatitis C virus.

Due especially to the insidious subclinical anicteric course of HCV infection, it is highly difficult to diagnose in its acute phase. In healthy individuals, the transaminases ALT and AST are normally found in lower concentrations in the serum, due to normal cell cycle and regeneration. While ALT is relatively specific to the liver, AST is found in the skeletal muscle, myocardium, kidney, brain, pancreas, and erythrocytes other than hepatocytes. Therefore, ALT reflects hepatocellular injury more specifically than AST. An elevated ALT level suggests that elevated AST level is also hepatic in origin. In our study, we observed that elevated ALT and AST levels were significantly associated with anti-HCV seropositivity (Table III). However, the possibility of false anti-HCV seropositivity results or normal ALT levels in patients with chronic HCV infection should be considered. In published studies, 30% of the patients with chronic HCV infection had continuously normal ALT levels [19,20]. Many studies investigating the relationship between serum HCV RNA levels and ALT levels in patients with chronic HCV infection have yielded contradictory results [21]. In our study, higher levels of AST and ALT were observed in 138 (21.06%) and 242 (36.94%) of 655 patients with anti-HCV seropositivity, respectively. The relationship between elevated levels of ALT and AST and anti-HCV incidence was investigated. But it remained inconclusive due to the following difficulties in the diagnosis and follow-up of the disease: anti-HCV seropositivity and AST/ALT ratio alone is not sufficient for diagnosis; false negativity and false positivity may occur; ALT levels may be normal in patients with chronic HCV infection; and, despite being considered the gold standard in the diagnosis and follow-up of the disease, serum HCV RNA levels can have a fluctuating course. In our study, anti-HCV prevalence in the patients presenting to our hospital was found to be lower than the overall HCV prevalence rate throughout the world and in Turkey.

Competing interests

The authors declare that they have no competing interests.

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HUMAN PAPILLOMA VIRUS (HPV) PREVALENCE AND GENOTYPE DISTRIBUTION

HUMAN PAPİLLOMA VİRUS (HPV) PREVALANSI VE GENOTİP DAĞILIMI

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Öz

Human papillomavirus (HPV) prevelansını ve genotip dağılımının değerlendirilmesi, profilaktik HPV aşısının etkisinin izlenmesinde çok önemlidir. Bu çalışmanın amacı, Başkent Üniversitesi Adana Dr. Turgut Noyan Uygulama ve Araştırma Merkezinde, bayan hastalarda HPV prevalansı ve genotip dağılımını göstermektir. Nisan 2014 ve Kasım 2015 arasında, yaşları dağılımı 22-68 yıl olan 268 bayan hastadan servikal örnekler toplanmıştır. HPV DNA PCR ile çoğaltılmış ve HPV genotiplendirmesi Roche®linear array detection kit ile yapılmıştır. Histopatolojik inceleme 146 bayan hastaya yapılmıştır. Toplamda 268 uygun örneğin 124' ünde (%46.3) HPV için pozitif bulunmuştur ve bunların çoğu [84/124 (%67.7)] yüksek riskli (HR) HPV enfeksiyonlarıdır. HPV-16 pozitifliği %20.9 (n=26) ve HPV-18 pozitifliği %4 (n=5) olarak bulunmuştur. Grade I-III Servikal intraepitelyal neoplasiler (CIN) de HPV tip spesifik prevelansı sırasıyla %63.9, %53.8 ve %80' dir. Yüksek dereceli servikal lezyonlarda HPV-16 dışında diğer HR-HPV tipleri, HPV-31, 45, 51, 53 ve 56' yı içermektedir. Sonuç olarak, hastanemizde HPV-16 servikal lezyonlarla en sık ilişkili HPV genotipi olarak saptanmıştır. Bu çalışma, ayrıca yüksek ve düşük riskli HPV genotiplerini aynı zamanda birden fazla HPV enfeksiyonların prevalansı hakkında da bilgi vermektedir.

Anahtar Kelimeler

HPV; Genotiplendirme; İntra Epitelya Servikal Neoplaziler

Abstract

Assessment of Human papillomavirus (HPV) prevalence and genotype distribution is important for monitoring the impact of prophylactic HPV vaccination. This study aimed to demonstrate the HPV prevalence and type distribution in women from the Baskent University Adana Dr. Turgut Noyan Practice and Research Center. Cervical specimens from 268 women aged 22-68 years were collected between April 2014 and November 2015.Histopathological examinations were performedfor 146 women. HPV DNA was amplified by PCR and HPV and genotyping was undertaken using the Roche® linear array detection kit. In total, 124 out of 268eligible samples (46.3%) tested positive for HPV, with the majority of these [84/124 (67.7%)] having high-risk (HR) HPV infection; 20.9% were positive for HPV16 (n=26), and 4% for HPV18 (n=5). HPV type-specific prevalence was 63.9%, 53.8%,and 80% among cervical intraepithelial neoplasias (CIN) Grades I-III, respectively. The coverage of other HR-HPV genotypes apart from 16, included HPV31, 45, 51, 53, and 56in high-grade cervical lesions. In conclusion, HPV-16 was identified as the main HPV genotype associated with cervical disease in our hospital. The study reports the identification of high-and low-risk HPV genotypes as well as the prevalence of multiple HPV infections.

Keywords

HPV; Genotyping; Cervical Intraepithelial Neoplasms.

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Introduction

Human papilloma virus (HPV) is one of the most common causes of sexually transmitted disease in both men and women worldwide. Genital HPV infection is not a reportable disease, so actual incidence and prevalence figures are not known.Papillomaviruses are ubiquitous and have been detected in a wide variety of animals as well as in humans and are specific for their respective hosts. More than 200 types of HPV have been recognized on the basis of DNA sequence data showing genomic differences [1].

Cervical cancer (CC) represents the second-most common malignancy in women around the world and contributes to 9.8% of all female cancers. Increasing evidence suggests that multiple factors contribute to the development of cervical cancer, including genetic susceptibility or host genome, co-infection of HPV and other agents, and life-style factors. Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped into high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81. High-riskHPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Although all genotypes of HPV correlate with cervical cancers, HPV-16 and HPV-18 infection accounts for about 70% of all cases [1-5].

Although HPV-16, 18, 31, 52, and 58 are cited among the most common HPV genotypes in women with high-grade cervical lesions worldwide, there is significant variation in the reported prevalence of HR-HPV genotypes amongcountries.Since the establishment of HPV as the central cause of CC, data on HPV type distribution in CC have proven useful to predict the potential impact of HPV16 and 18 vaccines, as well as to determine priorities for inclusion of carcinogenic HPV types in future HPV vaccines and HPV-based screening tests [2,3,5,6].

The aim of the present study was therefore to provide an estimate of the background prevalence of HPV infection and age-specific HPV type distrubition, and to highlight the HPV genotypes most frequently present in cervical cancer tissue and precursor lesionsin Baskent University Adana Dr Turgut Noyan Practice and ResearchCenter, Adana, Turkey.

Materials and Method

Study Population

Between April 2014 and November 2015, an HPV prevalence study was conducted among the female patients who attended the Baskent University Adana Dr. Turgut Noyan Practice and Research Center. Samples were collected from women with routine cervical screening.

Cervical samples were collected with a cytobrush during gynecological exaninations. This was inserted into the endocervical canal and then placed into the transport medium (PreservCyt solution; Hologic, Bedford, MA, USA) and stored at 4°C until DNA extraction for HPV genotyping.

Clinical specimens

The 268 cervical cytology specimens collected were analyzed for the presence of DNA of HPV. Histopathological examinations were performed in 146 women by the pathologist according to the Bethesda Diagnostic Criteria. Lesions were classified as normal cytology, CIN I-III, or adenocarcinoma.

Linear Array HPV genotyping test

The Linear Array® (LA) HPV Genotyping test is registered for use in Europefor detecting 37 high- and low-risk HPV genotypes. The test is based on four major processes: 1) DNA extraction by the AmpliLute Liquid Media Extraction Kit; 2) PCR amplification of target DNA using HPV primers; 3) hybridization of the amplified products into oligonucleotide probes (Linear Array HPV genotyping test); and 4) detection of probe-bound amplified products by colorimetric determination (Linear Array Detection Kit). Briefly, using PGMY09/11 primers, a region approximately 450 base pairs in length within the L1 gene of the HPV genome was amplified by PCR. This assay simultaneously amplified a region within the human β globin gene as a control for cell adequacy, nucleic acid extraction, and PCR efficiency. PCR assays were performed in a reaction volume of 100 µl, using 50 µl of LA HPV master mix (Roche Molecular Systems) and 50 µ of DNA. The amplification parameters were: 2 min at 50°C and 9 min at 95°C; 40 cycles of 95°C for 30s, 55°C for 1 min, and 72°C for 5 min or until samples were collected. Nucleic acid hybridization using a reverse line blot system was then performed. Briefly, the PCR amplicons were denatured with the addition of 100 µl of LA denaturarion reagent (Roche Molecular Systems). After 10 min at room temperature, the denatured amplicons (100 µl) were hybridized and detected using the recommended LA protocol. Thirty-seven anogenital HPV genotypes were detected simultaneously, including 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51-56, 58, 59, 61, 62, 64, 66-73, 81-84, IS39, and CP6108. The LA HPV genotyping strips were visually read using the HPV reference guide provided.

Results

In total, 268samples were received between April 2014 and November 2015. The 146samples were acquired through punch biopsies (54.5%).

Prevalence of HPV Infection

In total 124/268 samples tested positive for HPV (46.3%), with the majority of those (84/124,67.7%) having HR-HPV infection, 20.9% beingpositive for HPV-16 (n=26), and 4% being positive forHPV-18 (n=5). A total of 144/268 (53.7%) of samples were HPV negative.Figure outlines the overall HPV genotype profile among the cohort and HPV multiplicity. The six most common HPV genotypes detected across all samples examined were HPV-16, HPV-CP6108 (n=17), HPV-53 (n=17), HPV 56 (n=13), HPV 51 (n=10), and HPV-84 (n=10) (Fig.)

HPV Type-Specific Prevalence

The majority of cervical pathologies were from CIN I cases (36/146, 24.7%). HPV DNA was detected in 23/36 (63.9%) of CINI samples, 7/13 (53.8%) of CIN II lesions, and 12/15 (80%) of CIN III specimens. HPV DNA was not detected inAC samples (2/146, 1.4%). Table I details the number of HPV genotypes detected by pathological subtype. One-third of all samples (28.8%) had only one HPV genotype detected (n=19). HPV-16 DNA was present in 33.3% (5/15) of CIN III samples (Table II). Other HR-HPV genotypes were more prevalent in CIN I-II pathologies. LR-HPV genotypes were most common in CIN I lesions (Table II). Almost one-half (54.8%) of all pathologies were HPV negative.

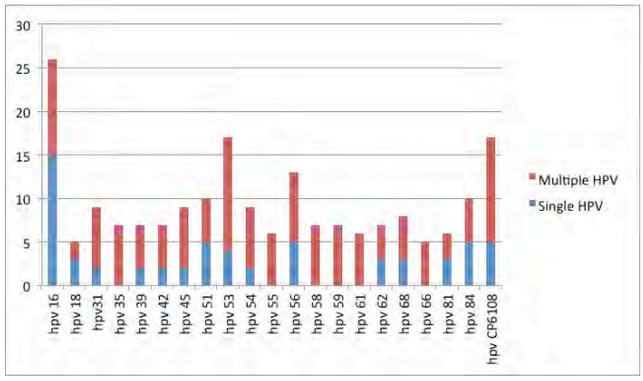

Fig. Overall HPV genotype profile denoting the prevalence of single and multiple HPV infections. HPV genotypes omitted above (no. of single/multiple infections): HPV 33 (1/1), HPV 40 (2/0), HPV 64 (0/1), HPV 67 (0/1), HPV 70 (0/4), HPV 72 (0/2), HPV 82 (1/2), and HPV 83 (1/3).

Table I. Percentage Distribution of the Number of HPV Genotypes Detected by Pathological Subtype and 5-Year Age Group

Number of HPV genotypes detected (% of each pathology)						
	HPV negative	1	2	3	4 or more	Total n (%)
Pathology						
CIN I	13 (36.1)	8 (22.2)	4 (11.1)	10 (27.8)	1 (2.8)	36 (24.7)
CIN II	6 (46.1)	3 (23.1)	2 (15.4)	1 (7.7)	1 (7.7)	13 (8.9)
CIN III	3 (20)	8 (53.4)	2 (13.3)	2 (13.3)	0	15 (10.3)
AC	2 (100)	0	0	0	0	2 (1.4)
Age group (yrs)						
Under 25	3 (60)	0	2 (40)	0	0	5 (1.9)
25-29	14 (45.2)	8 (25.8)	2 (6.4)	5 (16.2)	2 (6.4)	31 (11.6)
30-34	25 (58.2)	8 (18.6)	5 (11.6)	5 (11.6)	0	43 (16)
35-39	35 (60.3)	14 (24.1)	3 (5.2)	3 (5.2)	3 (5.2)	58 (21.6)
40-44	21 (42.8)	14 (28.6)	7 (14.3)	7 (14.3)	0	49 (18.3)
45-49	17 (56.7)	9 (30)	1 (3.3)	3 (10)	0	30 (11.2)
50-54	18 (62.1)	6 (20.7)	1 (3.4)	4 (13.8)	0	29 (10.8)
55-59	4 (30.8)	7 (53.8)	0	2 (15.4)	0	13 (4.8)
60-64	6 (75)	1 (12.5)	1 (12.5)	0	0	8 (3)
65+	1 (50)	0	0	0	1 (50)	2 (0.8)
Total	144	67	13	29	6	268

CIN, cervical intraepithelial neoplasia (Grades I-III); AC, adenocarcinoma.

The distribution of HPV genotypes detected within each cervical pathology is detailed in Table III. HPV-16 was the most common HPV detected across all cervical pathologies (Table III). We found that the prevalence of HPV infection without cervical abnormalities was 39.7% (58/146).

Age-Specific Prevalence for HPV Infection

The pathological distribution of samples by 5-year age groups is shown in Table IV. The mean age of women included in the study was 41 years (range 22-68 years, standard deviation (SD) 9.8 years). In total, 5 samples were from women aged 24 years and under,74 from thoseaged 25-34 years, and 189from those aged 35 years and over. CIN I was more common in women aged 50-54 years and CIN III most common in women aged 30-34 years (Table IV).

The number of HPV genotypes decreased with increasing age, with just over half (57.2%) of all HPV infections found in tissue from women aged between 40 and 44 years (Table I). Most tissue samples had a single HPV genotype and this was more

Table II. Type of HPV Genotypes Detected by Cervical Pathology and 5-Year Age Group

	HPV-16 and or HPV-18 n (%)	Other high-risk HPV genotypes n (%)	Low-risk HPV genotypes only n (%)	HPV negative n (%)	Total
Pathology					
CIN I	4 (11.1)	10 (27.7)	31 (86.1)	13 (36.1)	36
CIN II	2 (15.4)	7 (53.8)	4 (30.8)	6 (46.2)	13
CIN III	5 (33.3)	3 (20)	10 (66.7)	3 (20)	15
AC	0	0	0	2 (100)	2
Age group (yrs)					
Under 25	2 (6.4)	0	2 (1.9)	3 (60)	5
25-29	3 (9.7)	17 (23.6)	11 (10.5)	14 (48.4)	31
30-34	5 (16.1)	8 (11.1)	19 (18.1)	25 (60.5)	43
35-39	5 (16.1)	16 (22.2)	19 (18.1)	35 (60.3)	58
40-44	7 (22.6)	13 (18)	26 (24.8)	21 (44.9)	49
45-49	2 (6.5)	9 (12.5)	7 (6.6)	17 (56.7)	30
50-54	2 (6.5)	4 (5.6)	14 (13.3)	18 (62.1)	29
55-59	4 (12.9)	4 (5.6)	5 (4.8)	4 (12.5)	13
60-64	0	1 (1.4)	2 (1.9)	6 (75)	8
65+	1 (3.2)	0	0	1 (50)	2
Total n	31	72	105	144 (53.7)	268

CIN, cervical intraepithelial neoplasia (Grades I-III); SCC, squamous cell carcinoma; AC, adenocarcinoma.
[a]Including high-risk HPV genotypes other than HPV 16/18, that is: HPV-31, 33,35,39,45,51,52,56,58,59, and 68.

Table III. HPV Genotype Distribution by Cervical Pathology

Cervical histologya n (%)					
HPV genotype	AC	CIN I	CIN II	CIN III	Total
HPV 16	0	2 (5.6)	1 (7.7)	5 (33.3)	8 (12.1)
HPV 31	0	1 (2.8)	2 (15.4)	1 (6.7)	4 (2.7)
HPV 18	0	2 (5.6)	1 (7.7)	0	3 (2.1)
HPV 51	0	2 (5.6)	2 (15.4)	0	4 (2.7)
HPV 45	0	2 (5.6)	1 (7.7)	1 (6.7)	4 (2.7)
HPV 39	0	1 (2.8)	0	0	1 (0.7)
HPV 58	0	1 (2.8)	0	0	1 (0.7)
HPV 66	0	1 (2.8)	0	1 (6.7)	2 (1.4)
HPV 35	0	2 (5.6)	1 (7.7)	0	3 (2.1)
HPV 6	0	2 (5.6)	0	0	2 (1.4)
HPV 73	0	1 (2.8)	0	0	1 (0.7)
HPV 53	0	3 (2.8)	0	2 (13.3)	5 (3.4)
HPV 70	0	2 (5.6)	0	1 (6.7)	3 (2.1)
HPV 42	0	2 (5.6)	0	1 (6.7)	3 (2.1)
HPV 61	0	2 (5.6)	0	2 (13.3)	4 (2.7)
HPV 11	0	2 (5.6)	0	0	2 (1.4)
HPV CP6108	0	1 (2.8)	1 (7.7)	1 (6.7)	3 (2.1)
HPV 82	0	0	2 (15.4)	0	2 (1.4)
HPV 62	0	3 (2.8)	0	0	3 (2.1)
HPV 84	0	4 (11.1)	0	1 (6.7)	5 (3.4)
HPV 81	0	2 (5.6)	0	0	2 (1.4)
HPV 55	0	3 (2.8)	0	1 (6.7)	4 (2.7)
HPV 83	0	0	1 (7.7)	0	1 (0.7)
HPV 67	0	1 (2.8)	0	0	1 (0.7)
HPV 40	0	1 (2.8)	0	0	1 (0.7)
HPV 56	0	2 (5.6)	1 (7.7)	1 (6.7)	4 (2.7)
HPV 72	0	1 (2.8)	0	0	1 (0.7)

[a]Several patients may have had multiple HPV genotypes on testing.

Table IV. Age-Specific Prevalence for Cervical Pathology

Age group (yrs)	CIN I n, (%)	CIN II n, (%)	CIN III n, (%)	AC n, (%)	Total, n (%)
Under 25	2 (1.4)	0	0	0	2 (1.4)
25-29	2 (1.4)	4 (2.7)	0	0	6 (4.1)
30-34	3 (2.1)	2 (1.4)	5 (3.4)	0	10 (6.8)
35-39	3 (2.1)	4 (2.7)	3 (2.1)	1 (0.7)	11 (7.5)
40-44	7 (4.8)	2 (1.4)	3 (2.1)	0	12 (8.2)
45-49	7 (4.8)	0	0	0	7 (4.8)
50-54	10 (6.8)	1 (0.7)	0	0	11 (7.5)
55-59	1 (0.7)	2 (1.4)	0	0	3 (2.1)
60-64	1 (0.7)	0	1 (0.7)		2 (1.4)
65+	0	0	1 (0.7)	1 (0.7)	2 (1.4)
Total n	36 (24.7)	13 (8.9)	15 (10.3)	2 (1.4)	66 (45.2)

common in those aged over 55 years. Four or more HPV genotypes were detected in some women and this was more common under the age of 40 years (Table I). 17% of women with cervical pathology had HPV-16 or HPV-18 detected, and the highest proportion of HPV positive (16/18)were women aged 40-44 years (Table II). Other HR-HPV genotypes were more common in younger women, particularly those aged 25-29 years. LR-HPV genotypes were most common in those aged 40-44 years (Table II).

Discussion

This was a retrospective study investigating the HPV genotype distribution in women in Baskent University Adana Dr Turgut Noyan Practice and Research Center. HR-HPV was detected in 67.7% of all samples, with HPV-16 being the most common (20.9%) HPV genotype identified. This is consistent withprevalencesdescribed elsewhere across Europe in countries such as Spain, Germany, Finland, North Ireland, and internationally [3, 5, 7-9].The prevalence of HPV in CIN lesions in our study was 63.9% in CIN I, 53.9% in CIN II, and 80% in CIN III cases. We didn't detect any HPV DNA in AC samples across all cervical samples investigated. We found that HPV-16, CP6108, 53, 56, 51, and 84 were the most common genotypes in all cases and HPV-16, 31, 45, 51, 53, 56, and 61 were the most common genotypes in high-grade cervical lesions. The number of HPV genotypes detected in the current study varied across pathological grade, with the lowest percentage of single genotypes (22.2%) in CIN I lesions and the highest proportion (53.4%) in CIN III lesions.

In our study, the proportion of HPV positivity (67.7%) was similar to Europe (73.8%), Central/South America (64.2% vs. 67.3%), North America (76.4%), Asia (66.9%), Africa (70%), and Turkey (66%) [7, 11]. However, our prevalence rate of HPV 16/18 (25%) is lower than in Europe (57.6%) and Africa (67.7%) [6].

In general, precancerous cervical lesions, i.e. CIN II-III, have been accepted as a threshold of initiating definite treatment of precancerous lesion of squamous cell carcinoma (SCC). Identifying HPV genotype distribution in CIN II-IIIlesions that potentially progress to SCC is of utmost important in gaining insight into oncogenic potential of the different HPV genotypes, designing protocol for screening, and estimating the efficacy of type-specific HPV vaccines. As a substantial geographical variation in the HPV genotype distribution has been observed, data regarding HPV type-specific prevalence in each country are therefore required[11,12].

In an examination of FFPE tissue from more than 6,000 women from 17 European countries using the SFF10-LiPA25 assay, Tjalma et al. [13]found HPV-16 was the most frequent HPV type detected in both CIN and invasive cervical cancer. HPV-16 and/or HPV-18 prevalence (among HPV positive cases) was reported as 45.8% in CIN II and 67.3% in CIN III cases, higher than in our study. The prevalence of HPV-16 and/or-18 in our study was 15.4% in CIN II cases and 33.3% in CIN III cases. The authors reported HPV-31, 33, 35, 51, 52, 58, and 68 as the most frequently detected genotypes in women with high-grade CIN lesions. It has been reported that, worldwide, HPV-16 is the genotype with highest prevalence, followed by HPV-18 and HPV 31. Apart from HPV-16, we found that HPV- 31, 45, 51, 53, 56, and 61 were the most common genotypes identified in high-grade lesions. A study from Turkey by Ateşer et al. found that HPV- 16, 6, 11, 58, and 18 were the most common genotypes identified in high-grade lesions [3,10, 14, 15].

Clifford et al.[12]have suggested that worldwide, CIN II-III infected with HPV16, 18, or 45 are more likely to progress to SCC than CIN II-III infected with other HR types. They performed a meta-analysis of published data to compare HPV type distribution in CIN II-III and SCC. These data suggest that CIN II-III infected with HPV16, 18, and 45 more oftenprogress to SCC.Overall, HPV prevalence was slightly higher in SCC cases (87.6%) than in CIN II-III (84.2%). HPV 16 was the most common type in both SCC (54.3%) and CIN II-III (45%). HPV18 was also more prevalent in SCC (12.6%) than in CIN II-III (7%). When estimated from studies in Asia, Europe, and South/Central America, respectively, there was no material difference in SCC:CIN II-III ratios for HPV16, HPV18, HPV45, HPV33, HPV52, or HPV58. However, notably high ratios were observed for HPV31 in South/Central America in comparison toEurope and Asia, and for HPV58 in China (including Taiwan and Hong Kong) in comparison tonon-Chinese Asian countries, raising the possibility of localised variation in the malignant potential of particular HPV types [2,11].

There were only two cases of AC included in the current investigation. HPV DNA was not detected in AC samples. Therefore our study is probably not powerful enough to investigate HPV prevalence in this subgroup. A recent study in FFPE tissue detected using the SPF10-DEIA/LiPA25-PCR assay reported thatthe prevalence of HPV-16 and/or HPV-18 was 64.3%, lower than reported in an English multi-site investigation of HPV DNA in cervical cytology and cervical cancer biopsies using the Roche Linear array typing system (81.9%, among HPV positive cases) and among AC cases from other European studies (94.6%)[3].

We found that the prevalence of HPV infection without cervical abnormalities was 39.7%. Forman et al. reported that, worldwide, the prevalence of HPV infection without cervical abnormalities is 11% to 12%. De Sanjosé et al. found that, overall, in Asia and China the prevalence of HPV in females without cytological abnormalities was 8.0% and 11.4-20.3%, respectively (Zeng2016).Ogembo et al. found that HPV infection among women in Africa with normal cervical cytology was 57.3% in Southern Africa, followed by Eastern Africa (42.2%), Western Africa (7.8%), and Northern Africa (12.8%) [6].

A previous meta-analysis showed that, worldwide, HPV prevalence was highest in the younger age categories (<34 years), with a second peak in the older age categories (≥45 years). We observed a similar pattern, with peaks of prevalence in subjects aged <34 years and these older than 40 years. The mechanism of the association between HPV infection and age is not clear. Lee et al. showed that changes in vaginal microbiota in postmenopausal women made them more susceptible to HPV infection. Other research found that bacterial vaginosis was associated with susceptibility to HPV infection. Moreover, the social activities of the younger age groups can lower immunity to HPV and increase chance exposure [15, 16].

In this study, multiple HPV infections were identified in 38.7% of the positive specimens, and the age-specific prevalence of multiple HPV infections also showed peaks at ages 25-29 and 55-59 years. Zeng et al.[15] speculated that the decline of immunosurveillance in the younger and older age groups may increase the risk of multiple HPV infections. Also it should be noted that HPV has the ability to evadehost defenses. According to previous studies, people infected with >2 HPV genotypes might have an increased risk of developing cervical cancer. However, the interaction af various genotypes in co-infections remains unclear, and future studies are needed to verify whether coordinated mechanisms in co-infections exist.

Although we achieved a few novel findings in the present study, there remain other relevant factors that should be considered. Firstly, we collected the samples from the general female population, and not specifically cervical cancer patients. Therefore the findings and conclusions drawn from this study may not be applicable for estimating HPV genotype-specific prevalence in woman affected by cervical cancer. Secondly, HPV also causes diseases in men, including cancer of the penis; Smith et al. [17] reported that the prevalence of overall HPV was 16% in men. However, the objectives of our study did not include an evaluation of gender-specific prevalence of HPV infection. It would be interesting in future studies to investigate whether the prevalence of HPV infection in men matches that of women, since vaccinating males is also considered important[15].

In conclusion, HPV-16 was identified as the main HPV genotype associated with cervical disease in our hospital. The study reports the identification of high-and low-risk HPV genotypes as well as the prevalence of multiple HPV infections. When comparing the HPV prevalence between countries it is important to consider that variations in HPV positivity may be explained by differences in the quality and type of samples analyzed (biopsies, surgical specimens, or fresh tissue), as well as the methods of HPV detection and assessment.

Competing interests

The authors declare that they have no competing interests.

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SCREENING FOR ABDOMINAL AORTIC ANEURYSM IN GERIATRIC POPULATION

YAŞLI TOPLUMDA ABDOMİNAL ANEVRİZMA TARAMASI

GERIATRIC AND ANEURYSM

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Öz

Amaç: Abdominal aort anevrizması (AAA) tanı konmakta gecikilen durumlarda ölümle sonuçlanabilen,yaygın olmayan, erkek cinsiyet, yaş ve sigaranın en önemli risk faktörü olarak görüldüğü bir durumdur. Bu çalışma anevrizma mevcut olan ve ölen 4 yaşlı hasta nedeniyle taramanın gerekliliğini vurgulamak amaçlı yapıldı. Gereç ve Yöntem: Acil servisdeki ve huzurevindeki 320 olgu çalışmaya dâhil edildi. Abdominal aort çapları ölçülüp risk faktörleri ile birlikte incelendi. Bulgular: Çalışmaya alınan hastaların 232si (%72.5) erkek, ortalama yaşları 75.65± 7.76(62-95) idi. Hipertansiyon en sık görülen risk faktörü olarak belirlendi. Ortalama aort çapı 18.87± 2.74(15-26mm) tespit edildi. Risk faktörleri, yaş grupları ve aort çapları arasında tek başına AAA için anlamlılık tespit edilmedi. AAA tespit edilen 4 olgu öldü. Tartışma: AAA anevrizmalar arasında sık görülen bir türdür. En sık görülen risk faktörleri erkek cinsiyet, yaş, sigara öyküsü ve 65 yaş üstü olmaktır. İleri yaşlı özellikle erkek olgular rüptür riskini azaltmak için taranmalıdır. Olgular risk faktörleri de göz önüne alınarak cerrahi girişim açısından değerlendirilmelidir. Yapılacak geniş çaplı tarama çalışmaları ölüm riskini azaltabilir.

Anahtar Kelimeler

Abdominal Aort Anevrizması; Risk Faktörleri; Ölüm; Tarama

Abstract

Aim: An abdominal aortic aneurysm (AAA) is uncommon in people. Male gender and smoking are the most important risk factors. AAA is a condition that may be fatal when diagnosis is delayed. This study aimed to emphasize the necessity for screening due to four fatal cases with abdominal aortic aneurysm in a geriatric population. Material and Method: The study included 320 patients from a nursing home and an emergency department. The diameters of abdominal aortas were measured and assessed for risk factors. Results: Of the patients, 232 (72.5%) were male and the mean age was 75.65±7.76 (range: 62-95 years). Hypertension was the most frequent risk factor determined. Mean aortic diameter was found as 18.87 ± 2.74 mm (range: 15-26 mm). No significant associations were detected among risk factors, age groups, and aortic diameter. Four cases with abdominal aortic aneurysm died. Discussion: AAA is the most frequently seen aneurysm among true aneurysms. Major risk factors for AAA include male gender, smoking history, and age >65 years. In advanced ages, particularly in men, screening for AAA reduced deaths caused by rupture. The patients should be assessed for surgical intervention by taking risk factors into consideration. Large-scale screening studies can reduce risk for mortality.

Keywords

Abdominal Aortic Aneurysm; Risk Factors; Death; Screening

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Introduction

Abdominal aortic aneurysm (AAA) is defined as a doubling of the diameter of the abdominal aorta or an aortic diameter >30 mm (Figure 1). Male gender and smoking are the most important risk factors for AAA. AAA should be considered in patients who present with a pulsatile abdominal mass, abdominal pain, and shock. Sonography is a readily available and rapid diagnostic tool in the diagnosis of AAA [1]. AAA can be fatal when diagnosis is delayed. Screening can allow for early diagnosis in elder population because AAA is more frequently seen in elderly patients with known risk factors. This study aimed to emphasize the necessity for screening due to four fatal cases with abdominal aortic aneurysm in our study population.

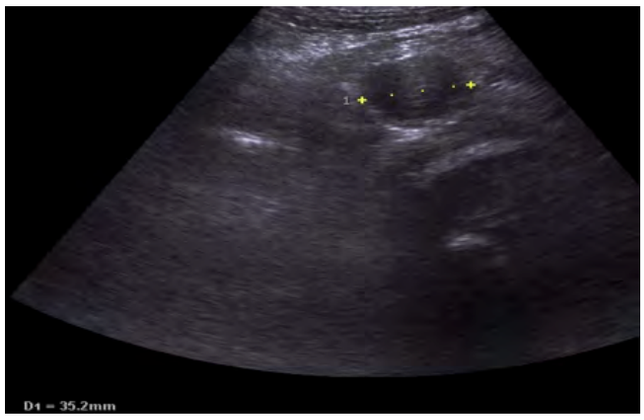

Figure 1. Diameter of abdominal aorta was measured by using portable ultrasound device.

Material and Method

In this study, we prospectively assessed 320 individuals living in a nursing home and those in an emergency department. The patients included were assessed regarding age, gender, smoking, hypertension, diabetes mellitus, history of cardiac or pulmonary disease, and previous history of surgery. Diameters of abdominal aortas were measured by using a portable ultrasound device (Mindray M5). Data were analyzed using SPSS version 16.0. The associations between aortic diameters and risk factors and age groups were assessed. Independent variables were analyzed using the Mann Whitney U test. A p value <0.05 was considered to be significant.

Results

Of the patients included, 232 (72.5%) were male and 88 (27.5%) were women. The mean age was 75.65±7.76 (range: 62-95 years) (Table 1).

Hypertension, smoking, heart disease, diabetes mellitus, previous history of surgery, and pulmonary disorders were assessed as risk factors. Hypertension (n=120; 37.5%) was found to be the most frequent risk factor (Table 2).

After patient fasting, the aortic diameter was measured at the supine position by using a portable ultrasound. Mean aortic diameter was found as 18.87±2.74 mm (range: 15-26 mm). No significant associations were detected among risk factors, age groups, and aortic diameter. AAA was detected in four of the patients with an aortic diameter >30 mm. Risk factors were assessed regarding their relationship with age groups and aortic diameter separately. No significant association was detected between risk factors and age groups or aortic diameters (Table 2).

During follow-up, it was found that the four of the study patients with AAA died due to aortic dissection and rupture.

Table 1. Distribution of age groups in study population

Age	n	%
60-64	16	10.0
65-70	36	22.5
71-75	16	10.0
76-80	64	40.0
81-100	28	17.5
Total	160	100

Table 2. Assessment of aortic diameter, age groups and risk factors

Risk factors	n	%	P value (aortic diameter)	P value (age groups)
Hypertension	60	37.5	1.000	0.678
Smoking	52	32.5	0.892	0.241
Heart disease	48	30.0	0.889	0.678
Diabetes mellitus	28	17.5	0.867	1.000
History of surgery	16	10.0	0.671	0.176
Pulmonary disease	12	7.5	0.333	0.294

Discussion

AAA is the most frequently seen aneurysm among true aneurysms. It has been reported that AAA is seen in 2-10% of patients aged >50 years [1,2]. It was reported that AAA incidence is increased in patients aged >65 years; the rate is 10% in patients aged >74 years [3-5]. Individuals living in a nursing home and those who report to emergency departments are considered a risk group that should be screened for chronic disorders, risk for cardiovascular diseases, and complications. Thus, we determined risk factors and screened for AAA, using sonography, in patients aged >65 years and residing in a nursing home or reporting to emergency departments.

Major risk factors for AAA include male gender, smoking history, and aged >65 years. Male gender and advanced age are the most important risk factors [4]. In addition, minor risk factors include family history, hypertension, coronary artery disease (CAD), hypercholesterolemia, obesity, and cerebrovascular disease [1]. In previous studies, AAA rates of male and female genders were suggested to be different, indicating that both genders should be screened [1,6].

If timely diagnosis of AAA is not made, fatal complications such as rupture, embolism, and dissection can develop. It has been reported that AAA accounts for 1-3% of all deaths among men aged 65-85 years [7]. Overall operative mortality is 5% but it is 50% in AAA [8]. Overall mortality is 85-95% in cases of AAA rupture [4,9]. There were four patients, two men and two women, with aneurysm in our study. The only known risk factor in these patients was smoking.

Early recognition of potentially fatal cardiovascular diseases in elderly individuals and taking required measures is essential.

Thus, early diagnosis is important in AAA. Identifying risk factors can be a guide for screening [4]. The main goal of screening is to prevent fatal complications such as rupture, embolism, and dissection. In advanced ages, particularly in men, screening for AAA has reduced deaths caused by rupture. Moreover, it is suggested that screening of patients with risk factors is relatively inexpensive [3-5,8,10,11]. Thus, screening can improve quality of life and can reduce mortality risk.

Conclusions

Elderly individuals, smokers, and men in particular should be screened for AAA. The cases with AAA should be assessed for surgical intervention by taking risk factors into consideration. Large-scale screening studies can reduce mortality risk.

Competing interests

The authors declare that they have no competing interests.

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A PERSPECTIVE ON OCCUPATIONAL MUSCULOSKELETAL DISEASES IN TURKEY; CASE CLUSTER STUDY

TÜRKİYE'DE MESLEKİ KAS İSKELET SİSTEMİ HASTALIKLARINA BİR BAKIŞ; OLGU KÜMESİ ÇALIŞMASI

ERGONOMICS AND SOCIOECONOMICS IN AUTO INDUSTRY

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Öz

Amaç: Mesleki kas iskelet sistemi (MKİS) hastalıkları tüm dünyada en sık görülen meslek hastalıkları grubunu oluşturmaktadır. Bu araştırmanın amacı, elektrik ekipmanları üreten bir işyerinde çalışan bir grup işçide iş koşullarından kaynaklanan kas iskelet sistemi sorunlarını ortaya koymak ve meslek hastalığı tanısı sonrası iş güvencesizliğine dikkat çekmektir. Gereç ve Yöntem: Araştırma kesitsel türdedir. Meslek hastalıkları polikliniğimiz tarafından aynı fabrikada çalışmakta olan 34 olguya mesleki kas iskelet sistemi hastalığı tanısı konuldu. İşyerindeki ergonomik riskleri değerlendirmek için Rapid Entire Body Assessment (REBA) ve Ovako Working posture Assessment System (OWAS) ölçekleri kullanıldı. Bulgular: Olguların 25 (%73.5)'i erkek, 9(%26.5)' u kadındı. Olguların ortalama yaşı 34.6±5.0 idi. Ortalama çalışma süresi 132.2±57.8 idi. 21 (%61) olguya servikal disk hernisi, 13 (%38) olguya lomber disk hernisi tanısı konuldu. Olguların tümü meslek hastalığı tanısı aldıktan sonra işveren tarafından işten çıkarıldığını belirtti. Tartışma: Mesleki kas iskelet sistemi hastalıkları işyerinde yapılacak düzenlenmeler ile iyileştirmeler ile önlenebilir hastalıklardır. Çalışanların meslek hastalığı tanısı sonrası medikal sonuçların yanında sosyal ve ekonomik güçlüklerle de karşı karşıya kaldığı unutulmamalıdır. Çalışanların meslek hastalığı tanısı sonrası işsiz kalma olasılıkları düşünülerek yasal düzenlemeler yapılmalı ve tanı sonrası çalışma durumları izlenmelidir.

Anahtar Kelimeler

Mesleki Kas İskelet Sistemi Hastalıkları; Ergonomik Risk Değerlendirme; İşten Çıkarılma

Abstract

Aim: All over the world, occupational musculoskeletal diseases represent the most common occupational and work-related health diseases. According to the World Health Organisation's data, OMSD account for 10% of all occupational workforce loss. Many ergonomic factors such as repetitive trauma, working in static postures for prolonged periods, heavy lifting, and monotonous working conditions have been described as risk factors thatcontribute to the development of these diseases. Material and Method: Thirty-four cases were diagnosed with occupational musculoskeletal diseases in Dokuz Eylül University Hospital Occupational Diseases outpatient clinic. Results: Twenty-five (73.5%) of the cases were men; 9 (26.5%) of them were women. The mean age was 34.6±5.0 years. Mean period of employment was 132.2±57.8 months. The Rapid Entire Body Assessment (REBA) and Ovako Working posture Assessment System (OWAS) scales were used to assess the ergonomic risks. All cases had been dismissed from work by their employers. Discussion: This article aims to present a cluster of cases with occupational musculoskeletal diseases at a place that manufactures electrical equipment for a global automotive corporationgto draw attention to the medical and socioeconomic consequences that these employees endure after they are diagnosed with an occupational disease.

Keywords

Automobile Industry; Dismissal Ergonomics; International Company; Occupational Musculoskeletal Disease; Redundancy

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Introduction

Two-thirds of adults in industrialized countries have reported that they have suffered from lower back pain during some point in their lives [1]. Due to advanced imaging technologies it has become easier to diagnose the reasons for musculoskeletal diseases. For instance, the data acquired with these imaging techniques have shown that findings of spinal degeneration are frequently found in asymptomatic cases. The incidence of findings related to spinal column degeneration has been surveyed and has shown that 64.5%-11.5% of 40 to 60+ year old symptomatic people have disk narrowing, facet joint osteoarthritis, and spondylolysis. It has been claimed that this might be related to the influence of disease-promoting factors such as smoking. There have been conflicting results regarding the influence of factors such as anthropometry, body weight, and physical activity[2,3].

Occupational musculoskeletal diseases (OMSD) represent the most common occupational and work-related health diseases[4]. Lakeh et al. have calculated the crude DALYs rate 1606.0 per 100.000 cases in the Eastern Mediterranean Region [5]. Linaker etal have reported that an annual 9.26 million working days were lost in 2008/9 from self reported work related musculoskeletal disorders. Kim etal have reported that OMSD are the most common occupational diseases in Korea and Japan [6,7].

Ergonomic inadequacies such as monotonous tasks, repetitive movements, movements that require force, unhealthy body posture, and vibration have important impact on the development of musculoskeletal diseases [8].Furthermore, it has been emphasized that factors such as poor social relationships at the workplace, work-related distress due to intensified workload, mobbing, situations where the employees cannot make decisions on their own, and insufficient break times effect the development of these diseases and increase the severity of a pre-existing condition[9].

Occupational musculoskeletal diseases of the upper extremity and neck, as well as the lower extremity and back, are common in employees of automobile manufacturing industry due to more than one increased ergonomic risk, including: repetitive hand, wrist, and arm movements; working in a static posture for prolonged periods and increased neck movements; heavy lifting; and monotonous working conditions. Furthermore, increased psychosocial risk factors are also one of the significant problems of this industry[10, 11].

This article aims to put forth the musculoskeletal diseases resulting from the working conditions of a group of employees working at a place that manufactures electrical equipment for the an international automotive corporation and to draw attention to the medical and socioeconomic problems these employees endure after they are diagnosed with an occupational disease.

Material and Method

Thirty-four cases who applied to the Dokuz Eylul University Hospital Occupational Diseases outpatient clinic between October 2014 and May 2015, with a history of working at the same factory were assessed. The clinical assessment of the cases consisted of their working history, medical history, physical examination, and laboratory investigations. The Rapid Entire Body Assessment (REBA) and Ovako Working posture Assessment System (OWAS) scales were used to assess the ergonomic risks [12, 13]. The working conditions were assessed according to the information and images provided by the cases. The clinical assessments were performed by Physical Therapy and Rehabilitation, Neurology, and Occupational Health specialists. The final diagnosis was reached by an occupational health council. The diagnosis of occupational disease was reached because of the health problems associated with their occupations. Also, the clinical, radiological, and electrophysiological findings of the patients were compatible with high ergonomic risk.

The working environments were divided into six main categories according to the working history. Static posture and repetitive hand, wrist, and arm movements were considered as common ergonomic risk factors of all categories. Other risks and working environments were grouped under six titles [Table 1].

This is a descriptive study. The data has been presented with descriptive statistics, and mean ±SD for continuous variables. The entire analyses were carried out by SPSS 15.0 package program.

Results

Thirty-four cases applied to our outpatient clinic with the Republic of Turkey Social Security Institution referral. All of the cases came from a multinational automotive company which was located in the industrial free zone, operating for the automotive industry. They had a history of working 8 hours a day and 5 days a week. It was noted that they had 15 minutes of break twice a day and a half hour meal break once a day. During their application to our outpatient clinic, 34 (100%) of the cases declared that they had been dismissed from work by their employers. Twenty-one (61%) of them were still unemployed at the time, while 13 (49%) had begun to work at another place. Thirty-four (100%) cases were diagnosed with occupational musculoskeletal diseases. Twenty-five (73.5%) of the cases were men; 9 (26.5%) of them were women. The mean age was 34.6±5.0 years. Mean period of employment was 132.2±57.8 months. The distribution of cases according to the department they worked in was: 3 cases (8%) cutting cables, 15 cases (44%) assembly at the fixed vertical board, 15 cases (44%) assembly at the fixed horizontal board, 8 cases (23%) assembly at the rotating board, 2 cases (5%) control and packaging, one case (4%) depot. Thirty-two (94%) cases reported that they worked in two or more departments. While being interviewed about their previous working history, only two (5%) cases reported working at a job involving ergonomic risk.

Twenty-six patients (76%) applied to the outpatient clinic with neck pain, the most common complaint. The time elapsed before the complaint began was 68.9±47.7 (12-180) months. Twenty-one (61%) of the cases were diagnosed with cervical disk hernia and 13 (38%) were diagnosed with lumber disk hernia (table 2).

Thirty-four (100%) cases had undergone pre-employment medical assessments and had taken the Occupational Health and Safety trainingwhen they began employment. All of the cases could use their annual leave. Thirty (88%) of the cases were aware that there was an Occupational Health and Safety board at their workplace and 29 (91%) of the cases knew that there was an employee representative at the workplace. Twenty-

Table 1. The cases' assignments and ergonomic risks

Assignment	Job description	Daily production (average) (piece/employee)	Ergonomic risk*	Type of OMSD	Number of OMSD
Cutting cables	Lifted to the fixed horizontal line and cut into pieces. Height 150 cm	100-350	Repetitive hand movement Heavy lifting (>25 kg) Bending and rotating the body Bending the neck	Carpal tunnel syndrome Lumber disk hernia Other** Cervical disk hernia	2 (66.6%) 3(100.0%) 1(33.35) 2 (66.6%)
Assembly at the fixed vertical board	Assembly on the fixed board. Height 50 cm Length 1.5 m	700-1000	Repetitive neck movement Heavy lifting (<10 kg) Bending and rotating the body	Cervical disk hernia Other** Lumber disk hernia	13(86.6%) 2(13.3%) 6 (40.0%)
Assembly at the fixed horizontal board	Assembly, fusing, taping and routing on the fixed oblique board. Height 40 cm	150-500	Repetitive movement Bending and rotating the neck	Other** Cervical disk hernia	1(0.06%) 4(26.6%)
Assembly at the rotating board	Assembly, fusing and welding procedures on the moving board. Height 50 cm	200	Repetitive movement Bending and rotating the neck	Lumber disk hernia Cervical disk hernia	3(37.5%) 2 (25.0%)
Control and packaging	Control and packaging on the fixed board. Height 170 cm	300-500	Heavy lifting (<10 kg).	Other** Meniscus pathologies	1(50.0%) 1(50.0%)
Depot	Unloading the truck and placing the items on the shelves.	50-100	Repetitive movement Heavy lifting (25-75 kg) Flexion and extension of the knee	Lumber disk hernia Meniscus pathologies	1(100.0%) 1(100.0%)

*Defined with REBA and OVAS ergonomic risk assessment
**Bicipital tendinitis, capsulitis, joint contracture, trigger finger, heel spur

eight (90%) of the cases believed that the employer interfered with the election process of the employee representative, while 6 (10%) believed that the election of the employee representative was done independently. None of the cases were informed about their legal rights. Twenty-five (73%) of the cases believed that the workplace did not register health records regularly, while 9 (27%) of the cases had no opinion of this topic.

Twenty-two (64%) of the cases were aware that risk assessment was done at the workplace and 34 (100%) of the cases thought that there were risks at their environment. Fourteen of the cases (41%) stated that no precautions were taken following the risk assessments, while 20 (58%) employee stated that ergonomic improvements were carried out.

Table 2. The complaints and final diagnosis of the cases (n: 34)

	n(%)
Complaint	
Upper Extremity	
Neck pain	26(76)
Arm pain	8(23)
Weakness	4(11)
Numbness and pins-and-needles sensation in hands	3(38)
Lower Extremity	
Lower back pain	21(61)
Leg pain	6(17)
Weakness	4(11)
Numbness and pins-and-needles sensation in feet	4(11)
Final Diagnosis	
Cervical disk hernia	21(61)
Lumber disk hernia	13(38)
Carpal tunnel syndrome	2(5)
Meniscus pathologies	2(5)
Other*	5(14)

*Bicipital tendinitis, capsulitis, joint contracture, trigger finger, heel spur.

Discussion

With the contribution of competition and intensified workload, the automotive industry presents important ergonomic risk factors such as heavy lifting, repetitive movements, and prolonged static posture. In a study conducted at two automobile factories in the USA, the incidence of occupational musculoskeletal diseases was found to be 31% [11]. At an automotive factory in Malaysia, which also produced electrical cables, the prevalence of musculoskeletal system symptoms among the employees were 49% neck, 48% wrist, and 46% shoulder-related [14]. At another automotive factory in Turkey, the prevalence of lower back complaints was reported to be 52% and neck complaints were reported at 30%. From most to least frequent , the cases stated the reason for their pain as heavy lifting, working in a position which bends the neck forward, sudden movements, staying at a bad position for a long period of time, accident, and work stress [8]. We also studied 34 cases from the same industry who worked at an electrical cable manufacturing line and who were also exposed to similar ergonomic risk factors described in previous studies, and we diagnosed them with musculoskeletal diseases.

Revealing the relationship of occupational risk factors with the disease remains a challenge for the physician because musculoskeletal system related complaints are already widely seen in the general population and their frequency increases with age. However, when we look at our cases, they are from a younger age group, they have been working with similar risks for a long time, and they constitute a cluster coming from the same workplace. They have not stated any other ergonomic risk factors that could have caused the problems. The cases' complaints and their clinical and laboratory findings comply with their job specifications. As mentioned in previous studies, the structural

damage developed in areas of the body that carry the potential of being impacted by the job's requirements, such as heavy lifting and repetitive movements [8-10, 15, 16].The time elapsed for the complaints to develop is approximately half of the total employment period, as short as 12 months. High daily production rates create ergonomic risks, and are an indication of intensified workload. They are one of the important factors that contribute to unhealthy employment conditions [2, 3].

To prevent occupational musculoskeletal diseases, it is known that interventions to working conditions, such as how the employee works (repetitive trauma or body posture problems), to the production system (the mode of production or products used during production), and interventions to improve the health of employees through training and exercise, etc. all have a positive effect [17-19]. However when the cases were interviewed for this study, we were informed that there had been no attempt at any interventions to the production procedure or working conditions and that health improving exercises were not incorporated.

Apart from the morbidity caused by their existing health problem, another important issue for the employees is that they were dismissed from work after lodging their complaints. Dismissal from work due to occupational or work-related diseases is a frequent problem. Cases with occupational diseases such as asthma and contact dermatitis also face a similar employment outcome and then suffer from socioeconomic problems [20-22]. It has been reported that the total annual cost of musculoskeletal diseases for the three major U.S. automobile manufacturing factories is over $18 billion [23]. Even though we have not systematically assessed all the employees working at the factory, our findings indicate that the employees exposed to similar working conditions may also be subject to occupational risks, which would results in high direct and indirect costs of the employees' health problems. It is known that improving the ergonomic conditions of workplaces may decrease and even prevent costs caused by musculoskeletal diseases[23]. However, after our cases developed musculoskeletal system complaints, their workplace did not improve or rehabilitate the working environment; on the contrary, the cases were dismissed from employment.

Occupational diseases may be prevented by implementing interventions to the working conditions. In order to amend the working conditions, it is necessary to have potent national inspection and audit mechanisms. Right after our assessment of the work-related injuries and diseases, we notified the national governmental audit entities to protect the welfare of the other employees by asking that the working conditions be improved.

The Republic of Turkey is a part of the global economic structure. The global structure of the economy implies responsibilities to the international community as much as to the national community. Occupational diseases developing at the employees of factories that manufacture global trademarks is a global problem. Also, maintaining the welfare of the employees' health is not only a national, but an international goal. One of the main interventions to this problem is to create social awareness. In order to maintain this social awareness, it is important to inform the national and international publically about employees' health problems, and the social, economic, and about the legal consequences of these health problems. It is especially important to increase the social sensitivity by informing all relevant health organisations, employee and employer organisations, consumer associations, and the media. These kinds of notifications, such as our article, may have an important influence on both identifying the problem and raising awareness.

Competing interests

The authors declare that they have no competing interests.

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FACIAL CANAL DEHISCENCE AND COEXISTING ABNORMALITIES; RADIOLOGICAL- SURGICAL CORRELATION

FASİAL KANAL DEFEKTİ VE EŞLİK EDEN ANOMALİLER; RADYOLOJİK CERRAHİ KORELASYON

CATEGORY OF MANUSCRIPT: ORIGINAL RESEARCH

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Öz

Amaç: Fasial kanal defekti (FKD) kolesteatom cerrahisinde en dikkat edilmesi gereken durumlardan biridir. Vakaların büyük çoğunluğunda timpanik porsiyon defektin en çok görüldüğü lokalizasyondur. ÇKBT temporal kemik görüntülemesinde standart metottur. Bu çalışmada cerrahide FKD saptanan olgularda eşlik eden radyolojik-cerrahi bulguları karşılaştırmayı amaçladık. Gereç ve Yöntem: Retrospektif olarak Fakültemizde Nisan 2011 ve Nisan 2016 tarihleri arasında opere olan 351 hastadan peroperatif MDBT tetkiki olan 64 hastanın radyolojik ve cerrahi bulgularını karşılaştırdık. Bulgular: Pozitif cerrahi bulgular dış kulak yolu (DKY) hasarı (31.2%), FKD (100%), antrum genişlemesi (AG) (57.8%), kemikçik erozyonu (96.8%), lateral semisirküler kanal (LSSK) defekti (18.7%), süperior semisirküler kanal (SSSK) defekti (1.5%) ve kohlear defekt (4.6%) idi. Pozitif ÇKBT bulguları dış kulak yolu (DKY) hasarı (37.5%), FKD (93.7%), antrum genişlemesi (AG) (82.8%), kemikçik erozyonu (96.8%), lateral semisirküler kanal (LSSK) defekti (18.7%), süperior semisirküler kanal (SSSK) defekti (6.2%) ve kohlear defekt (4.6%) idi. Bu çalışmada ÇKBT'nin en hassas belirlediği patolojiler FCD (93.7%), AG (82.8%),kemikçik erozyonu (96.8%) and scutum hasarı (68.7%) idi. Kemikçik erozyonu, AG ve LSSK fistula cerrahi ve BT bulguları korelasyon analizinde pozitif ilişki gösterdiler (p=0.001). Tartışma: ÇKBT ve klinik bulgular arasındaki korelasyonlar cerrahi öncesi muhtemel sorunların daha iyi teşhisine yol açabilir ve kolesteatoma cerrahilerinin başarısını artırır. Çok düzlemsel görüntülemenin kombine analizi, özellikle timpanik bölgede FKD'nin pozitif teşhis oranını geliştirmektedir.

Anahtar Kelimeler

Çok Kesitli BT; Fasial Kanal; Defekt

Abstract

Aim: Facial canal dehiscence (FCD) is the most important consideration in the cholesteatoma surgery. The tympanic portion is the most common localization of FCDlization in the majority of cases. MDCT is the standardt imaging modality for temporal bone screening. In this study we aimed to compare coexisting the radiological and -surgical findings of patients who have were found during surgery to have FCD in surgery. Material and Method: We examined retrospectively 351 patients with cholesteatoma who have beenwere operated on between April 2011and April 2016. In terms ofFor this study FCD, we compared the preoperative temporal bone MDCT and the surgery findings of 64 patients with FCD. Results: Positive surgical findings included external auditory canal (EAC) destruction (31.2%), FCD (100%), aditus ad antrum widening (AW) (57.8%), ossicular erosion (96.8%), lateral semicircular canal (LSSC) defect (18.7%), superior semicircular canal (SSSC) defect (1.5%), and cochlear defect (4.6%). Temporal bone MDCT positive findings included EAC destruction (37.5%), FCD (93.7%), AW (82.8%), ossicular erosion (96.8%), LSSC defect (18.7%), superior semicircular canal (SSSC) defect (6.2%), and cochlear defect (4.6%). The maximal precision of MDCT imaging in this study was in defining FCD (93.7%), AW (82.8%), ossicular erosion (96.8%), and scutum destruction (68.7%). Surgical and CT findings of ossicular chain erosions, AW, and LSCC fistula showed positive relations inwere positively correlated correlation analyses (p=0.001). Discussion: The significant correspondence between MDCT and clinical findings indicates that MDCT may lead to better a diagnosis of probable likely problems before cholesteatoma surgery, and and to a higherimproves the success rate of cholesteatoma those surgeries. The combined analysis of multi-planar imaging improves the positive diagnosis rate of FCD, especially ion the tympanic portion.

Keywords

MDCT; Facial Canal; Dehiscence

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Introduction

Cholesteatoma is a keratin- producing stratified squamous epithelium accumulation in the middle ear or in the other pneumatized areas of temporal bone such as the mastoid and petrous apex [1]. Although it is rare in the middle ear, facial nerve paralysis can be seen in %20-64% of extensive cholesteatoma cases [2]. Facial nerve damage during ear surgery is considered among one of the most dangerous potential complications for the otologic surgeon.

Facial canal defect increases the risk of injury and may serve as a warning to surgeons of the underlying hazard. The prevalence of facial canal dehiscence (FCD) has been reported to be 25–57% in histological studies of the temporal bones of normal humans [3]. The surgical rates of dehiscence reach 0.5–11.4 % in conditions other than chronic otitis surgery [4] and 33 % in chronic otitis surgery [4-6]. Although dehiscences are most commonly detected in the tympanic segment and at the level of fenestra ovalis , they may also be seen at the level of geniculate ganglion and in the mastoid segment [7].

The iatrogenic facial nerve damage due to cholesteatoma-related bone erosion or anatomical variations may occur during the dissection of the cholesteatoma from the middle ear cavity, epitympanum, and mastoid cavity. An accurate preoperative evaluation of facial canal anatomy and its relationship with the surrounding pathology is necessary in these cases. Understanding the ear anatomy with detailed radiographic information on the bony canal of the facial nerve and determining the extentsion and site of cholesteatoma can minimize the likelihood of facial nerve damage during the operation. High-resolution multi-detdector computed tomography (MDCT) provides important informations in this regard since it can determine the cholesteatoma sac and, assess the ossicles, the facial nerve, tegmen, scutum, and inner ear structures.

To our knowledge, there are few reports concerning the correlation of MDCT findings with surgical findings on the condition of the FCD of cholesteatoma [8-9]. In this study we aimed to assess the usefulness of a preoperative MDCT imaging in depicting the dehiscence of the facial canal and the status of middle ear structures in the presence of cholesteatoma and to compare the MDCT findings with the clinical intraoperative findings.

Material and Method

We examined retrospectively 351 patients with cholesteatoma who have beenwere operated on in Ondokuz Mayıs University Medical School Hospital, Ear, Nose, and Throat Clinic between April 2011and April 2016. To avoid repetition of the same data fromin ears that had been operated on more than once, only the data for one ear were included in the study. Based on the operation notes, 125 of the patients have been found withexperienced facial canal dehiscence in the operation. In terms of facial canal dehiscence Of these patients, 64 of these patients had preoperative temporal bone MDCT investigation.

Based on the patient files, the age, gender, preoperative CT, and intraoperative findings were determined. The data were examined in terms of the presence or absence of destruction of the external auditory canal, scutum, and tegmen;, the localization of cholesteatoma;, the presence or absence of facial canal dehiscence;, the localization of the dehiscence;, the presence of semicircular-circular canal fistulas; and, the conditions of the ossicle chain, Pprussak's sSspace, and mastoid air spaces.

MDCT imaging was performed with a 16-slice multi-detector row CT scanner (Aquilion 16 system, Toshiba Medical Systems Corporation, Tokyo, Japan) and 128-slice multi-detector row CT scanner (Discovery, GE Healthcare, Milwaukee, WI). The scanning parameters used were a collimation of 1 mm, mAS: 250, kV: 120, matrix: 512×512, algorithm: bony, and reconstruction thickness: 0.5 mm. DICOM files were retrieved from the archive system and transferred to the Osirix Workstation for review.

Statistical analyses wereas done with SPSS, version 21.version (IBM Corporation, Armonk, NY, USA). The Shaphiro-Wilk test was used to determine the normality in of the distribution of the quantitative data. To compare two independent groups, Student's t-test wasere used. Correlation analyses were performed with the Spearman's rho test. A p value less than 0.05 was considered statistically significant.

Results

Sixty-four patients, including 43 males (67%) and 21 females (33%), were enrolled into the study. The mean age of the patients was 36.5 (range, 8-75) years. Of the 64 subjects, 9 (14%) were aged below 18 years and 55 (86%) were aged above 18 years at the time of the operation. The facial canal dehiscence was observed on the right side in 31(48%) and on the left side in 33 (52%) patients.

Positive surgical findings included external auditory canal (EAC) destruction (31.2%), FCD (100%), aditus ad antrum widening (AW) (57.8%), ossicular erosion (96.8%), lateral semicircular canal (LSSC) defect (18.7%), superior semicircular canal (SSSC) defect (1.5%), and cochlear defect (4.6%). Temporal bone MDCT positive findings included EAC destruction (37.5%), FCD (93.7%), AW (82.8%), ossicular erosion (96.8%), LSSC defect (18.7%), superior semicircular canal (SSSC) defect (6.2%), and cochlear defect (4.6%). The maximal precision of MDCT imaging in this study was in defining FCD (93.7%), AW (82.8%), ossicular erosion (96.8%), and scutum destruction (68.7%). The accuracy, sensitivity, specificity, and predictive values for different MDCT findings are shown demonstrated in Table 1.

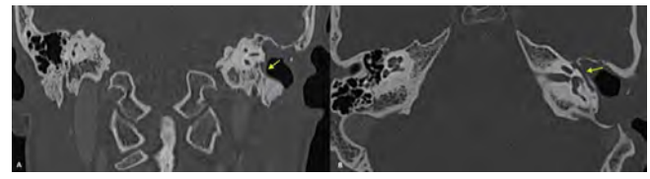

Fig.1. A. Facial canal dehiscence in the mastoid segment (arrow) of left side on the coronal temporal bone MDCT image. B. Facial canal dehiscence in the tympanic segment (arrow) of the left side and soft tissue in the left tympanic cavity on the axial temporal bone MDCT image.

The facial canal dehiscence was observed on the right side in 31(48%) and on the left side in 33 (52%) patients. The localization of the dehiscence was classified as being in the tympanic segment, in the mastoid segment, in the tympanic + mastoid segments, or in the first or second genu. According to surgery reports, the dehiscence was detected in the tympanic segment in 52 (80%) subjects, in the mastoid segment in 3 (4.6%) subjects, in the tympanic + mastoid segments in 4 (6.1%) subjects,

in the first genu in one (1.5%) subject, and in the second genu in 4 (6.1%) subjects. The CT findings of facial canal dehiscence-FCD was detected in the tympanic segment in 56 (93.,3%) subjects, in the tympanic + mastoid segments in 4 (6.6%) subjects, and in the first genu in one (1.5%) subject. According to surgery reports, Oof the 64 subjects with FCD, 3 (4.6%) had isolated malleus defects, 10 (15.6%) had isolated incus defects, 4 (6.2%) had isolated stapes defects, 12 (18.7%) had incus + malleus defects, 12 (18.7%) had incus + stapes suprastructure defects, and 23 (35.9%) had defects in all ossicles according to surgery reports. The CT findings revealed isolated malleus defect in one (1.5%) subject, isolated incus defect in 7 (10.9%) subjects, isolated stapes defect in 6 (9.3%) subjects, incus + stapes suprastructure defect in 6 (9.3%), subject and all ossicle defects in 43 (67.1%) subjects. When isolated involvement is considered, the presence of incus defect was higher thaen the others in both CT and surgery findings.

Surgical and CT findings of ossicular chain erosions, AW, and LSCC fistula showed positive relations in correlation analyses (p=0.001). The presence of LSCC fistula related correlated with scutum defect on CT findings (p=0.002) (Table 2). While LSCC fistula and AW were correlated positively according toin the surgical findings, they did were not correlated in theon CT findings. The CT findings of scutum defect and AW also did were not correlatedd significantly.

The CT findings revealed soft tissue in the Prussak's space, also known as pouch of the outer attic, in %92% of patients, while the surgical findings noted it only inin only %12% of patients.

The CT findings revealed low-lying tegmen in 2 (3.1%) subjects, thinned tegmen in 18 (28.1%) subjects, tegmen tympani defect in 16 (25%) subjects, high jugular bulb (HJB) in 12 (18.7%), subjects and HJB defect in 2 (3.1%) subjects.

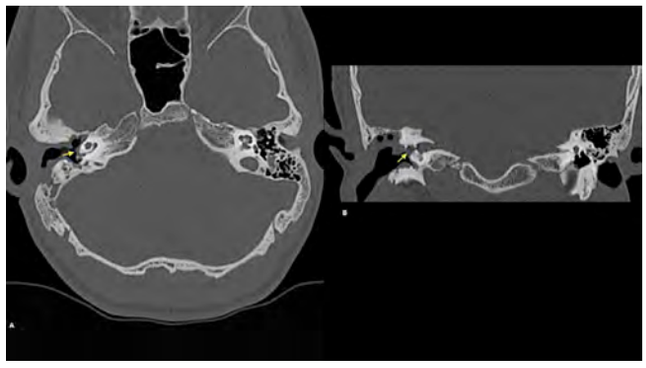

Fig.2. Lateral semicircular canal defect due to cholesteatoma on the axial (A) and coronal (B) temporal bone MDCT images (arrows).

Discussion

Today MDCT is considered the standard imaging method for the temporal bone. However,, but its value in the preoperative examination of chronic otitis media and cholesteatoma patients remains unclear. MDCT imaging with screening in three planes, has the ability tocan display pathologies of the temporal bone in detail. The present study revealed demonstrated good relcorrelationation between MDCT findings of temporal bone andwith surgical findings in patients with facial canal dehiscenceFCD. The facial canal dehiscenceFCD may be developmental due to inadequate ossification of the bony canal or it may also arise from resorption caused by chronic otitis media, with or without cholesteatoma. Although there is In the presence of a wide range of opinion in the literature concerning about the incidence of dehiscence [10,11], most sources of them concur that the tympanic portion is the most frequent site in the localizations of dehiscence [12-14]. In concordance with these reports, our study also demonstrated the furthest most frequent occurrence of FCD in the tympanic segment. As mentioned documented in previous CT studies [8,10], the dehiscence of the bony wall of the tympanic portion and their its position and extent can be noted on both axial-transverse and coronal CT images. The MDCT and surgical findings hadve good radio-surgical relationship in most the predominance of our cases. Based on our study, Wwe believe that combining use of analysis of multi-planar viewsanalysis, which visualizes the subject from multiple angles to the wall, with advantage of showing from different angels to the wall improvesd the positive rate of diagnosis of dehiscence in the tympanic portion of the facial nerve canal in our study. However, in four4 cases we could not reach a diagnosis about the condition of the tympanic portion from CT imaging in 4 cases due to partial volume averaging with adjacent soft tissue. Thus there is no guarantee of diagnosis and surgeons should keep oncontinue to take additional care during surgical treatment. At this point, there areis no radiological means to observe the dehiscence of the facial nerve canal with complete accuracy.

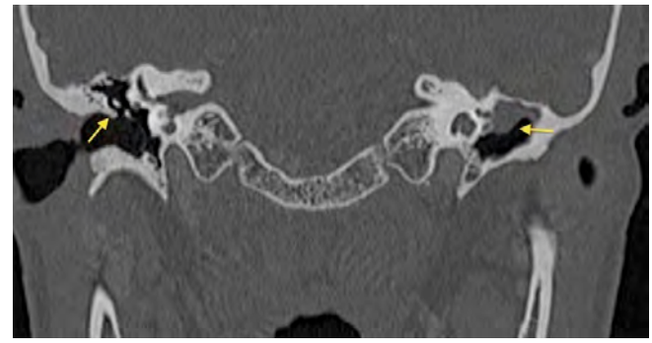

Fig.3. Scutum erosion due to soft tissue in the left epi-mesotypanium seen on the coronal temporal bone MDCT image (transverse arrow). Note that intact scutum (oblique arrow) on the right side.

This study has demonstrated a good correlation between temporal bone MDCT scans with and surgical findings, particularly in ossicular chain erosions, AW, and LSCC fistula. Rogha et al. have also reported good radio-surgical correlation of AW in cholesteatoma patients (9). The current study also demonstrated the advantage of MDCT imaging in the detection of tympanic and mastoid cholesteatoma, ossicular chain erosion, scutum and EAC destruction, SSSC, and cochlear defect.

Bone erosion is an important pathological finding in otitis media; it can, which leads to hearing loss due to an impaired impairment of the sound transmission mechanism. Although the presence of cholesteatoma is not necessary forthe only possible cause of the destruction of the ossicleossicle destruction, bone destruction is known to be more common in patients with cholesteatoma [15]. In the current CT study, we also found defects in the ossicle chain, at an incidence of 67.1%, similar with to previous studies [16]. Ossicular chain erosion demonstrated

occurred as an isolated defect most commonly at the incus in both surgical (15.6%) and CT (10.9%) findings. The Llow rate of incus defects on the CT images may be due to a partial volume effect. In this regard, an the defect of incus defect may alert the surgeon about to the dehiscence of the facial nerve canal. Low detection rates of isolated malleus and malleus + incus involvement and high detection rates of all ossicles involvement on CT findings may be due to the small size of these bones.

Ozbek et al. [17] detected LSCC fistula in 21.1% of subjects with facial nerve dehiscence and Gulustan et al. [16] detected it in 27.8% LSCC fistula of subjects with facial nerve dehiscence. In our study, Bboth the MDCT and surgical findings of our study revealedindicated a similar LSCC fistula range occurrence rate of 18.7% LSCC fistula in patients with facial nerve dehiscence. Presence of LSCC fistula in this study may alert the surgeon to that detection of one may indicate the existence of the otherFCD, potentially leading to a decrease in iatrogenic complications.

Although there is noare no reports in the literature of a correlation, in our study, 37.5% of subjects with facial nerve dehiscence also had destruction in the posterior wall of the EAC. We think that it is athis high range of incidence that should be considered in terms ofmay indicate a correlation between the two. association of dehiscence.

In our study, the Ccoexistence of scutum defects and facial canal dehiscence was as high as in the previous study of Genc et al. [18]. This suggests that the presence of a scutum defect is a significant finding in thein predictingion of the extent of the disease and facial canal dehiscence. Beside a good anatomical knowledgeThis it indicates that the surgeons should, in addition to having good anatomical knowledge, pay more attention to avoiding facial nerve injury during the operation ofwhen operating on patients with a scutum defect.

Our study demonstrated HJB and defect in HJB and tegmen tympani. Tegmen tympaniTegmen tympani is the thin layer of bone that forms the roof of the tympanic cavity, separating it from the cranial cavity. It has an important protection function in protecting theof brain from extending cholesteatoma. Its dehiscence and whether it is a low-lying type should be considered before surgery to avoid iatrogenic additional injuries. Thus,So apart from facial nerve dehiscence, CT imaging has an important role in detecting not only facial nerve dehiscence but also of detecting cholesteatoma propagation that can not be precisely evaluated exactly duringin surgery.

Conclusion

In this study, we compared the surgical and preoperative MDCT findings of patients who have were detected to have facial canal dehiscence during cholesteatoma surgery. Our study reveals that preoperative MDCT imaging can show the tympanic portion of the facial nerve canal accurately in the vast majority of cases, and there is high correlation of MDCT data with surgical findings in these cases. The combined analysis of multi-planar imaging improves the positive diagnosis rate of FCD, especially in on the tympanic portion.

In our study, Tthe incus was the most commonly destroyed ossicle. LSCC fistulas, scutum defects, and EAC defects were coincidental findings of FCD. The significant correspondence between MDCT and clinical findings may lead to better a diagnosis of probable likely problems before surgery, and it improves the success rate of cholesteatoma surgeries.

Competing interests

The authors declare that they have no competing interests

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ASSOCIATION BETWEEN FIRST-TRIMESTER ANEUPLOIDY MARKERS AND BIRTH WEIGHT

İLK TRİMESTER ANÖPLOİDİ BELİRTEÇLERİ VE DOĞUM KİLOSU ARASI İLİŞKİ

FIRST-TRIMESTER SCREENING AND BIRTH WEIGHT

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Öz

Amaç: İlk trimester ultrasonografik ve biyokimyasal anöploidi belirteçleri ile doğum kilosu arasında ilişki olup olmadığını ve bu belirteçlerin gebelik yaşına göre küçük (SGA) ve büyük (LGA) yenidoğanları öngörmedeki rolünü belirlemeyi amaçladık. Gereç ve Yöntem: Nukal translusensi (NT) kalınlığı, anne serum serbest beta-human koryonik gonadotropin (fβ-hCG) ve gebelikle ilişkili plazma protein-A (PAPP-A) ölçümü ile ilk trimester anöploidi taraması yapılan, tekil gebeliğe sahip 1356 kadın çalışmaya dahil edildi. Yenidoğanları, doğum ağırlığı ≤ 10. persentil ise SGA ve ≥90. persentil ise LGA olarak tanımlandı. Bulgular: Serum PAPP-A düzeyi anlamlı ancak zayıf şekilde doğum kilosu ile ilşkili iken fβ-hCG düzeyi ve NT ölçümü ilişkili değildi. <0.795 MoM luk PAPP-A değeri 73.9%'luk duyarlılık, 63.1%'lik özgüllük, 18.5%'lik PPV, 95.5%'lik NPV ve 64.2%'lik doğruluk ile SGA yenidoğanı öngördü. Diğer taraftan, PAPP-A için 1.005 MoM'luk eşik değer, LGA yenidoğanı öngörmede 61.0%'lık duyarlılığa, 62.7%'lik özgüllüğe, 26.6%'lik PPVye, 87.9%'lik NPVye ve 62.4%'lik doğruluğa sahipti. Tartışma: İlk trimester PAPP-A düzeyi doğum kilosunu öngörmede katkı sağlayabilir. Ancak düşük duyarlılıktan dolayı, SGA ya da LGA yenidoğanları öngörmede klinik uygulamada uygun bir tarama testi değildir.

Anahtar Kelimeler

Doğum Ağırlığı; Serbest Beta-Human Koryonik Gonadotropin; Gebelikle İlişkili Plazma Protein-A

Abstract

Aim: We aimed to investigate whether first trimester ultrasound and biochemical markers of aneuploidy were related to birth weight and to determine the predictive role of these parameters for small for gestational age (SGA) and large for gestational age (LGA) newborns. Material and Method: 1356 women with singleton pregnancy who had undergone first-trimester aneuploidy screening by nuchal translucency (NT) thickness, maternal serum free beta-human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma protein-A (PAPP-A) were retrospectively included. Newborns with a birth weight of ≤ 10th percentile were defined as SGA and ≥90th percentile as LGA, respectively. Results: Serum PAPP-A level was significantly but weakly (r=0.168; p=0.011) correlated to birth weight whereas maternal serum fβ-hCG levels and NT measurements were not significantly correlated. A single PAPP-A level of <0.795 MoM predicted SGA newborn with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and accuracy of 64.2%. On the other hand, a PAPP-A level of 1.005 MoM was identified as the optimal cut-off point for the prediction of LGA newborn with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4%. Discussion: First-trimester PAPP-A levels may contribute to the prediction of birth weight. However, due to low sensitivity, it is not a clinically relevant screening test for prediction of SGA or LGA newborn.

Keywords

Birth Weight; Free Beta-Human Chorionic Gonadotropin; Pregnancy-Associated Plasma Protein-A

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Introduction

There are many factors regulating birth weight, including gestational age at delivery, maternal age, body mass index (BMI), parity, ethnicity, habits (smoking, etc.), and medical (diabetes mellitus, etc.) conditions [1-3]. Abnormal fetal growth may increase neonatal morbidity and mortality. The risks of stillbirth, chronic lung disease, necrotizing enterocolitis, and neurodevelopmental problems in childhood, as well as hypertension, vascular disease, and diabetes in adulthood increase in small for gestational age (SGA) newborns (defined as less than 10th percentile birth weight) [4,5]. Similarly, large for gestational age (LGA) newborns (defined as greater than 90th percentile birth weight) have an increased risk of delivery complications such as shoulder dystocia, other birth injuries, and cesarean delivery, as well as obesity, cardiovascular disease, and metabolic complications in adulthood [6,7]. Early determination of fetal growth abnormalities may be beneficial for obstetricians in order to take essensial precautions. However, today's screening modalities are limited by varying sensitivities and high false positive rates. Thus early prediction of fetal growth abnormalities is still challenging.

Placental volume and maternal biochemistry reflecting placental function at 11-13 weeks of gestation have been studied in order to determine whether they have any predictive role for birth weight abnormalities [8-10]. But the results are highly variable and controversial.

In our study, we aimed to investigate whether first trimester biochemical parameters used to screen for Down syndrome were related to birth weight in a Turkish population and to determine the prediction accuracy of these parameters for SGA and LGA newborns.

Material and Method

This retrospective study was approved by the instituional review board of Zekai Tahir Burak Woman's Health Education and Research Hospital, a tertiary referral research hospital located in the central region of Turkey. Pregnant women who had undergone first-trimester aneuploidy screening by nuchal translucency (NT) thickness, maternal serum free beta-human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma protein-A (PAPP-A) between January 2014 and January 2015 at the Obstetrics Department of the hospital participated. Women who had multiple gestation pregnancy, preexisting diabetes, detected fetal chromosomal or major structural defects, miscarriage or fetal death before 24 weeks, diagnosed gestational diabetes, or intrauterine growth restriction in their follow-up and those with insufficient data were excluded.

All data were collected from hospital records. Between the 11th and 14th week of gestation, transabdominal or transvaginal (if necessary) ultrasonographic assessment of all pregnancies was performed for the measurements of fetal crown-rump length (CRL). When a CRL between 45 and 84 mm was detected, NT thicknesses were also measured by trained obstetricians. Furthermore, at that time maternal serum PAPP-A and fβ-hCG levels were measured by automatic fluorometric immunoassays. Results were reported as multiples of the median (MoM) adjusted for gestational age, maternal weight, and smoking status. Smokers were defined as those who had smoked at a continuous rate of at least one cigarette per day, starting at conception or earlier.

At delivery, birth weight was converted into a percentile for gestational age at delivery and by gender according to the Turkish population data [11]. Gestational ages at delivery were adjusted using the gestational age and CRL obtained during NT measurement. Newborns with a birth weight of ≤ 10th percentile were identified as SGA, newborns with a birth weight ≥ 90th percentile as LGA, and those in the 10th-90th percentile as average for gestational age (AGA).

Statistical analysis was performed using the using SPSS software version 17.0 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test was performed to determine whether the data were sampled from a normal distribution. Continuous variables with normal distribution are presented as mean±standard deviation. For these variables, the difference between the groups was evaluated by one-way analysis of variance test. When the p value from the variance analysis was statistically significant, post-hoc Tukey test was used to determine which group differed from which others. Categorical variables were analyzed with the Chi-square test. Receiver-operating characteristic (ROC) curves were constructed to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for different measures of maternal serum PAPP-A levels in predicting SGA and LGA newborns. Correlations between birth weight and first trimester markers were estimated using the Spearman's correlation coefficient. $p<0.05$ was considered statistically significant.

Results

For this study, 1558 singleton pregnancies with a live fetus who had undergone first trimester aneuploidy screening were reviewed. Because of miscarriage and fetal death before 24 weeks of gestation, 45 women were excluded. 33 women were excluded because of detected fetal chromosomal or major structural defects. 124 women were excluded due to insufficient data. The final study population included 1356 screened singleton pregnancies with their live born infants. Of these newborns, 138 (10.2%) were SGA, 246 (18.1%) were LGA, and 972 (71.7%) were AGA.

The characteristics of SGA, LGA, and AGA groups are listed in Table 1. In the SGA group, maternal serum PAPP-A level and birth weight were significantly lower than the other groups. In contrast, the LGA group had statistically higher serum PAPP-A levels and birth weights than the AGA group. Maternal serum fβ-hCG level was lower in the SGA group than the AGA and LGA groups, but the differences between the groups were not statistically significant. There was also no difference between the groups with regard to other variables listed in Table 1.

The correlations between the first trimester markers and birth weight are shown in Table 2. Maternal serum PAPP-A level was significantly but weakly correlated to birth weight, whereas maternal serum fβ-hCG levels, NT, and CRL measurements were not significantly correlated.

ROC curve for maternal serum PAPP-A level in predicting SGA newborn is displayed in Figure 1. The curve constructed for measured PAPP-A level was above the 45° line, showing that there was a significant relationship between these two vari-

Table 1. Characteristics of the groups

	SGA group (n=138)	AGA group (n=972)	LGA group (n=246)	P
Maternal age (years)	27.13±7.09	27.80±5.73	27.88±6.25	0.871
Maternal weight at screening (kg)	65.08±6.34	64.51±5.48	66.65±6.78	0.365
Maternal height (cm)	160.30±3.40	159.86±3.64	160.32±2.98	0.885
Smoking	20 (14.4)	119 (12.2)	29 (11.8)	0.356
Gestational age at screening (week)	12.18±0.33	12.26±0.56	12.44±0.30	0.405
Weight gain during pregnancy (kg)	11.55±1.88	11.00±1.38	11.32±1.16	0.505
CRL (mm)	58.17±7.58	58.70±9.43	61.56±10.20	0.194
NT (MoM)	0.87 (0.47-1.69)	0.83 (0.48-1.57)	0.84 (0.41-1.30)	0.855
PAPP-A levels (MoM)	0.64 (0.12-0.97)	0.94 (0.14-3.18)	1.16 (0.23-3.10)	<0.001
fβ-hCG levels (Mom)	0.71 (0.20-2.10)	0.96 (0.18-4.21)	0.97 (0.11-4.33)	0.087
Gestational age at delivery (week)	39.0 (35.5-41.2)	39.2 (35.5-42.0)	39.4 (37.3-41.5)	0.163
Birth weight (gram)	2566.52± 204.71	3357.78± 313.09	4089.75±199.49	<0.001
Male newborn gender	67 (48.6)	488 (50.2)	123 (50.0)	0.686

Values were given as mean±standard deviation; median (minimum-maximum) or number (%)
SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age; CRL: Crown-rump length; NT: nuchal translucency; fβ-hCG:free beta-human chorionic gonadotropin; PAPP-A: Pregnancy associated plasma protein-A ; Mom: Multiples of the expected median
p<0.05 was considered statistically significant.

Table 2. Correlation between birth weight and first trimester markers

	r	p
PAPP-A levels (Mom)	0.168	0.011
fβ-hCG levels (Mom)	0.101	0.129
NT (Mom)	0.034	0.613
CRL (mm)	0.084	0.210

PAPP-A: pregnancy associated plasma protein-A; fβ-hCG: free beta human chorionic gonadotropin; NT: nuchal tranclucency; CRL: Crown-rump length; MoM: multiples of the expected median
r: Spearman's coefficient
p<0.05 was considered significant

ables (area under the curve 0.752; standard error 0.040; 95% confidence interval 0.673–0.830; p<0.001). The best cut-off value of maternal serum PAPP-A level for the prediction of SGA newborn was 0.795 MoM with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and accuracy of 64.2% (Table 3).

Figure 2 shows the ROC curve for maternal serum PAPP-A level in predicting an LGA newborn. The curve constructed for PAPP-A level was above the 45° line, showing that there was a weak but significant relationship between these two variables (area under the curve 0.611; standard error 0.054; 95%, confidence interval 0.505–0.717; p=0.026). The best cut-off value of maternal serum PAPP-A level for the prediction of LGA newborn was 1.005 MoM with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4% (Table 3).

Table 3. Cut-off points for PAPP-A levels in predicting SGA and LGA newborns

	Cut off PAPP-A (MoM)	Sensitivity (%)	Spesificity (%)	PPV (%)	NPV (%)	Accuracy (%)
For SGA newborn	0.795	73.9	63.1	18.5	95.5	64.2
For LGA newborn	1.005	61.0	62.7	26.6	87.9	62.4

SGA: Small for gestational age; LGA: Large for gestational age; PAPP-A: Pregnancy associated plasma protein-A ; Mom: Multiples of the expected median; PPV: Positive predictive value; NPV: Negative predictive value

Discussion

In our retrospective cohort study, maternal serum PAPP-A levels measured by the first trimester aneuploidy screening was weakly associated with birth weight. ,Pregnant women with low PAPP-A levels were more likely to have an SGA newborn while women with high levels were more likely to have an LGA newborn. However, there were no relationships found between maternal serum fβ-hCG level, ultrasonographic measurement of NT thickness, and birth weight.

PAPP-A is a protease in glycoprotein structure, produced by syncytiotrophoblast during pregnancy; its concentration in the maternal circulation increases as pregnancy progresses [12]. By means of its proteolytic activity, PAPP-A acts as a regulatory protein in the insulin-like growth factor system (IGF) [13]. It has been suggested that the IGF system modulates trophoblast invasion and cell growth [14]. Therefore PAPP-A appears to be important for placental formation and regulation of fetal growth.

In the literature, it has been consistently suggested that low PAPP-A level is a reliable predictor for SGA delivery [8,10,15]. However, studies investigating the association between high PAPP-A levels and birth weight have reported conflicting results. Namely, some reports have indicated that there is a relationship between high PAPP-A level and LGA newborn [9,15], while others have found no association [16,17]. As mentioned above, our results revealed that first trimester PAPP-A level is weakly and positively associated with birth weight in uncomplicated pregnancies. In our study, a single PAPP-A level of <0.795 MoM predicted SGA newborn with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and an accuracy of 64.2%. This high NPV with relatively low sensitivity reflects that measurement of PAPP-A level during the first trimester is beneficial in determining women who are unlikely to deliver SGA newborns. On the other hand, a PAPP-A level of 1.005 MoM was identified as the optimal cut-off point for the prediction of an LGA newborn with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4%. Similarly, this cut-off point with high NPV and low sensitivity is an effective indicator of women who are unlikely to deliver an LGA newborn. The overlap in PAPP-A levels between the AGA group [0.94 (0.14-3.18) MoM] and the LGA group [1.16 (0.23-3.10) MoM] might decrease the sensitivity of maternal serum PAPP-A level in predicting a LGA newborn.

Plasma filtrate from maternal circulation is the main nutrition source of the embryo during the mid-first trimester [18]. As serum PAPP-A level increases, IGF-binding protein-3 levels decreases [13]. IGF-binding protein-3 levels are inversely asssociated with capillary permeability [19]. Thus, due to the increase

of maternal serum PAPP-A level, capillary permeability increases at mid-first trimester, enhancing the plasma filtrate taken by the embryo. This could result in an increase of fetal growth. However, this association still needs to be proven. Some toxic agents such as tobacco smoke might damage the blood flow to the placenta resulting in some placental necrosis areas occurring. This may result in insufficient PAPP-A expression and IGF axis disorders, reduced active transport of essential nutrients to the fetus, and may lead to fetal growth failure. In our study, smoking rates in the groups were statistically similar; we think this eliminates bias about the impact of smoking when comparing PAPP-A levels between the groups.

In obstetrical practice, the predictive role of first trimester maternal serum fβ-hCG level for birth weight is still controversial. Several studies reported a significant relationship between fβ-hCG and birth weight [3,20], whereas others demonstrated none [21,22], possibly because of different variables format (IU/ml, MoM, or percentile). Our findings did not confirm the relationship between these two parameters. Thus, we believe that further studies are needed to clarify this topic.

In our study, we observed no relationship between NT thickness and birth weight, similar to some previous studies [1,3,23] and contrary to others [16,24,25]. We speculate that there may be several factors that affect the NT in a euploid fetus—genetic, structural, and developmental—that cannot be detected during the antenatal period. Therefore, this topic remains to be explained with additional and larger prospective studies.

This study has some limitations. The main limitation is its retrospective design. Given this study design, some clinical details including placental volume, placental sufficiency, and pathological investigation of placenta were not included in the study. This study also has a relatively small study population. And lastly, this study included data from a single center in Turkey, so cannot be generalized to other populations.

In conclusion, among the parameters used for first-trimester aneuploidies screening, only maternal serum PAPP-A levels may contribute to the prediction of birth weight in uncomplicated pregnancies. However, due to low sensitivity, this parameter is not a clinically relevant screening test for prediction of pregnancies at risk of SGA or LGA delivery. Nevertheless, further prospective studies are needed to justify our results and to suggest more definitive recommendations.

Competing interests

The authors declare that they have no competing interests.

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INTRATHECAL BACLOFEN THERAPY FOR SPASTICITY: EXPERIENCE OF 48 CASES

SPASTİSİTEDE İNTRATEKAL BAKLOFEN TEDAVİSİ: 48 VAKALIK TECRÜBE

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Öz

Amaç: Intratekal baklofen (ITB) tedavisi farklı etiyolojik nedenlere bağlı spastisitenin tedavisinde yaygın olarak kullanılmaktadır. Bir gama aminobutirik asidB (GABAB) reseptör agonisti olan baklofen, nöronal eksitabiliteyi düşürerek etki gösterir. Bu çalışmanın amacı kliniğimizde ITB tedavisi verilen hastaların sonuçlarını komplikasyonları ile birlikte sunmaktır. Gereç ve Yöntem: Kliniğimizde ağır spastisite nedeniyle 2005 ve 2016 yılları arasında ITB tedavisi uygulanan yaş ortalaması 36.45 yıl olan, 29 erkek ve 19 kadın olmak üzere toplam 48 hasta (6 pediatrik hasta) dahil edilmiştir. Spastisite düzeyi Ashworth skalası ile değerlendirilmiştir. Ortalama takip süresi 3.1 yıldır. Bulgular: Bu seride spastisite etiyolojisinde en sık multipl skleroz olduğu (n=18), bunu takiben serebral palsi (n=7) ve diğer nedenler (n=23) olduğu görüldü. ITB tedavisi öncesi ortalama Ashworth skoru 3.52 iken, uzun dönem takipte 162.66 mcg / gün ortalama ITB dozu altında Ashworth skorunun ortalama 2.0'a düştüğü bulundu. Uzun dönem takipte 6 hastanın Ahworth skorunun başlangıç ile aynı olduğu, toplam 9 hastada komplikasyon yaşandığı; ancak bunların sadece 3 tanesinde pompa çıkarılmasının zorunlu olduğu saptandı. Tartışma: Ağır spastisite hastalarının tedavisinde ITB tedavisi oldukça etkili olmakla beraber, ITB tedavisinde başarı, doğru hasta seçimi ve özenli hasta takibine bağlıdır.

Anahtar Kelimeler

Spastisite; İntratekal; Baklofen

Abstract

Aim: Intrathecal baclofen (ITB) treatment is widely used in various etiological conditions resulting in severe spasticty. Baclofen, used in the treatment of spasticity, decreases the neuronal firing by acting on gamma aminobutyric acid receptorB. The aim of this study is to present results and complications of 48 patients treated with ITB at our institution. Material and Method: In this study, 29 male and 19 female patients who underwent ITB pump implantation due to severe spasticity between 2005 and 2016 were included. Mean age was 36.45 years, where six of 48 patients were pediatric. Spasticity of each patient was evaluated according to Ashworth scale. Average follow-up period was 3.1 years. Results: The most frequent etiological factor was multiple sclerosis (n=18), followed by cerebral palsy (n=7) and others (n=23). Baseline mean Asworth score was 3.52 which decreased to 2.0, with an average ITB dose of 162.66 mcg/day at long term follow-up. Nine patients had complications; of which only 3 needed pump removal. Discussion: ITB, applied with adequate patient selection and cautious regular follow up, is an effective treatment modality in patients with severe spasticity.

Keywords

Spasticity; Intrathecal; Baclofen

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Introduction

Spasticity, characterized by velocity dependent increase in muscle tone, presents with difficulty in coordinated movements, painful spasms, rigidity and hyperactive reflexes [1]. Loss of inhibitory effect on alpha and gamma motor neurons following upper motor neuron damage results in spasticity. Main etiological factors for spasticity are multiple sclerosis (MS), stroke, traumatic brain or spinal cord injury and cerebral palsy (CP) [2]. Proper treatment of spasticity to lessen functional disability of the patients mandates multidisciplinary approach. Oral therapy, physical therapy, botulinum toxin injection, surgical interventions like dorsal rhizotomies or peripheral neurotomies and intrathecal baclofen infusion are current treatment options for spasticity.

Intrathecal baclofen (ITB) therapy is an effective and useful technique for management of spasticity [3,4]. Baclofen is an agonist of γ-aminobutyric acidB (GABAB) receptor, which is a transmembrane protein that affects calcium and potassium channels; and when activated it reduces the influx of calcium into the presynaptic terminals of afferent fibers which reduces the release of excitatory transmitters [5]. It has also effect at the postsynaptic membrane by increasing potassium influx, so that the membrane potential increases and neuronal firing becomes inhibited.

This study evaluates patients treated with ITB at our institution regarding the outcome and complications, and results were discussed.

Material and Method

This study includes forty-eight patients with severe spasticity who underwent ITB treatment at Cerrahpasa Medical Faculty Department of Neurosurgery between 2005 and 2016. There were 29 male and 19 female patients with a mean age of 36.45 (range:5-67) years. There were six pediatric patients with an age range of 5 to 18 years. Mean follow-up was 3.10 (range:1-11) years. Two patients were lost to follow-up. Muscle tone in lower extremities (including hip abduction, hip flexion, knee flexion, and ankle dorsiflexion) and upper extremities (including shoulder abduction, elbow extension, elbow flexion, and wrist extension) were examined. Level of spasticity was evaluated according to the Ashworth Scale.

All patients with severe spasticity lasting more than 6 months and failure in response to oral anti-spasmodic treatments were screened for ITB test bolus injections with a dose of either 25 or 50 mcg depending on age group, children or adult, respectively. Four to 6 hours after bolus injections, patients were re-evaluated by the same physician. The patient was considered as a candidate for ITB pump implantation if any improvement on Ashworth scale was Present. In cases of no improvement in Ashwoth scale, a repeat ITB test injection with a double dose was performed 24 hours later. Figure 1 shows workflow of the ITB pump patient selection applied at our institution. All patients or their legal caregivers signed the patient consent form. Details of the surgical procedure can be found in our previous study which covered the first 25 patients of our study population [6].

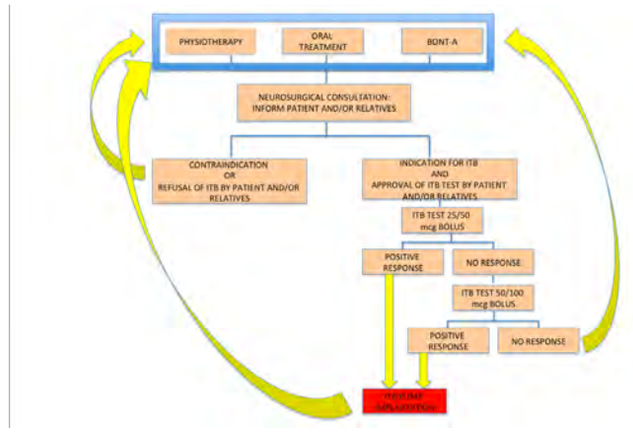

Figure 1. ITB patient selection algorithm used in our institution.
BONT-A: Botulinum NeuroToxin -A ITB: Intrathecal Baclofen

Results

Etiology of spasticity was MS in 18 cases followed by CP (n=7), and other factors (n=23) (Figure 2). Average Ashworth score of the patients was 3.52 and 2.0, before ITB treatment and at long term follow-up, respectively. Ashworth score was 0 in 1 patient, 1 in 17, 2 in 14, 3 in 9, 4 in 5 patients at the last outpatient visit. Improvement in Ashworth score was 3, 2 and 1 point in 6, 19, 15 patients, respectively. Six patientshad no change in Ashworth score at long term. Interestingly 3 of these six patients showed benefit in means of spontaneous spasms.

Catheter tip location was always checked at the early postoperative period with plain radiograms. Tip level was found between cervical C7 and T9 vertebrae throughout the series and in majority of cases it was located at T6-7 level.

Initial ITB dose was 50 mcg/day in majority of adult patients (n=36 patients) and 25 mcg/day in four of 6 pediatric cases. In order to maintain their ambulatory status, infusions were started at 25 mcg/day in two adult patients. Initial infusion rate was set to a higher dose in remaining four adult and two pediatric patients, since they responded to the double dose ITB test injection (second test). . Mean ITB daily infusion rate of the patients at last follow-up was 162.66 mcg (range: 25-600 mcg). We have experienced complications in 9 patients (18.75%). Catheter dysfunction or disconnection was present in 4 patients, which were treated by re-implantation of a new catheter. In another patient requiring a revision surgery due to a broken catheter, the new catheter was introduced through one upper level, since previous catheter could not be removed safely and left inside (Fig 3). CSF accumulation due to catheter

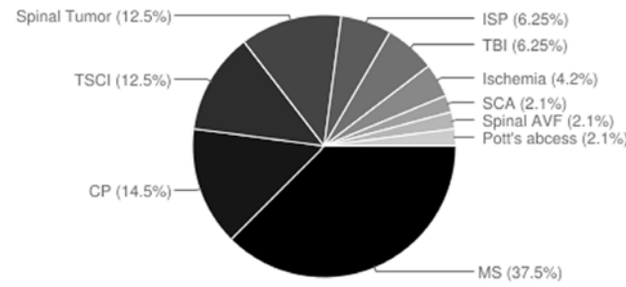

Figure 2. Etiological factors for spasticity of 48 patients
CP: Cerebral Palsy, MS: Multiple Sclerosis, ISP: Idiopathic spastic paraparesis, SCA: Spinocerebeller ataxia, TBI: Traumatic brain injury, TSCI: Traumatic spinal cord injury, Spinal AVF: Spinal arterio-venous fistula

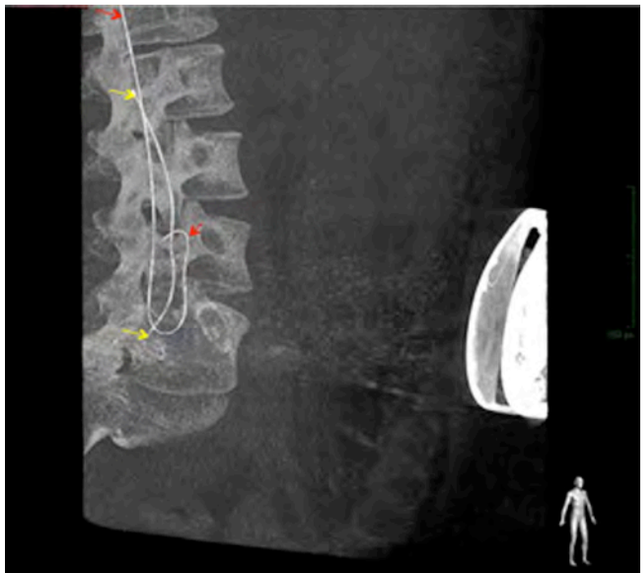

Figure 3. Three dimensinal radiographic image of the patient showing two spinal catheter, one of which could not be removed during revision surgery. The tip of the previous catheter marked with yellow arrows whereas the new one was marked with red arrows.

dysfunction around the pump was observed in a patient, which finally required new catheter replacement. One patient had experienced intrathecal baclofen toxicity after reservoir filling, which needed ICU care and eventually new pump replacement [7]. Wound detachment was observed in two patients. One of them treated by hyperbaric therapy whereas the other required reconstruction with a local flap (Fig 4). In two cases, the pump system was removed permanently due to infection and in one patient due to patient's own will. Although she had benefited from ITB, 6 months after the pump implantation she refused to have a foreign material.

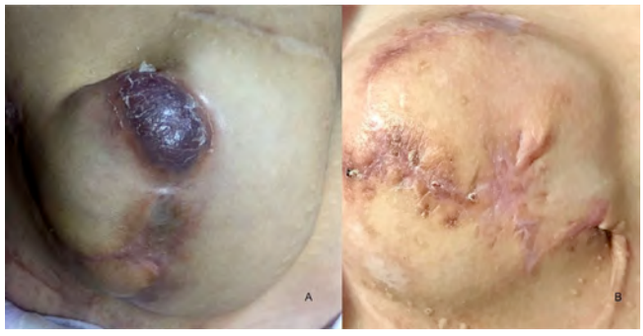

Figure 4. One of the pediatric patients in the series developed wound necrosis [A], which then reconstructed with local flap [B].

Discussion

Baclofen, an agonist of GABAB receptor, is approved by the Food and Drug Administration for the treatment of severe spasticity [8]. Baclofen binds to presynaptic and postsynaptic GABAB receptors at the dorsal horn of the spinal cord and inhibits mono- and polysynaptic reflexes [9]. ITB is a widely accepted treatment modality in severe spasticity [10]. Intrathecal administration of baclofen has some advantages over oral baclofen treatment such as obtaining higher concentrations at spinal cord level that cannot be provided by oral baclofen treatment without systemic side effects. Most important factors for favorable outcome for ITB treatment are patient selection and regular follow-up of the patients [6]. We believe that functional improvement as perceived by patients should be the main factor in evaluating the beneficial effects of ITB treatment, since outcome scales currently used in follow-up may not cover level of improvement in quality of life, while they focus mainly on spasticity and spasm levels [11, 12].Accordingly, three patients in our series have beneficial effect from ITB on spasms although they did not show a decrease in Ashworth score.

ITB is a treatment option of severe spasticity in both cerebral and spinal origins and there is no significant difference in the efficacy of ITB between paraplegic and tetraplegic patients [13,14]. Catheter tip level has no shown effect on outcome [14]. Moreover catheter tip level does not have any correlation with the maintanance dose of ITB and complications with catheter like migration, disconnection and infection [15]. Catheter tip level was around T6-7 in majority of patients in this study. Although catheter level is reported to be unrelated to outcome, we try to introduce the catheter as higher level as possible in spastic quadriplegic patients. In order to rule out downward migration and kinking of the catheter, we routinely take plain radiograms at early postoperative period. Then we check and compare the level of the catheter determined during surgery with the fluoroscopy.

Besides decreasing Ashworth score, ITB also improves pain score and self care of the patients with spasticity [16,17]. Fares et al. [18], reported that, with a mean follow up period of 52 months, patients are found to be still diminished in mean Ashworth score compared to the baseline, and mean ITB dose was reported as 137.81 mcg/day. In another study, daily ITB dose was compared on the basis of etiology, which had no significant difference between cranial and spinal etiological groups. However it has been reported that ITB dose needed to be increased significantly in long term[19]. In our series with a mean follow up of 3.1 years, average daily dose of ITB was 162.66 mcg. Patients showed a mean 1.52 points decrease in Ashworth score at long term follow up.

Complications related to ITB treatment was analyzed in a review of 558 complications reported in 1352 patients, with a mean 0.41 unwanted event per implant. Majority of these events were related to the catheter, which was followed by complications due to surgical procedure and pump device. Studies with a long term follow up, especially longer than 18 months, reported increased complication rates. It has been concluded that higher complication rates should be expected in centers that follow patients for a longer period of time [20]. We have experienced 9 complications in 48 patients; removal of the ITB device was needed only in 3 patient, where one was due to the patient's own will.

In order to minimize the complications, care should be taken not only during surgical procedure but also at follow up. Sterile conditions must be provided during refill procedure. Patients and their caregivers must be warned about the withdraval signs of ITB, which are rebound increase in spasticity, rigidity, tachycardia, piloerection, pruritis, seizure, halucinations, fever, sudden fluctuations in blood pressure, and change in conciousness. Regular follow up is the most crucial factor for proper and early management of complications. It should be kept in mind that

drug refills must be performed with 6 months intervals at most to prevent withdraval signs.

In conclusion, ITB is currently the best and effective treatment modality in patients with severe spasticity, when it is applied with adequate patient selection and cautious regular follow up.

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Competing interests

The authors declare that they have no competing interests.

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EFFECT OF ADENOTONSILLECTOMY ON THE RIGHT VENTRICULAR DIASTOLIC FUNCTIONS IN CHILDREN WITH ADENOTONSILLAR HYPERTROPHY

ADENOONSİLEKTOMİ'NİN ADENOİD'Lİ ÇOCUKLARDA SAĞ VENTRİKÜLER DİASTOLİK FONKSİYONLARA ETKİSİ

ADENOTONSILLECTOMY EFFECT ON DIASTOLIC FUNCTIONS

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Öz

Bu çalışmada obstrüktif adenotonsiller hipertrofi olan çocuklarda sağ ventrikül fonksiyonlarının araştırılması amaçlanmıştır. Bu amaçla, sağ ventrikül diyastolik fonksiyonları adenotonsillektomi öncesi ekokardiyografi ile ve en erken ameliyattan 6 ay sonra değerlendirilmiştir. Kliniğimize horlama, ağız solunumu ve / veya apne şikayetleri ile başvuran adenotonsiller hipertrofi olan çocuklar dahil edildi. Ameliyat öncesi tam bir kan sayımı, rutin biyokimyasal kan tetkikleri, göğüs radyografisi, elektrokardiyografi ve doku Doppler ekokardiyografi yapıldı. Elektrokardiyografi ve doku Doppler ekokardiyografi, en erken 6 aylık adenotonsillektomi sonrası hastaların takip ziyaretleri sırasında tekrarlandı. Postoperatif 6. ayda değerlendirmede, hastaların hiçbirinde horlama veya apne görülmedi. Ameliyat sonrası bazı ekokardiyografik parametrelerde önemli değişiklikler saptanmasına rağmen sağ ventrikül morfolojik anormallikleri saptanmadı. Sol ventrikül boyutlarının ekokardiyografik ölçümleri normal sınırlardaydı. Bununla birlikte, triküspid kapağın pik erken ve geç doku hareket hızına doku Doppler görüntüleme oranı post-operatif dönemde preoperatif perioddan daha yüksekti. Bu, diyastolik fonksiyonların görece-li olarak düzelmesinden kaynaklanabilir.

Anahtar Kelimeler

Adenotonsiller Hipertrofi; Obstrüktif Uyku Apnesi; Kardiyak Disfonksiyon; Adenotonsillektomi

Abstract

The present study aimed to investigate the right ventricular function in children with obstructive adenotonsillar hypertrophy. For this purpose, right ventricular diastolic functions were evaluated via echocardiography before adenotonsillectomy and after a minimum of 6 months following surgery. Children with adenotonsillar hypertrophy who were admitted to our clinic with the complaints of snoring, mouth breathing, and/or witnessed apnea were included. Pre-operatively, a complete blood cell count, routine biochemical blood tests, chest radiography, electrocardiography, and tissue Doppler echocardiography were performed. Electrocardiography and tissue Doppler echocardiography were repeated on the follow-up visits of the patients after a minimum of 6 months following adenotonsillectomy. Evaluation of the patients in the post-operative 6th month revealed no snoring or apnea in any of the patients. Although significant changes were detected in certain echocardiographic parameters after the surgery, right ventricular morphological abnormalities were not detected. Also, echocardiographic measurements of left ventricular dimensions were within the normal limits. Nevertheless, the ratio of peak early to late tissue motion velocity of the tricuspid valve as determined by tissue Doppler imaging was higher in the post-operative period than in the pre-operative period. This might be attributed to the relative improvement in diastolic functions.

Keywords

Adenotonsillar Hypertrophy; Obstructive Sleep Apnea; Cardiac Dysfunction; Adenotonsillectomy

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Introduction

Adenotonsillar hypertrophy is the most common cause of obstructive sleep apnea syndrome in children [1] It is known that several cardiovascular complications such as right and left ventricular dysfunction, pulmonary hypertension, heart rate variability, and heart failure can develop as the result of hypercarbia and hypoxemia, which occur in such children due to mechanical airway obstruction [2-8]. Adenotonsillectomy is the first treatment of choice in obstructive sleep apnea syndrome and early surgery prevents and/or reverses many complications [9,10]. The presence of cardiac involvement is also a risk factor for complications that are likely to occur following adenotonsillectomy [11]. For these reasons, detection of subclinical cardiac dysfunctions, in particular, is of great importance. Although there are invasive and noninvasive parameters for the assessment of ventricular function, it remains difficult and challenging to quantify right ventricular function. Quantification of myocardial function has become available with the introduction of tissue Doppler echocardiography [12].

Patients with severe upper airway obstruction can experience cor pulmonale later in life; however, there is little information about right ventricular function early in the disease. Therefore, the present study aimed to investigate the right ventricular function in children with obstructive adenotonsillar hypertrophy as detected by tissue Doppler echocardiography. For this purpose, right ventricular diastolic functions were evaluated via echocardiography before adenotonsillectomy and after a minimum of 6 months following surgery.

Material and Method

Children with adenotonsillar hypertrophy who were admitted to our clinic with the complaints of snoring, mouth breathing, and/or witnessed apnea for more than 8 months were included in the study. Patients having heart or renal failure or severe lung disease and those having upper airway obstruction due to other reasons, such as presence of nasal polyps, in their history, physical examination, or laboratory data were excluded. Data regarding history of snoring and apnea symptoms of the patients were obtained from their parents. Measurements of arterial oxygen saturation were performed using an oximetry monitor (Hewlett Packard M3046A, Viridia M3, Germany), which simultaneously measures oxyhemoglobin concentration, cardiac rhythm, and breath rate. A complete blood cell count, routine biochemical blood tests, chest radiography, electrocardiography, and tissue Doppler echocardiography were performed preoperatively. A complete ear, nose, and throat examination was also performed, which was supported by nasal and nasopharyngeal endoscopy as appropriate for additional assessment of the nasal patency and adenoid size. The nasopharyngeal air column was imaged using lateral skull radiography in all patients. Adenotonsillectomy was performed by curettage and cold dissection methods under general anesthesia. Electrocardiography and tissue Doppler echocardiography were repeated on the follow-up visits of the patients after a minimum of 6 months following surgery.

Upper airway obstruction was pre-operatively graded as follows: Grade I, tonsils being in the tonsillar fossa, barely visible behind the anterior pillars; Grade II, tonsils being easily visible behind the anterior pillars; Grade III, tonsils extending three-quarters of the way to the midline; and Grade IV, tonsils completely obstructing the airway [13]. Adenoid hypertrophy was graded according to the severity of the airway obstruction: mild (1°) indicates <25% obstruction; moderate (2°) indicates 25%-50% obstruction; moderately severe (3°) indicates 50%-75% obstruction; and severe (4°) indicates >75% obstruction [14].

Snoring was classified as follows: mild, with snoring being present only in the supine position and not being present every night; moderate, with snoring being present every night and diminishing with positional changes; and severe, with snoring being present every night and not changing with the position [15].

M-mode echocardiography, two-dimensional echocardiography, pulsed and continuous wave Doppler studies, and tissue Doppler imaging were performed using an echocardiography unit (Vingmed System Five Performance, General Electric Co., Cincinnati, OH, USA) with a 5 MHz duplex imaging transducer. The echocardiographic measurements were performed by an experienced cardiologist who was blinded to the diagnosis of the patients. Parameters were averaged over 3 cardiac cycles and all measurements were performed according to the guidelines of the American Society of Echocardiography [16]. Left ventricular fractional shortening and ejection fraction were calculated by M-mode echocardiography according to the Teichholz method [17]. The pulsed Doppler method was used to measure blood flow through cardiac valves (mitral, tricuspid); flow velocity during early filling; flow velocity during atrial contraction; and isovolumic relaxation time. Then the ratio of early to late ventricular filling velocities was calculated. Measurements obtained from pulsed tissue velocity imaging were systolic right ventricular free wall, early and late diastolic myocardial velocities, and their ratios.

The present study was approved by the Ethics Committee of Atatürk University and informed consents of the patients were obtained from their parents or legal representatives.

Statistical Analysis

Data were analyzed using the Predictive Analytics Software (SPSS Inc., Chicago, IL, USA) version 18.0 for Windows program. Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. The Wilcoxon signed-rank test was used to determine the change in time for non-normally distributed variables. A p value of <0.05 was considered statistically significant.

Results

The present study included 25 patients with a mean age of 8.5±2.9 years, of whom 8 were female (mean age 9.4±2.7 years) and 17 were male (mean age of 8.2±3.0 years). Characteristics of the patients with adenotonsillar hypertrophy are shown in Table 1.

Chest radiography revealed cardiomegaly in 2 patients with a moderate degree of apnea. Electrocardiographic abnormalities were as follows: right axis deviation in 2 (8%) patients, right ventricular hypertrophy in 1 (4%), and right atrial hypertrophy in 1 (4%) (these 4 patients had moderate apnea), and left axis deviation in 1 (4%) patient, sinus tachycardia in 3 (12%), and

Table 1. Characteristics of children with adenotonsillar hypertrophy

Characteristics	
Gender	
Girl	8 (32.0)
Boy	17 (68.0)
Age, year	8.0 (2.5-13.0)
Tonsil size	
Grade I	3 (12.0)
Grade II	10 (40.0)
Grade III	11 (44.0)
Grade IV	1 (4.0)
Adenoid size	
1°	0 (0.0)
2°	9 (36.0)
3°	7 (28.0)
4°	9 (36.0)
Snoring	
None	1 (4.0)
Mild	2 (8.0)
Moderate	11 (44.0)
Severe	11 (44.0)
Witnessed apnea	16 (64)
Arterial oxygen saturation, %	97 (95-99)
Respiratory rate, breath/min	25 (18-32)
Pulse rate, beat/min	98 (84-154)
Systolic blood pressure, mmHg	90 (80-100)
Diastolic blood pressure, mmHg	60 (50-60)

Values are presented as number (%) or median (minimum-maximum), where appropriate.

Mobitz type 1 second-degree atrioventricular block in 1 (4%). Sixteen (64%) patients did not have any electrocardiographic abnormalities. In the post-operative period, it was observed that sinus tachycardia in 2 patients, right axis deviation in 1 patient, and Mobitz type 1 second-degree atrioventricular block in 1 patient were improved.

The echocardiographic results of pre- and post-operative periods are presented in Table 2. The increase in the left ventricular end-diastolic dimension and the increase in the left atrium values were significant in the post-operative period as compared to the pre-operative period. In addition to the significant increase in the left ventricular inflow deceleration time in the post-operative period, significant increases in the right ventricular inflow acceleration and deceleration times were also detected. There was also a significant increase in the peak early to late diastolic tissue motion velocity of the tricuspid valve in the post-operative period.

Evaluation of the patients in the post-operative 6th month revealed that none of the patients had snoring or apnea.

Discussion

Studies have demonstrated that subclinical cardiac dysfunctions can be detected via echocardiography in children with obstructive sleep apnea syndrome due to adenotonsillar hypertrophy and that these abnormalities are reversible with the treatment of obstructive sleep apnea syndrome [18-22]. In their study on 42 children with obstructive sleep apnea syndrome due to adenotonsillar hypertrophy and 45 healthy children, Attia et al. [18] assessed the right and left myocardial performance indexes by tissue Doppler echocardiography before and after adenotonsillectomy. They demonstrated impairment in the left and right ventricular functions in the patient group and they reported that subclinical changes in cardiac performance improved after the surgery and that the post-operative echocardiographic parameters did not differ between the patients and the controls. Chan et al. [19] selected 101 children from a community based questionnaire survey, grouped them according to the degree of obstructive sleep apnea using polysomnography, and evaluated cardiac functions by echocardiography. They reported that right ventricular systolic volume index was greater, right ventricular ejection fraction was lower, right ventricular myocardial performance index was higher, and the risk of abnormal left ventricular geometry was higher in the moderate to severe obstructive sleep apnea group than in the reference group. Moreover, an improvement in cardiac functions was reported after 6 months of treatment (adenotonsillectomy or nasal steroids). In their study of children with adenotonsillar hypertrophy (n=30) and healthy children (n=30), Cincin et al. [20] demonstrated high pulmonary artery pressure and impaired

Table 2. Comparison of echocardiographic results of the patients between pre- and post-operative periods

	n	Pre-operative Period Median (Min-Max) (Mean)	Post-operative Period Median (Min-Max) (Mean)	p
LVEDD (mm)	25	32.20 (22.70-43.10) (34.26)	37.10 (26.00-42.60) (36.33)	0.007
IVS (mm)	25	6.80 (4.50-9.00) (6.70)	6.60 (4.80-9.40) (6.77)	0.932
LA (mm)	25	23.20 (16.60-29.10) (22.86)	24.90 (16.60-30.30) (24.74)	0.011
EF (%)	25	76.00 (63.00-87.00) (74.84)	74.00 (64.00-87.00) (74.32)	0.875
LV inflow				
AT (ms)	24	66.67 (32.79-85.25) (64.59)	63.94 (39.34-98.36) (66.74)	1.000
DT (ms)	24	119.49 (76.08-183.45) (121.04)	133.52 (80.99-280.63) (145.39)	0.009
E (ms)	24	1.01 (0.74-1.26) (0.99)	1.02 (0.67-1.46) (1.04)	0.095
A (ms)	24	0.64 (0.51-0.80) (0.63)	0.62 (0.38-0.86) (0.62)	0.886
E/A	24	1.54 (1.38-2.00) (1.60)	1.66 (1.31-2.22) (1.71)	0.086
RV inflow				
IVRT (ms)	24	69.10 (44.77-118.23) (67.52)	63.51 (46.72-91.97) (62.71)	0.218
AT (ms)	25	68.85 (35.04-101.63) (72.06)	87.41 (59.02-122.95) (85.01)	0.011
DT (ms)	25	107.51 (59.34-166.35) (111.47)	144.00 (83.74-210.87) (147.99)	0.001
E (ms)	25	0.78 (0.54-1.09) (0.80)	0.78 (0.45-1.07) (0.78)	0.798
A (ms)	25	0.6 (0.41-0.81) (0.60)	0.56 (0.31-0.91) (0.57)	0.217
E/A	25	1.33 (0.85-2.14) (1.36)	1.40 (0.98-2.04) (1.40)	0.339
TV annular TDIe (ms)	25	0.14 (0.11-0.26)(0.15)	0.15 (0.10-0.19) (0.15)	0.124
a (ms)	25	0.10 (0.08-0.20) (0.12)	0.11 (0.06-0.16) (0.11)	0.527
e/a	24	1.30 (0.77-1.86) (1.26)	1.30 (0.99-2.14) (1.42)	0.041

LVEDD, left ventricular end-diastolic dimension; IVS, interventricular septum; LA, left atrium; EF, ejection fraction; AT, acceleration time; DT, deceleration time; E, peak velocity of early diastolic filling; A, late diastolic filling due to the atrial contraction; E/A, ratio of early to late ventricular filling velocities; RV, right ventricle; IVRT, isovolumic relaxation time; TV, tricuspid valve; TDI, tissue Doppler imaging; e: peak early diastolic tissue motion velocity , a: peak late diastolic tissue motion velocity, e/a: peak early to late diastolic tissue motion velocity.

right ventricular functions in the patients having obstructive sleep apnea symptoms due to adenotonsillar hypertrophy. In addition, they reported improvement in the right and left ventricular myocardial performance indexes after adenotonsillectomy. Goldbart et al. [21] performed a study on children with obstructive sleep apnea (n=90) and healthy children (n=45) and demonstrated that tricuspid regurgitation abnormality and increased pulmonary pressure detected by Doppler in 40 children with obstructive sleep apnea were decreased after adenotonsillectomy. Miman et al. [22] measured pulmonary pressure by Doppler echocardiography in 17 children with pulmonary hypertension secondary to adenotonsillar hypertrophy and demonstrated that pulmonary pressure dramatically decreased to normal levels following adenotonsillectomy. In the study by Lee et al. [23], children (n=21) with adenotonsillar hypertrophy and healthy age- and gender-matched controls (n=21) were compared. Through questionnaires administered to the families, they determined that all the children with adenotonsillar hypertrophy, except for one, snored loudly and experienced sleep apnea. They also reported that there was no significant difference between the children with adenotonsillar hypertrophy and controls in terms of echocardiographic parameters.

In the present study, although significant changes were detected in certain echocardiographic parameters after the surgery, as could be expected due to the mild degrees of sleep-related breathing disorders and the lack of associated obstructive lung disease, right ventricular morphological abnormalities were not detected. Also, echocardiographic measurements of left ventricular dimensions were within the normal limits [24]. Nevertheless, the ratio of peak early to late tissue motion velocity of tricuspid valve determined by tissue Doppler imaging was higher in the post-operative period than in the pre-operative period. This might be attributed to the relative improvement in diastolic functions.

Competing interests

The authors declare that they have no competing interests.

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EXPRESSION AND POTENTIAL ROLE OF miR200b AND miR1274a IN LUNG CANCER PATIENTS

AKCİĞER KANSERLİ HASTALARDA miR200b VE miR1274a EKSPRESYONLARI VE POTANSİYEL ROLLERİ

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Çalışmamız "Association of miR-200b-3p and miR-1274a expressions in peripheral blood mononuclear cells with lung cancer" başlığı ile "European Society of Human Genetics (ESHG) 2016 –May 20, 2016, Barcelona, Spain" kongresinde poster bildiri olarak sunulmuştur.

Öz

Amaç: Akciğer kanseri genetik veya çevresel etkenler nedeniyle hava yolu epitel hücrelerinin kontrolsüz çoğalmasıyla oluşan ölümcül bir hastalıktır. En sık görülen kanser tiplerinden biridir ve kanser sebepli ölümler arasında ilk sırada yer almaktadır. Etiyolojisindeki en önemli neden sigara kullanımı ve tütün dumanı maruziyetidir. Mikro RNA'lar (miRNA) saç tokası yapısı içeren, yaklaşık 18-24 nükleotidlik kısa ve kodlamayan RNA'lar olup, diğer genler gibi DNA üzerinden transkribe edilir ve proteine dönüştürülmeden küçük RNA molekülleri halinde gen regülasyonunda görev alırlar. Yapılan çalışmalarda miRNA ekspresyon seviyelerinin malignant tümörlerin gelişimi ve ilerlemesi ile ilişkili olduğu ve miRNA'ların onkogen veya tümör süpresör etki gösterebileceği belirlenmiştir. Çalışmamızda da miR200b ve miR1274a ekspresyonlarının akciğer kanseri ile ilişkisinin belirlenmesi amaçlanmıştır. Gereç ve Yöntemler: Çalışmamıza 90 sağlıklı kontrol birey ve 90 akciğer kanseri hastası dahil edildi. EDTA'lı tüplere alınan kan örneklerinden periferal mononükleer hücreler (PBMC) izole edildi. Mononükleer hücreler total RNA izolasyonunda kullanıldı. miRNA ekspresyonları qRT-PCR (kantitatif gerçek zamanlı-PCR) ile belirlendi ve sonuçlarımız uygun istatistiksel yöntemler ile değerlendirildi. Bulgular: Araştırmamız kapsamında akciğer kanser riski üzerine etkinliğini araştırdığımız miR200b ve miR1274a'nın her ikisi de akciğer kanserli bireylerde anlamlı oranda düşük ekspresyon özelliği göstermiştir (p=0.005 ve p=0.021). Tartışma: Araştırmamız sonuçlarına göre miR200b ve miR1274a'nın akciğer kanserinde tümör süpresör özellik gösterdiği düşünülmektedir.

Anahtar Kelimeler

Akciğer Kanseri; miR200b; miR1274a; qRT-PCR

Abstract

Aim: Lung cancer (LC) is a fatal disease characterized by uncontrolled proliferation of airway epithelial cells and caused by genetic or environmental factors. LC is one of the most common types of cancer and the leading cause of cancer-induced deaths. The most important factors in the etiology of LC are smoking and exposure to tobacco smoke. Micro RNAs (miRNAs) are short and non-coding RNAs that contain hairpin structure and approximately 18-24 nucleotides. Like the other genes, miRNAs are transcribed from DNA and involved in gene regulation without converting to protein. Previous studies have determined that miRNA expression levels are associated with the development and progression of malignant tumors and that miRNAs can act as oncogene or tumor suppressors. The aim of our study was to determine any association between expression levels of miR200b and miR1274a and lung cancer. Material and Method: Ninety controls and ninety LC patients were included in our study. Total RNA isolation was performed in peripheral blood mononuclear cells (PBMC) isolated from whole blood collected with ETDA; miRNA expressions were evaluated with qRT-PCR (quantitative Real Time-PCR). Results were evaluated by appropriate statistical methods. Results: We evaluated the effect of miR200b and miR1274a expression levels on lung cancer risk and found decreased levels of these miRNA expression levels in lung cancer (p=0.005 and p=0.021). Discussion: We conclude that miR200b and miR1274a have a tumor suppressor function in lung cancer.

Keywords

Lung Cancer; miR200b; miR1274a; qRT-PCR

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Introduction

Lung cancer is a fatal disease caused by uncontrolled proliferation of lung tissue cells. The disease is the most common cancer type and the leading cause of cancer-related death worldwide [1]. Lung cancer has been histologically categorized by the World Health Organization (WHO) according to the tissue origin. Since 95% of lung tumors originate from the bronchial epithelium, these group of tumors are called bronchogenic carcinomas [2]. Lung cancer is divided into two major subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which vary in their biology, treatment, and prognosis [3]. There are many factors in the etiology of lung cancer such as active and passive smoking; occupational exposure to materials such as asbestos, nickel, chromium, and arsenic; radiation exposure; and indoor and outdoor air pollution [4].

Family history and hereditary factors can also increase the risk of developing lung cancer. Functional changes that occur in oncogenic or tumor suppressor genes, which can be part of or within genes that control important physiological pathways such as cell proliferation, DNA replication, and DNA repair, can cause cancer and can be inherited [5,6]. These pathways, however, are also controlled by "mitotically and/or meiotically heritable changes in gene expression that occur without a change in DNA sequence," that is, with epigenetic regulation [7,8]. Epigenetic mechanisms can be classified as DNA methylation, histone modifications, and non-coding RNAs [8,9].

MiRNAs, a class of non-coding RNAs, are short, non-coding RNAs of about 18-24 nucleotides that contain the hairpin structure and are transcribed through DNA like other genes. They are involved in gene regulation as small RNA molecules without being converted to protein [10-14]. MiRNAs reduce the expression of the target gene by base pairing with 3' UTR regions of mRNAs or by preventing target mRNA degradation or interrupting translation [10-13].

MiRNAs exert tissue-specific expression and are identified as oncogenic or tumor suppressor miRNAs according to the molecular pathway characteristics of the mRNA they are targeting. In a variety of cancer cases, miRNAs with increased expression have been described as oncogenic miRNAs or oncomirs, and these group miRNAs often function as an uncontrolled growth enhancer and/or anti-apoptotic pathway in cancer types [14-16].

In contrast to oncomirs, miRNAs that are effective on the expression of oncogenes are referred to as tumor suppressor miRNAs. Tumor suppressor miRNAs inhibit tumor formation by suppressing oncogenes and increasing the activity of the differentiating genes. Thus, decreased expression of tumor suppressor miRNAs leads to increased expression of oncogenes and tumorigenesis [17].

In our previous study, we reported a relationship between lung cancer and 35 genetic variations of miRNA genes targeting DNA methyltransferases and Methyl-CpG-binding proteins, and reported that the rs318039 variant of the miR1274a gene is associated with lung cancer subtypes. Although we did not find a relationship between the rs72563729 variant of the miR200b gene from the investigated variations and lung cancer, it was suggested that miR200b expression changes, which is a tumor suppressor miRNA, may be associated with lung cancer [6].

The miR-200 family has 5 members (miR-200a, miR-200b, miR-200c, miR-141, and miR-429) and comes together as two transcripts of polystistronic pri-miRNA. MiR200b-200a-429 is located on chromosome 1p36, and miR200c-141 is located on chromosome 12p13. MiR200 family is a family of miRNAs reported to have tumor suppressor function in many types of cancer, including breast cancer, colorectal cancer, pancreatic cancer, gastric cancer, and endometrial carcinoma [18].

MiR1274a, among cancer-related miRNAs such as miR200, has been reported to be associated with proliferation in breast cancer [19], is responsible for epithelial-mesenchymal transformation, and increases expression in human gastric tumors [20]. Functional effects have not yet been fully determined and there is a limited number of studies in the literature.

The aim of this study was to determine the expression levels of miR1274a and miR200b in patients with lung cancer who have not yet been determined to be associated with lung cancer, miRNAs that have not yet been determined to be associated with lung cancer.

Material and Method

Study group and collection of samples

Ninety lung cancer patients and 90 healthy control subjects were included in the study. The Ethics Committee for Clinical Research approved our work and the content of the study is in accordance with the Helsinki Declaration Principles. The study was described in detail and signed informed consent forms were obtained from all patients.

PBMC collection and RNA isolation

Blood samples were collected in EDTA-treated tubes and PBMCs were isolated by standard Ficoll density-gradient centrifugation by using Biocoll Separating Solution (D = 1.077g / ml, Biochrom, Berlin, Germany). Briefly, 5 mL of venous blood samples were diluated in 1:1 ratio sterile phosphate buffer saline (1XPBS) and phase was formed by adding Ficoll to the same volume of blood. The tubes were centrifuged at 400xg for 30 min (4Co), then the opaque white mononuclear cells in the middle (buffy coat) between plasma and Ficoll were collected. After the washing with PBS, PBMCs were stored at -80 °C until RNA isolation.

Total RNA was isolated from PBMCs using the mirVANA miRNA Isolation Kit (Ambion, Austin, TX, USA) in accordance with the manufacturer's protocol. Isolated RNA samples were assessed for purity with a Thermo Scientific NanoDrop (TM) 1000 (Thermo Fisher Scientific Inc., Wilmington, DE, USA) and stored.

qRT-PCR

Following the kit procedure, the RNA concentrations were adjusted to 5ng/1µL and then passed to the cDNA synthesis stage. Exiqon miRCURY LNATM Universal cDNA Synthesis Kit II (Exiqon, Vedbaek, Denmark) was used for cDNA synthesis. The cDNA synthesis reaction was prepared in the following manner with a total volume of 10 µl; 5x reaction buffer (2µl), nuclease-free water (4.5µl), enzyme mix (1µl), synthetic RNA spike (0.5µl), template total RNA (5ng /µl, 2µl). The total of 10 µl reaction mixture was incubated for 60 min at 42 °C and 5 min at 95 °C, respectively. Prior to qRT-PCR amplification, the cDNA reaction products were diluted 80x (395 µL nuclease-free water + 5 µL

cDNA). The qRT-PCR reaction was prepared in a total volume of 10 µl as follows: PCR master mix (5µl), PCR primer mix (1µl), diluted cDNA template (4µl). RT-PCR analysis was performed by the LightCycler® Nano System (Roche Diagnostics, Mannheim, Germany) with the "Exiqon miRCURY LNATM Universal RT microRNA PCR primers" and the SYBR® Green master mix (Exiqon, Vedbaek, Denmark). The amplification conditions are indicated in Table 1. Primer sets for a total of 3 gene regions, hsa-mir-1274a (product no: 206999), hsa-mir-200b-3p (product no: 206071), and housekeeping gene SNORD48 (product no: 203903) were obtained from Exiqon (Vedbaek, Denmark).

Raw data, expressed as threshold cycle (Ct) values, were computed with the LightCycler® Nano SW 1.1 (Roche Diagnostics, Mannheim, Germany). Relative expression was calculated with the comparative Ct method (2−ΔCt) as follows; Relative ratio= 2−ΔCt (ΔCt miR1274a – ΔCt SNORD48) and 2−ΔCt (ΔCt miR200b-3p – ΔCt SNORD48)

Statistical analysis

Expression levels of miR200b-3p and miR1274a were determined by one-way ANOVA using the IBM SPSS Statistics 21 Software; p value <0.05 was considered significant and the results were expressed as mean ± standard deviation.

Results

Expression levels of SNORD48, miR200b-3p and miR1274a of lung cancer and control individuals were determined in this study and the miR200b-3p and miR1274a expressions were normalized to SNORD48 expression as the housekeeping gene. When miRNA expression levels were compared, miR200b-3p expression levels of lung cancer patients were significantly lower than in the control (p = 0.005) (Graph 1).

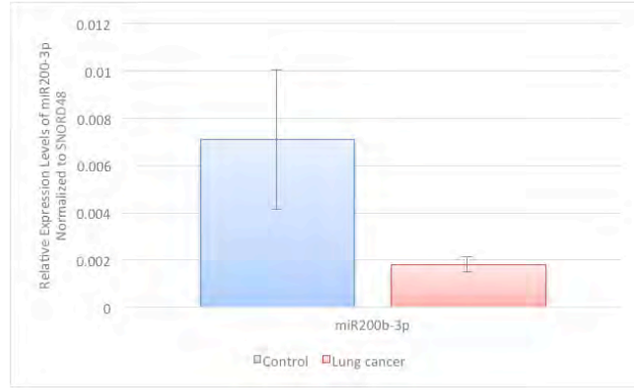
Similarly, expression of miR1274a was significantly reduced in lung cancer patients when compared to control (p = 0.021) (Graph 2).

Discussion

Lung cancer is the most common types of cancer and is the most frequent cause of cancer deaths in both males and females. Among lung cancer causes, smoking and tobacco smoke exposure are the first order. Tobacco causes 80-90% of lung malignant lesions, while exposure to physical and chemical carcinogens is another effect in the etiology [21-23].

Recognition of the importance of non-coding miRNAs in relation to tumor progression and progression is increasing day by day. While some miRNAs are identified as oncogenes (miR-17-92, miR-155 and miR-21) and others as tumor suppressor (miR-15a, miR-16a and let-7) [24].

The MiR200 family consists of five members: miR-200a, miR-200b, miR-200c, miR-141, and miR-429 [25]. MiR200b is an important member of the miR200 family. It has been indicated that miR200 inhibits cell invasion and metastasis in lung adenocarcinomas [24]. MiR200 has been reported to be a key regulator of cancer formation and metastasis prevention due to its key role in epithelial-mesenchymal transformation (EMT) [26,27]. Similarly, miR200b and miR200c expressions were also reported to be associated with carcinogenesis in gastric cancer tissues and cell lines, and downregulated in these tissues



Graphic 1. The miR200b-3p expression levels of controls individuals and patients with lung cancer.

Graphic 2. The miR1274a expression levels of controls individuals and patients with lung cancer.

[18]. Unlike these studies, Lin et al. evaluated serum miR200 expression in metastatic NSCLC patients and reported that serum miR200 expressions were not associated with lung cancer metastasis, SCLC, and adenocarcinoma risk [28].

In our study, miR200b-3p expression levels of lung cancer patients were significantly lower than in control subjects, and miR200b was downregulated in lung cancer. Our results support studies that emphasize that miR200b is a tumor suppressor [18,25,26].

There is no study investigating miR1274a expression levels and lung cancer risk. However, Janssen and colleagues have found that miR1274a is associated with proliferation in breast cancer [19].

Wang et al. have reported that miR1274a is involved in EMT and that expression in human gastric tumors is increased. However, overexpression of miR1274a has been shown to activate PI3K / Akt signaling and to increase expression of cyclin D1, MMP-2 and MMP-9 [20].

There is a limited number studies in the literature for miR1274a and our study showed that expression of miR1274a in lung cancer patients decreased significantly in comparison with the control.

Lung cancer is a fatal disease that is known to be caused by various carcinogens such as asbestos and especially cigarette smoke. Also, genetic factors have an important role in the etiology. One of the main goals of contemporary cancer research is to identify the molecular causes of lung cancer and to develop treatments for these targets, because lung cancer is the leading cause of cancer deaths.

Both miR200b and miR1274a, which we investigated for efficacy on lung cancer risk in our study, showed significantly low expression characteristics in lung cancer patients. It is well known that miR200b is a tumor suppressor, and our results show that miR1274a also has tumor suppressor properties. It is predicted that miR200b and miR1274a levels will be the candidates to be investigated and used as molecular biomarkers because of the ability to identify peripheral cancers.

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Competing interests

The authors declare that they have no competing interests.

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WHAT IS THE CLINICAL IMPORTANCE OF WHITE SPOTS IN THE DUODENUM?

DUODENUMDA GORULEN BEYAZ NOKTALANMALARIN KLINIK ONEMI NEDIR?

CLINICAL IMPORTANCE OF WHITE SPOTS IN THE DUODENUM

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Öz

Amaç: Bu çalışmanın amacı duodenumdaki beyaz noktalanmaların sıklığını, etiyolojisini ve klinik önemini belirlemektir. Gereç ve Yöntem: Üst gastrointestinal endoskopi sırasında duodenumda beyaz noktalanmalar tespit edilen 127 hasta çalışmaya dahil edildi. Duodenum 2.kısımda beyaz noktalanmalardan ikişer biyopsi alındı. Tüm biyopsiler tek bir uzman patolog tarafından değerlendirildi. Bulgular: Hastaların 57'si erkek, 70 'i kadındı. Ortalama yaş 43.27 ± 16.7 idi. Patolojik inceleme sonucunda, azalan sıra ile; %73 nonspesifik duodenit, %13.3 intestinal lenfanjiektazi, %11 intraepitelyal lenfositoz(IEL) ve %2,3 villus atrofisi(VA) olarak değerlendirildi. Sonuç olarak, spesifik semptomu ve endoskopik bulgusu olmayan ve IEL ve VA ile prezente olan 6 hastaya çölyak tanısı konuldu. Tartışma: Bu çalışma duodenumdaki beyaz noktalanmaların prevelansını %4.8 olarak bulmuştur. Bunların 37'nde spesifik bulgular tespit edilmiştir. Duodenum 2.kısımın dikkatli incelenmesi ciddi hastalıkların tanısını koymayı sağlayabilir.

Anahtar Kelimeler

Gastroskopi; Duodneum; İntestinal Lenfanjiektazi; Çölyak Hastalığı

Abstract

Aim: The aim of this study was to evaluate the incidence, etiological factors, and clinical importance of white spots in the duodenum. Material and Method: In total, 127 patients who were diagnosed as having white spots in the duodenum during an upper gastrointestinal endoscopic examination were included. Two duodenal biopsies were conducted from the second portion of the duodenum that contained the white spots. All biopsy samples were evaluated by a single expert pathologist. Results: Of the 127 patients, 57 (44.9%) were men and 70 (55.1%) were women. The mean age was 43.27 ± 16.7 years (range: 18–72 years). The histological examinations revealed the following pathologies in decreasing order: nonspecific chronic duodenitis (73.2%), intestinal lymphangiectasia (13.3%), intraepithelial lymphocytosis (11%), and villus atrophy (2.3%). Finally, celiac disease was diagnosed in six patients who presented with intraepithelial lymphocytosis or villus atrophy but who had no specific feature of celiac disease upon an endoscopic examination. Discussion: This study showed that the prevalence of white spots in the duodenum is 4.8%. Specific disorders were diagnosed in thirty-seven of the cases studied. A careful examination of the second part of the duodenum could provide for a better diagnosis of a serious disease.

Keywords

Gastroscopy; Duodenum; Intestinal Lymphangiectasia; Celiac Disease

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Introduction

Several factors, such as acidic gastric content, Helicobacter pylori (HP), intestinal lymphangiectasia (IL), medications, infections, celiac disease (CD), eosinophilic gastroenteritis, autoimmune enteritis, Crohn's disease, tropical sprue, and malignancies affect the duodenum. Each of these conditions is associated with endoscopic and histopathological changes in the duodenum [1,2].

The endoscopic finding of white spots in the descending duodenum (WSD) is not commonly seen and its clinical importance has not yet been investigated. In reviewing the literature, there have been only two studies on white spot appearances in the duodenum. They showed that the prevalence of WSD was 3.2% and 1%, respectively [3,4]. No other studies have aimed to investigate the incidence, endoscopic course, and clinical importance of WSD. This study aimed to evaluate the incidence, etiological factors, and significance of WSD.

Material and Method

This prospective, single-center study was performed at the Gastroenterology Department of Siirt State Hospital in Turkey from October 2013 to August 2015.

All patients undergoing an upper gastrointestinal endoscopy (UGE) were included. In total, 2,635 consecutive adult patients were surveyed who were referred for an endoscopy from several departments and outpatient clinics for upper gastrointestinal system symptoms. Demographic and clinical information and presenting complaints were collected via a questionnaire administered by trained interviewers upon study entry. Data collection about WSD was performed using information from endoscopy and pathology reports. In total, 127 patients who had been diagnosed as having WSD were included.

All patients had presented after a 12-hour overnight fast. Written informed consent was obtained from all patients before the endoscopic procedures. The UGE was performed by a single endoscopist using a videogastroscope with forward viewing (Video Gastroscope EG-2985K with the Pentax EPK-i5000 video processor, Tokyo, Japan, 2011). Special attention was paid to the duodenum.

Two duodenal biopsies from the second portion of the duodenum containing white spots (Figure 1), as well as gastric antrum and corpus biopsy specimens from all patients, were taken for histological investigation. The biopsy samples were put into a 10% formalin solution before being embedded in paraffin. Hematoxylin and eosin (H&E)-stained sections from all biopsies from each patient were evaluated for pathogens (e.g. HP and giardia lamblia), lamina propria inflammation, intraepithelial lymphocytes, and villous architecture, and they were evaluated by a single expert pathologist. Nonspecific chronic duodenitis (NCD) was described as inflammation with edema and the infiltration of leukocytes; intraepithelial lymphocytosis (IEL) was described as more than 40 IELs/100 epithelial cells in the small intestine; and IL was described as dilatation of the lymphatic channels (Figure 2).

Data analysis was performed using the SPSS package (IBM SPSS software for Windows; version 19.1; SPSS Inc., Chicago, IL, USA). Intergroup comparisons of categorical variables were conducted using a Chi-square test and continuous variables were compared using the Student's t-test. Categorical variables were presented as percentages or counts, and continuous variables were presented as mean and standard deviation in a descriptive analysis. Differences in the presenting symptoms of each group were identified by a Cox regression. A p-value lower than 0.05 was considered statistically significant.

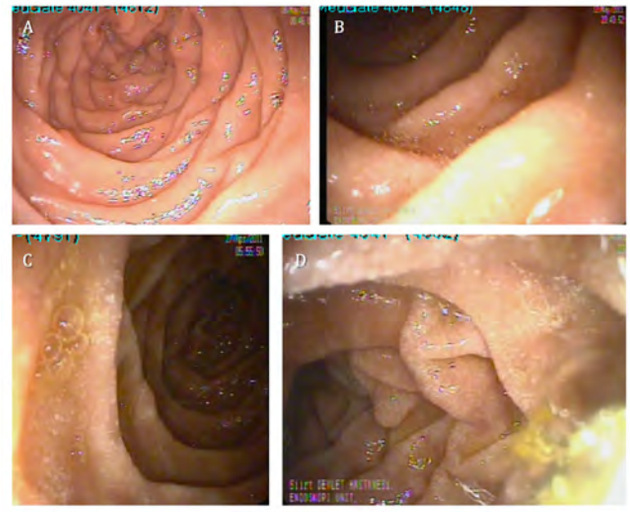

Figure 1. A, B; Rare appearance, C; Mild appearance, D; Dense appearance of white spots in the duodenum

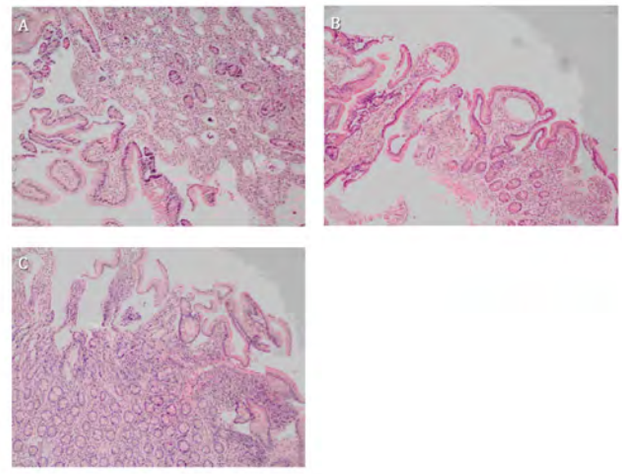

Figure 2; A, B; Dilation of the lacteals of the villi; Intestinal lymphangiectasia, C; Mild chronic inflammatory infiltration with polymorphonuclear leukocytes in lamina propria; Chronic nonspecific duodenitis

Results

Of the 127 patients, 57 (44.9%) were men and 70 (55.1%) were women. The mean age was 43.27 ±16.7 years (range: 18–72 years).

The pathologies revealed through a histological examination are presented in Table 1.

Table 1. Overall frequencies of histological diagnoses

	Frequency	Percentage
NCD	93	73.2%
IL	17	13.3%
IEL	14	11%
VA	3	2.3%

NCD: Nonspecific Chronic Duodenit; IL: Intestinal Lymphangiectasia; IEL: Intraepithelial Lymphocytosis; VA: Villus Atrophy

A gastric histology revealed HP positivity in 87 patients in all groups, and the distribution of the groups is shown in Table 2.

Presenting complaints of the patients are shown in Table 3. Weight loss as a presenting symptom was significantly less often found in NCD patients as compared to the other groups ($p< 0.05$).

A duodenal histology revealed reduced villous atrophy (VA) in three patients (2.3%), with a histology consistent with CD. The patients did not present with either PAS-positive macrophages in duodenal biopsy samples or with a specific histology for giardiasis.

Table 2. Helicobacter pylori positivity in all groups

	Hp (+) n %	Hp (-) n %
NCD	64 68.8%	29 -31.2%
IL	11 64.7%	63 5.3%
IEL	9 64.2%	5 3 5.8%
VA	1 33.3%	2 66.7%
		p>0.05

NCD: Nonspecific chronic duodenitis; IL: Intestinal lymphangiectasia; IEL: Intraepithelial lymphocytosis; VA: Villus atrophy

Table 3. Summary of presenting symptoms of the study population

	NCD(93)		IL (17)		IEL(14)		VA (3)		p
	n	%	n	%	n	%	n	%	
Epigastric pain or discomfort	75	80	10	59	9	64	2	67	
Nausea	16	17	4	24	4	29	0	0	0.58
Vomiting	18	19	3	18	4	29	O	0	0.68
Diarrhoea	14	15	9	53	3	21	1	33	0.06
Weight loss	6	6	4	25	4	29	1	33	<0.05
Lower extremity edema	0	0	0	0	3	21	0	0	<0.001

NCD: Nonspecific chronic duodenitis; IL: Intestinal lymphangiectasia; IEL: Intraepithelial lymphocytosis; VA: villus atrophy

Discussion

Although clinicians have not placed much emphasis on WSD, a few studies on this topic have been found in the literature. Has WSD been overlooked during endoscopic investigations? Perhaps if clinicians were more alert to WSD, a higher prevalence would have been reported. This paper investigated the prevalence of WSD in our study, 4.8%, which is much higher than has been previously found. WSD may occur because of several conditions, such as NCD, IL, IEL, infectious pathologies, and CD. It was found that NCD is the most common cause of WSD. NCD is defined by the presence of inflammatory cell infiltration in the lamina propria, with or without an architectural distortion of the intestinal villi. There are different etiologies of NCD, including peptic duodenitis secondary to HP, CD, Crohn's disease, and parasitic infestation. However, HP cannot exist on the intestinal epithelium, although it may colonise in areas of gastric metaplasia in the duodenal mucosa, thereby leading to chronic active duodenitis [5]. The association of HP with WSD has not yet been investigated. In this study, while the positivity of HP was 68.8% in NCD, it was 64.7% in the IL group and 64.2% in the IEL group, with no significant statistical difference. The positivity of HP was 66.9% in all groups, lower than the overall 82.% pevelance in Turkey [6].

IL is the second most common cause in these endoscopic findings. IL is a rare disorder caused by a congenital malformation or an obstruction of the intestinal lymphatic drainage system [7]. The elevated pressure of the lymph drainage system on the intestinal wall leads to dilatation and even a rupture of the lymphatic vessels, which results in a leakage of lymphatic fluid [8]. Because lymphatic fluid contains high levels of protein, fat, and lymphocytes, a leakage of lymphatic fluid will cause hypoproteinaemia, lymphocytopenia, and decreased serum levels of immunoglobulin. IL can be classified into primary or secondary IL, depending on the reason for the disease. Fewer than 200 primary intestinal lymphangiectasia (PIL) cases have been reported globally since Waldman et al. [9] reported the first case in 2010. PIL is a congenital malformation of the lymphatic system that can affect individuals of any age, but that most often affects younger patients [10]. Secondary causes include conditions that involve protein loss associated with impaired intestinal lymphatic drainage, such as congestive cardiac failure, constrictive pericarditis, Whipple's disease, Crohn's disease, intestinal tuberculosis, radiation and/or chemotherapy with retroperitoneal fibrosis and portal hypertension, or hepatic venous outflow obstruction [11-15]. Evidence of lymphangiectasia in the duodenum without the presence of malabsorption has been observed [16]. Consistent with these results, three of the patients in this study with IL had hypoalbumenia, lymphopenia, or chronic diarrhoea. Short- and medium-chain fatty acids are absorbed directly into the portal system without contributing to the formation of chylomicrons, thus providing energy and lessening lacteal engorgement and lymph loss [17]. A low-fat diet reduces lymphatic flow and pressure, preventing the lacteal dilatation and lymph leakage resulting from their rupture. Patients who had hypoalbumenia, lower extremity edema, and were diagnosed with IL were put on a low-fat diet for a period of eight weeks, after which a control endoscopy indicated improved WSD appearance and resolved peripheral edema.

The early diagnosis and treatment of IL is of great importance for effective diet therapy and for protection from malignant transformation. Edema is the main clinical manifestation due to hypoalbumenia. The patient may present with ascites, pleural effusion, and pericarditis. Lymphedema, abdominal pain, fatigue, moderate diarrhoea, weight loss, and a deficiency of fat-soluble vitamins may also be present and could be resolved by a specific diet. It is noteworthy that PIL may have a high malignancy grade potential for a long time after the first onset [18]. Therefore, clinicians should keep in mind this rare condition and should treat it urgently.

IEL forms the first line of the host immune defence system and plays an essential role in fighting infections caused by certain microorganisms and parasites [19]. IEL is thought to be an early lesion in the development of CD. Many investigators have demonstrated that IEL is the first abnormality seen after gluten challenge and that IEL alone may be a form of gluten sensitivity as type 1 CD, according to the Marsh Classification [20]. Otherwise, IEL in a normal small bowel biopsy is a somewhat nonspecific histological finding. Increased IEL counts have also been described in patients without CD, such as in cases of allergic enteritis, autoimmune disorders, tropical sprue, HP-associated gastritis, viral infections, and enteropathy-associated

T-cell lymphoma [21-25]. In this study, the HP-positive rates of all groups were 68.8%, 64.7%, and 64.2% in the NCD, IL, and IEL groups, respectively. These differences were not statistically significant.

Anti-tissue transglutaminase IgA was conducted in all patients with IEL or with VA. Three patients in the IEL group and three in the VA group had positive levels and they were diagnosed with CD. Importantly, CD was diagnosed in six patients who presented with IEL or VA and in whom an endoscopic examination had not indicated specific features of CD.

This study has a limitation in that an endoscopic evaluation was not performed after the specific treatment in all patients. The reason for not performing a second endoscopy is that the aim of the study was to investigate the clinical importance of WSD. This study has underlined the clinical importance of the use of WSD in diagnosing a serious clinical condition in cases without a specific symptom. Six patients were diagnosed with celiac disease and seventeen patients were diagnosed with IL because follow up was initiated, based on a suspicion because WSD had been observed. In our study, a few, but not all of, the patients had presented with specific symptoms.

Conclusion

WSD could be a valuable marker in the diagnosis of several diseases that are treated by diet and that require early treatment, such as CD and IL. To avoid overlooking these diagnoses, endoscopists should be alert to the appearance of WSD in the second part of the duodenum, and, if found, at least two biopsies should be obtained from this region.

Competing interests

The authors declare that they have no competing interests.

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PREVALENCE OF URINARY TRACT INFECTIONS IN WOMEN WITH URINARY INCONTINENCE AND OTHER RISK FACTORS

İDRAR KAÇIRAN KADIN HASTALARDA İDRAR YOLU ENFEKSİYONU GÖRÜLME SIKLIĞI VE DİĞER RİSK FAKTÖRLERİ

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Öz

Giriş: Üriner sistem enfeksiyonlarının oluşumuna bir çok faktörün etki ettiği varsayılmaktadır. Postmenapozal vajinal ve üretral atrofi, üriner inkontinans, sistosel ve işeme sonrası rezidü volüm bu faktörlerden en önemli olanlarıdır. Bunların yanında diabetes mellitus, Parkinson hastalığı gibi bazı nörolojik hastalıklar, obezite, sigara içimi, multiparite ve zor doğum hikayesi de üriner sistem enfeksiyonu gelişiminde etkili faktörler olarak düşünülmektedir. Bu çalışmada kadınlarda üriner sistem enfeksiyonu gelişimine müdahil olan risk faktörlerini, özellikle üriner inkontinansın etkilerini, belirlemeyi amaçladık. Gereç ve Yöntem: 1060 kadın hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Yaş, üriner inkontinans tipi, parite, doğum hikayesi, histerektomi öyküsü, konstipasyon, postmenapozal semptomlar, obstrüktif üriner semptomlar, üriner sistem enfeksiyon hikayesi, mevcut sistemik hastalıklar ve sigara içimi hikayesi ile ilgili veriler hastaların tıbbi kayıtlarından derlendi. Bulgular: Univaryat analizlerde yaşlanma, yüksek işeme sonrası rezidü volüm, düşük Qmax, postmenapozal semptomlar, diabetes mellitus, nörolojik hastalıklar, vajinal-üretral atrofi ve üroflovmetre grafiğindeki anormallikler risk faktörleri olarak bulundu. Multivaryat analizde ise sadece diabetes mellitus istatistiksel anlamlı risk faktörü olarak bulundu. Tartışma: Çalışmamızın sonuçlarının ve literatür bilgilerinin ışığında bu faktörlerin tamamının üriner sistem enfeksiyon riskini arttırdığını iddia etmek yanlış olmayacaktır. Ancak kadınları global olarak etkileyen bu kronik hastalığın risk faktörlerini, oluşum mekanizmalarını ve önleme stratejilerini belirlemek için daha ileri çalışmaların yapılmasına ihtiyaç bulunmaktadır.

Anahtar Kelimeler

Üriner İnkontinans; Üriner Sistem Enfeksiyonu; Diabetes Mellitus

Abstract

Aim: Many factors are presumed to contribute to the development of urinary tract infections. The most significant of these factors are postmenopausal vaginal and urethral atrophy, urinary incontinence, cystocele, and postvoid residual urine. Diabetes mellitus; neurological disorders such as Parkinson's disease; obesity; smoking; multiparity; and hard delivery history are also considered influential factors for urinary tract infections. In this study, we aimed to determine the risk factors involved in urinary tract infections in women, especially focusing on the effects of urinary incontinence. Material and Method: Medical records of 1,060 female patients were examined retrospectively. Data about age, urinary incontinence types, parity, delivery history, hysterectomy history, constipation, postmenopausal symptoms, obstructive urinary symptoms, urinary tract infection history, presence of systemic diseases, and smoking history were obtained from the medical records of the patients. Results: In the univariate analysis, aging, higher post void residual urine, smaller Qmax, postmenopausal symptoms, diabetes mellitus, neurologic disorders, vaginal-urethral atrophy, and the abnormality of the uroflow graphic were found as the risk factors. In multivariate analysis only diabetes mellitus was found to be statistically meaningful. Discussion: In light of our results and the literature, it would not be incorrect to assert that all of these factors increase the risk of urinary tract infections. Certainly, supplementary studies are needed to further identify the risk factors, mechanisms, and prevention strategies for this prevalent and chronic disorder affecting many women globally.

Keywords

Urinary Incontinence; Urinary Tract Infection; Diabetes Mellitus

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Introduction

Urinary tract infections (UTI) are common diseases that account for substantial morbidity and financial expenditure worldwide [1]. Forty percent of women have had a UTI at least once during their life and 27% of these women have had recurrent UTIs in the 6-12 month period following their first UTI episode [2]. The prevalence of asymptomatic bacteriuria without UTI is high as well. Studies have shown the prevalence of asymptomatic bacteriuria as 3.5% [3]. UTIs affect people of all ages; occurrence frequency and risk factors vary with age [1].

Many factors are presumed to contribute to the development of UTIs. The most significant of these factors are postmenopausal vaginal and urethral atrophy, urinary incontinence (UI), cystocele, and postvoid residual urine (PVR) [4]. Diabetes mellitus (DM); neurological disorders such as Parkinson's disease; obesity; smoking; multiparity; and hard delivery history are also considered influential factors for UTIs. DM and obesity are serious public health problems, and they interact with each other; some studies assert that these two pathological conditions substantially increase the prevalence of UI and UTI in women [5].

UI, described as involuntary urine leakage causing social and/or hygiene problems by the International Continence Society (ICS), is a significant public health problem that affects 200 billion people around the world every year. The overall prevalence of UI is 30% in the female population; however, this rate increases to 50% in elderly women [6]. UI has profound consequences on quality of life, including social isolation, depression, and the end of independent living for some elderly women [7]. Costs for incontinence may be as high as $30 billion per year in the United States, greater than the annual costs for breast, ovarian, cervical, and uterine cancers combined [8].

In this study, we aimed to determine the risk factors involved in UTIs, especially focusing on the effects of UI on UTIs.

Material And Method

Medical records of 1,060 female patients who applied to the women's urology department of Gazi University, School of Medicine, Urology Department between September 2002 and January 2010 were examined retrospectively; 979 patients with UI were included in the study. Patients with positive urine cultures were classified as Group A (72 patients), and patients with negative urine cultures were classified as Group B (907 patients).

Data regarding age, stress UI, urge UI, mixed UI, parity, type of delivery, hard delivery history, hysterectomy history, constipation, postmenopausal symptoms (PMS), obstructive urinary symptoms, UTI history, presence of systemic diseases (DM, neurological disorders), and smoking history were obtained from the medical records of the patients. Moreover, information obtained from urogenital examinations, that included body mass index (BMI), vaginal-urethral atrophy, cystocele grade, and rectocele grade, was evaluated. Physical examinations of the patients were performed in classical gynecological position with full bladders, and stress UI evaluation was performed via the coughing or straining of the patients. We used the criteria of ICS for definitions of stress, urge, and mix UI. [9]. Pelvic organ prolapse of the patients was evaluated according to the pelvic organ prolapse quantification (POP-Q) classification system, and pelvic organ prolapse was recorded as either positive or negative [10]. Recurrent UTI was defined as recurrent UTIs 6-12 months after the first infection.

Data of uroflowmetry (Medical Measurement System, Solar®, The Netherlands) and PVR results evaluated with Bladderscan® (Verathon, BVI-6100, USA) were included in the study. Also, data gained from the forms of the Urogenital Distress Inventory (UDI-6-short form) and Incontinence Impact Questionnaire (IIQ-7-short form), filled out by patients, were entered into the study [11,12]. The patients' uroflow charts were objectively evaluated by one researcher (A.F.B, M.D.) as normal or abnormal. Intermittent and/or obstructive patterns of voidings were classified as abnormal.

Type of delivery was classified as no parity, vaginal delivery, cesarean section delivery, or both vaginal and cesarean section delivery. The designation of hard delivery included the presence of at least one of the following situations: longer labor period, use of forceps and/or vacuum during labor, and/or high birth weight (4000 grams and higher).

Student's t-test and Pearson's chi-squared test were used for statistical analysis. In the statistical analysis, data found to be meaningful from univariate analysis were placed into a multivariate logistic regression analysis model. As a result, variables were evaluated as risk factors in terms of causation for UTI by the multivariate analysis model.

Results

The mean age of the women in Group A was calculated as 56.42±15.09 and in Group B, 50.14±12.53; the difference was statistically significant (p=0.001). Urine culture results showed that the 72 patients in Group A (7.4%) had positive urine cultures, and the 907 in Group B had negative urine cultures (92.6%). Infections for Group A were caused by Escherichia coli (26 patients, or 36.1%), Klebsiella series (40 patients, or 55.6%), Proteus species (2 patients, or 2.8%), or Enterococcus (4 patients, or 5.6%). The number of the patients having recurrent UTIs was calculated as 11, constituting 1.1% of all of the patients and 15.3% of the UTI patients.

The distribution according to UI patterns was 2 stress UI (18.2%), 3 urge UI (27.3%), and 6 mix UI (54.5%). In women with stress UI, the number of positive urine cultures was 9 (12.5%), whereas, in women without stress UI, the positives totaled 63 (87.5%). Similarly, in women with urge UI, positive urine cultures occurred in 18 (25%) patients but, without urge UI, this number was 54 (75%). Positive urine cultures in women with and without mix UI were 45 (62.5%) and 27 (37.5%), respectively. The difference between the UI patterns in terms of positive urine cultures was statistically insignificant (p=0.150).

The parity was 3.21±2.05 for Group A and 2.96±2.04 for Group B (p=0.317). When the delivery type, presence of hard delivery, and presence of constipation were evaluated as risk factors for UTI development, these factors were found statistically insignificant. On the other hand, the presence of PMS was found to be a statistically significant risk factor for UTI (p=0.002). Similarly, the presence of DM and neurological disorders were found to be statistically significant risk factors in univariate analysis (Table 1).

Positive urine cultures were found in patients with and without smoking as 11 (6.7%) and 61 (7.5%), respectively. Smoking was

Table 1. Univariate analysis with selected variables of Age, Qmax, and PVR

Variable	Group A	Group B	P -value
Age	22.04±11.24	28.70±14.22	0.001
Qmax	56,42±15,09	50,14±12,53	0,001
PVR	35.71±64.89	13.77±45.10	0.004

Group A: Positive urine culture group
Group B: Negative urine culture group
Qmax, maximum urinary flow rate; PVR, post void residual urine.

assessed as a statistically insignificant factor (p=0.734). Positive urine cultures were found with and without hysterectomy history as 11 (7.3%) and 61 (7.4%), respectively (p=0.973). Mean BMI value was 28.07±6.13 for Group A and 28.37±14.21 for Group B, and the difference was statistically insignificant (p=0.738).

The presence of vaginal-urethral atrophy, which has been mentioned as a strong risk factor for UTIs in previous reports, was also found statistically significant in our results. Positive urine cultures with and without the presence of vaginal-urethral atrophy were 21 (13.5%) and 42 (6.3%), respectively (p=0.003) (Table 1). When pelvic organ prolapse was evaluated, presenting as cystocele, positive urine cultures with and without its presence were 21 (5.2%) and 14 (4.6%), respectively, and the difference was statistically insignificant (p=0.959). Positive urine cultures with and without the presence of rectocele were 14 (5.3%) and 20 (5.5%), respectively, and the difference was statistically insignificant (p=0.596).

According to uroflow charts, positive urine cultures were found in 33 (6.7%) patients who scored normal and 17 (13.2%) who scored abnormal, and the difference was calculated as statistically significant (p=0.016) (Table 1). Mean Qmax value was 22.04±11.24 for Group A and 28.70±14.22 for Group B. The difference calculated was significant (p=0.001). Similarly, the mean PVR value was 35.71±64.89 for Group A and 13.77±45.10 for Group B, and the difference was statistically significant (p=0.004) (Table 2). When the responses on the UDI-6 and IIQ-7 forms were evaluated for increased risk for UTIs, the mean values were found to be statistically insignificant. Mean values of UDI-6 and IIQ-7 were calculated in Group A and Group B as 10.43±4.19, 10.15±4.03 (p=0.697) and 13.08±9.78, 11.39±8.57 (p=0.255), respectively.

Only DM was found to have a statistically significant relationship with increased risk of UTI when the variables of age (OR, 1014; 95% CI, 0.978-1.052), PMS (OR, 1005; 95% CI, 0.998-1.011), DM (OR, 2424; 95% CI, 1.025-5.732), neurological disorders (OR, 1530; 95% CI, 0.434-5.388), Qmax (OR, 0.989; 95% CI, 0.958-1.020), PVR (OR, 1234; 95% CI, 0.497-3.063), vaginal-urethral atrophy (OR, 0.901; 95% CI, 0.344-2.359), and uroflow charts, that had been found statistically significant in univariate analysis models, were placed into the multivariate regression analysis model (Table 3).

Table 2. Univariate analysis with selected variables of DM, Neurologic Disease, PMS, Vaginal- Urethral Atrophy, and Uroflow Chart

Variable		Group A (n,%)	Grup B (n,%)	Number of Patients		P-value
DM	+	19(%14.4)	113(%85.6)	132	976	0.001
	-	53(%6.3)	791(%93.7)	844		
Neurologic Disease	+	12(%14.5)	71(%85.5)	83	976	0.001
	-	60(%6.7)	833(%93.3)	904		
PMS	+	37(%10.6)	311(%89.4)	348	915	0.002
	-	29(%5.1)	538(%94.9)	567		
Vaginal - Urethral Atrophy	+	21(%13.5)	135(%86.5)	156	821	0.003
	-	42(%6.3)	623(%93.7)	665		
Üroflow Chart	Normal	33(%6.7)	459(%93.3)	492	621	0.016
	Abnormal	17(%13.2)	112(%86.8)	129		

Group A: Positive urine culture group
Group B: Negative urine culture group
DM, diabetes mellitus; PMS, postmenopausal symptoms.

Table 3. Multivariable logistic regression model with selected variables for urinary tract infection

	Beta	P	OR (95% CI)
Age	0,014	0,444	1,014(0.978-1.052)
DM	0,885	0,044	1.00*
			2,424(1.025-5.732)
Neurologic Disease	0,425	0,508	1.00*
			1,530(0.434-5.388)
Vaginal – Urethral Atrophy	-0,105	0,831	1.00*
			,901(0.344-2.359)
QMAX	-0,011	0,479	,989(0.958-1.020)
PVR	0,210	0,650	1,234(0.497-3.063)
PMS	0,005	0,154	1.00*
			1,005(0.998-1.011)

*Reference group

CI, confidence interval; OR, odds ratio; DM, diabetes mellitus; Qmax, maximum urinary flow rate; PVR, Post void residual urine; PMS, postmenopausal symptoms.

Discussion

While variables of age, PMS, DM, neurological disorders, Qmax, PVR, vaginal-urethral atrophy, and uroflow charts were found statistically significant for increased risk of UTI development in univariate analysis models, only DM was found statistically significant in multivariate regression models (p=0.044). Similar results exist in other studies in the literature [13].

UI is clearly a risk factor for UTI, according to studies conducted in the elderly population. Although there are limited numbers of studies evaluating the effect of urine amount on UTI, Hu et al. concluded that both UI and urine amount could result in increased UTI risk in double mass analysis, but multivariate regression models revealed only UI as a significant risk factor in their study [14]. Our research also revealed UI as a risk factor for UTI. We evaluated the effects of UI types separately, and our statistical analysis revealed that there is no significant difference between UI types. The pathophysiology of UI as a risk factor for UTI is a multifactorial issue that is still under review. Brostrøm et al. found that stress UI, especially, develops at statistically higher rates in patients who have pelvic organ prolapse, such as cystocele and rectocele [15]. Moreover, these organ prolapses, especially cystocele, have been shown to cause voiding dysfunction [16]. It is a well-known fact that risk of UTI development increases in the presence of both voiding dysfunction and UI. Therefore, it would make sense that multiparity, hard and vaginal delivery history, and cystocele and/or recto-

cele presence increase the tendency for development of UTIs. In this study, we evaluated these factors as independent variables, but multiparity, history of vaginal and/or hard delivery, and cystocele and rectocele presence were found to be statistically insignificant. Nonetheless, further research is needed to make a definitive judgment.

Another controversy among these risk factors is the effect of accompanying systemic illnesses. Two such systemic diseases were investigated: DM and neurological disorders. Boyko et al. revealed that DM is an important risk factor in UTI development, particularly in postmenopausal women [13]. Asymptomatic bacteriuria was twice as likely to occur in DM patients than in those without DM. Also, it is claimed that asymptomatic bacteriuria leads to pyelonephritis, which eventually results in decreased kidney function in type I DM patients [2]. Strikingly, these kinds of serious morbidities resulting from asymptomatic bacteriuria are not an expected outcome in healthy, non-pregnant women with normally functioning urinary systems, alhough asymptomatic bacteriuria could cause pyelonephritis or premature labor in pregnant women [17]. Aside from these complications, DM seems to worsen the probability of UTIs.

Emphysematous cystitis and pyelonephritis, abscess formation, renal papillary necrosis, and xanthogranulomatous glomerulonephritis could be designated uncommon conditions of UTI related to DM. The exact pathophysiological mechanism of the effects of DM on the tendency for UTIs is unknown, but weakness of glycemic control, leukocyte malfunction due to hyperglycemia, recurrent vaginitis, and anatomical and functional changes in the urinary tract are some proposed theories. The anatomical and functional changes in the urinary tract related to DM are listed as neuromuscular malfunction of bladder due to peripheric neuropathy, bladder outlet obstruction, incontinence, and increased PVR [2]. Both univariate and multivariate analysis in our study showed that DM is a statistically significant risk factor for UTI development. Importantly, DM was the only significant factor when placed into the multivariate regression models.

The effects of neurological disorders, especially Parkinson's disease, on the lower urinary system are well-known. Lower urinary system symptoms such as urge, frequency, pollakuria, and urge UI have been described in different studies with rates of frequency varying between 50 and 75% [18]. Detrusor overactivity is the most common urodynamic abnormality in this group of patients. Therefore, storage and voiding malfunction due to Parkinson's disease leads to a higher tendency for UTI development than in the normal population. In this study, we investigated the effects of any neurological disease on UTI, and they were found to be a significant factor in univariate analysis. However, our evaluation of the effects of neurological diseases as simply in terms of their presence or absence is one of the limits of this study.

The effect of smoking on UTI development is currently unknown, but Parazzini et al. stated that smoking could have an effect on UI risk in their epidemiologic studies [19]. Our study found no relationship between smoking and UTI development.

History of hysterectomy has been implicated as a risk factor for lower urinary system dysfunction and, indirectly, a factor in development of UTIs in some studies [20]. Also, some recent studies have concluded that urge UI and stress UI could develop after a hysterectomy [21]. The effects of hysterectomy on UTI development could be attributed to the modification of the pelvic organ anatomy and functions [22]. We evaluated the effect of hysterectomy on UTI development and could not reach any significant result.

Epidemiologic studies have shown that obesity is a strong and independent risk factor for UTI. Many research studies have concluded that every five units of increase in BMI lead to a 20% to 70% increase in UI, varying in proportion. Subak et al. stated that obesity could increase the tendency to develop stress UI and overactive bladder in their study of 6,424 obese female patients [23]. Obesity and abdominal fat may induce UI by increasing pressure on the bladder and straining the muscles and connective tissues that support the urethra [24]. Also, the strong positive correlation between obesity and insulin resistance suggests several potential mechanisms linking obesity and incontinence [25]. Improving blood glucose control and promoting weight loss have both been identified as potential targets for interventions to prevent or treat UI in women with DM. In contrast, we could not find a statistically significant link between BMI and UTI development.

The three interdependent factors that have been proven to have effects on UTI development are aging, menopause status, and the presence of vaginal-urethral atrophy. Especially, age has been identified as an independent factor by causing voiding dysfunction in the geriatric population. In an editorial review, Cho stated that older age is related to UI, overactive bladder, and lower urinary tract symptoms [26]. In most studies, postmenopausal symptoms and presence of vaginal atrophy are evaluated together. Some studies investigating the effects of intravaginal estrogen therapy revealed a statistically significant decreased risk of recurrent UTIs [27]. Moreover, epidemiologic studies have confirmed that stress UI appears at higher rates during the menopause development period. In the light of this data, lack of estrogen could lead to UI, in addition to the vaginal-urethral atrophy premise [28]. In this study, we found a significantly higher UTI risk with the presence of vaginal-urethral atrophy and postmenopausal symptoms in univariate analysis; as with other factors except DM, these factors were found insignificant in multivariate regression models.

Markedly elevated PVR volumes, abnormal uroflow charts, and decreased Qmax scores are defined risk factors for UTI development in women. The common effect mechanism of these factors is to increase PVR's facilitation of bacteria reproduction. It has been propounded that 30 ml or more of increased PVR volume could result in increased UTI prevalence [29]. In our study, we calculated PVR as a significant risk factor in univariate analysis. We evaluated the effect of PVR by measuring the amount of residual urine. Since bladder capacity varies from woman to woman, however, PVR volumes should be evaluated individually. In addition, abnormal uroflow charts, such as obstructive or intermittent patterns, and decreased Qmax values were statistically significant as risk factors. The mechanisms leading to UTIs could be the developments of sacculations, diverticules, and/or stones in high pressure bladders [30].

To the best of our knowledge, no studies exist to date on the effects of UDI-6 and IIQ-7 forms on UTI risk. In this study, when

evaluated individually, the results of these forms had no effect on UTI development risk, statistically.

In this study, we evaluated most of the factors that are presumed to contribute to the development of UTIs. Even though many of these factors were considered significant in univariate analysis, only DM was determined a significant factor in the multivariate regression model. In light of our results and the literature, it would not be incorrect to assert that all of these factors increase the risk of UTIs. The aim of this research was to discuss the risk factors of UTI and, especially, to understand the effects of UI, with its subtypes, as risk factors for UTIs. Certainly, supplementary studies are needed to further identify the risk factors, mechanisms, and treatments and also prevention strategies for this prevalent and chronic disorder affecting many women globally.

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Competing interests

The authors declare that they have no competing interests.

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THE EFFECTS OF SODIUM VALPROATE MONOTHERAPY ON THE BODY'S VITAMIN K STATUS IN CHILDREN

ÇOCUKLARDA SODYUM VALPROAT MONOTERAPİSİNİN VÜCUT K VİTAMİNİ DURUMUNA ETKİLERİ

VITAMIN K STATUS IN CHILDREN WITH EPILEPSY

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Öz

Amaç: Çalışmamızda, daha önce literatürde bulunmayan, sodyum valproat (VPA) kullanan çocuklarda vücut K vitamini durumunu ve bir yıllık VPA kullanımının K vitamini durumuna etkilerini incelemeyi amaçladık. Gereç ve Yöntem: Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk Nöroloji Bilim Dalında bir yıllık sürede, ileriye dönük olarak yapılan çalışmaya, 4-17 yaşlar arasında ilk kez antiepileptik ilaç (VPA) başlanan 25 olgu (14 erkek, 11 kız) ile benzer yaş gurubundan 25 (12 erkek, 13 kız) çocuk kontrol grubu olarak alındı. Tanner kriterlerine göre pre-puberte ve puberte olarak iki gruba ayrılan hastaların tedavi öncesi ve tedaviden bir yıl sonra osteokalsinin karboksile (cOC) ve unkarboksile (ucOC) fraksiyonları ELISA (enzime linked immun assay) yöntemi ile ölçüldü. Unkarboksile osteokalsinin karboksile osteokalsine oranı UCR (Uncarboksile Carboksile Rate) olarak, başlangıç ve sonuç UCR'leri arasındaki fark Delta-UCR olarak tanımlandı. Bulgular: Karboksile osteokalsin pre-puberte grubunda minimal bir artış göstermesine karşın puberte grubunda azaldığı görüldü. Unkarboksile osteokalsinin pre-puberte grubunda daha fazla olmak üzere her iki grupta da başlangıç değerlerine göre azaldığı görüldü. UCR değerleri pre-puberte grubunda azalma, puberte grubunda ise artma gösterdi. Puberte grubunda Delta UCR'nin negatif bir değer aldığı görüldü. Tartışma: Pre-puberte grubu hastalarımız için VPA kullanılmasının, kemik K vitamini durumunu negatif sonuçlar gösterecek kadar kötü etkilemediği görülmüştür. Çalışmamızın sonuçları, puberte grubu hastalarımızda vücut K vitamin durumunun bozulma eğiliminde olduğunu (UCR'de artış), ihtiyacı karşılamada zayıflama olduğunu (cOC'de azalma) ve kemik metabolizmasının olumsuz etkilendiğini (Delta UCR'nin negatif değeri) göstermektedir.

Anahtar Kelimeler

Valproik Asit; Vitamin K; Osteokalsin

Abstract

Aim: Our study aimed to investigate Vitamin K status in children using sodium valproate (VPA), a subject not formerly reported in the literature and the effects of VPA use for a period of one year on Vitamin K status. Material and Method: The study conducted prospectively at the Department of Neurology, Faculty of Medicine, Cumhuriyet University over a period of one year included 25 children (14 male, 11 female) aged between 4 to 17 who received VPA for the first time and 25 children (12 male, 13 female) in a similar age range as the control group. Patients were divided into two stages as pre-puberty and puberty according to Tanner's criteria, and the carboxylated (cOC) and undercarboxylated (ucOC) fractions of osteocalcin were measured using the ELISA (Enzyme Linked Immunoassay) method both pre-therapy and one year post-therapy. The ratio of undercarboxylated osteocalcin to carboxylated osteocalcin was described as UCR, and Delta-UCR the difference between start and end of UCRs. Result: Although carboxylated osteocalcin demonstrated a minimal increase following VPA treatment in the pre-puberty group, it was observed to decrease in the puberty group. We noted that, although higher in the pre-puberty group, undercarboxylated osteocalcin was observed to decrease compared with their start values in both groups. UCR values decreased in the pre-puberty group and increased in the puberty group. We noted a negative Delta-UCR value in the puberty group. Discussion: We noted that the use of VPA for our pre-puberty group of patients did not affect the body's Vitamin K status to the extent that it would have negative results. The results of our study demonstrate that the body's Vitamin K status tended to decline in our puberty group patients (increase in UCR), that there was a weakened capacity to meet the need (decrease in cOC), and that the bone metabolism was negatively affected (negative Delta-UCR value).

Keywords

Bone Metabolism, Sodium Valproate; Vitamin K; Osteocalcin

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Introduction

Treatment of common childhood epileptic disorder is primarily medical and lasts at least two years in patients with seizure control. Sodium valproate (VPA) is the most widely used drug for the treatment of epilepsy because it is the most preferred in both focal and generalized seizures. VPA negatively effects bone metabolism; the drug has disrupted the formation and resorption stability of bone turnover by stimulating osteoclast activity and thus is believed to cause bone loss [1]. However, it could not be developed as a fully explanatory model.

The main factors that play a role in bone mineral metabolism are the genetic and environmental factors, diet, vitamins and hormones, drug use, sport, and activity [2]. It is known that vitamin K plays an important role by carboxylation in making the active osteocalcin, which is an essential protein for bone mineral density in healthy children. Additionally, studies of the effects on bone mineral metabolism of vitamin K status in the body have been remarkable in recent years [3-5]. As a result of research done on this subject, it has been proposed to advocate vitamin K for healthy adolescent children and post-menopausal women [3, 4, 6].

Vitamin K status, effects of drugs on the body condition of vitamin K, and implications of bone metabolism in children with epilepsy using antiepileptic drugs have not been observed previously. Our study aimed to investigate Vitamin K status in children using sodium valproate (VPA), a subject not formerly reported in the literature and the effects of VPA use for a period of one year on vitamin K status.

Material And Method

This study was prospectively performed in Cumhuriyet University, Faculty of Medicine, and Division of Pediatric Neurology during a one-year period. It included 25 children (14 males, 11 females) aged between 4 to 17 who received antiepileptic drugs (VPA) for the first time and continued the therapy with the single drug, and 25 children (12 males, 13 females) in a similar age range as the control group. Patients were excluded from the study if they were receiving any other drug affecting bone metabolism, if they had a nutritional problem or difficulty, limitations in physical activity, mental retardation that might limit physical activity, muscle and skeletal system diseases, or diseases that cause growth and development disorders.

Informed consent was obtained from the families of both the control group and the patient group with epilepsy.

Age, body measurements (weight, height, and weight-height for age), medical history, neurological examinations, and types of seizures were recorded for all subjects at baseline and at the end of the one-year follow-up period. Patients were diagnosed according to ILAE 1989 classification based on evaluation of the types of seizures, medical history, examination results, and laboratory and EEG findings [7]. Caution was paid to ensure the regular use of the antiepileptic drugs selected by the diagnoses of the subjects (Sodium Valproate: 20 mg/kg/day) via per oral route, as tablets or suspension, continuously for one year.

To evaluate the growth and development of the subjects in the study period taking the puberty period into consideration, “height and weight for age” and “percentage of height and weight for age” were individually calculated for girls and boys at baseline and at end of the study utilizing the scales prepared for Turkish children [8]. Members of the patient group were assigned into two different age groups including pre-puberty (4-7 years of age) and puberty group (8-17 years of age) according to Tanner’s criteria, and the distribution of these two groups of data were examined for statistical differences.

Blood samples of the patients were taken intravenously in the morning hours. Serum samples obtained from centrifuged blood samples were stored at -70° C for work of carboxylated and uncarboxilated osteocalcin values. The baseline and end time of the study sample were studied together.

Carboxylated (cOC) and undercarboxylated osteocalcin (ucOC) fractioned osteocalcin were measured by ELISA method (enzyme linked immunoassay) using a commercial kit (Takara Bio Inc., Japan). The ratio of undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) were UCR described as a marker of vitamin K status in the body (UCR = ucOC/cOC).

High levels of UCR were used as an indicator of reduced and insufficient vitamin K in the body [9, 10]. The difference of calculated UCR at the beginning and end of a year in the study period was defined as Δ UCR (Δ-UCR = UCR1 (start) - UCR 2 (final)). Over time, the increase of Δ-UCR indicates the improvement of vitamin K status in the bone and the decrease in deterioration.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 software. The descriptive statistics criteria (median, min-max) was used in the study. Also, Chi-square test was used for the gender distribution of the research and control group and Wilcoxon test to compare values before and after treatment of the patient group. Mann Whitney-U test was used in the comparison of the investigation and control groups. $P<0.05$ values were considered as significant.

Ethics Board Approval

The study was approved by the local ethic board with the decree dated 30.09.2009, numbered B.30.CUM.O.1H.00.00/06 and 2009-09/05.

Results

Of 25 subjects enrolled into the study (14 males, 11 females), mean age was 10.0 ± 4.4 years (4-17 years) and mean age of control group (12 males, 13 females) was 10 ± 4.1 years (3-17 years). There was no statistically significant difference between gender groups ($p >0.050$) [Table 1]. Pre-puberty group were 11 cases (4 females, 7 males) and puberty group 14 (7 females, 7 males) [Table 2].

When compared to the results obtained at baseline and after one year, the height and weight of patients increased significantly in the pre-puberty group ($p = 0.003$). Height and weight gain were significantly higher in the puberty group ($p = 0.001$). These increases were for length; there was no significant difference for “the percentage of height for age” of both groups ($p> 0.050$). The increases of “weight percentages by age” were meaningless as statistics in the pre-pubertal group while in the puberty group they were significant ($p = 0.006$) [Table 2].

There was no statistically significant difference among age groups in terms of values of carboxyl-carboxylated osteocalcin, Δ-UCR, and UCR in the pre-puberty and puberty in comparison ($p >0.050$) [Table 2].

Carboxylated osteocalcin levels were decreased more in the puberty group than in pre-puberty group (p>0.050). It is seen that carboxylated osteocalcin values were reduced minimally in the pre-pubertal group, while there were minimal increases in the puberty group (p <0.050). UCR values did not change in the pre-pubertal group while showing an increase in pubertal groups (p> 0.050).

The values of Δ-UCR (0.11) having positive in the pre-pubertal group were observed to take a negative value in pubertal age groups (p> 0.050) [Table 2].

Table1. The comparison of the demographic characteristics and biochemical results of the patient and control groups

	* Patient Group (n=25) (Median) (min-max)	*Control Group (n=25) (Median) (min-max)	***P Value
Female (n)	11	13	****0.774
Age (year)	11.00 (4-17)	10.00 (3-17)	0.969
Weight (kg)	28.80 (12.00-68.50)	33.00 (12.00-75.00)	0.522
Height (cm)	140.00 (91.00-169.00)	139.00 (91.00-179.00)	0.861
**Percentage of weight for age (%)	89.90 (64.17-122.30)	94.00 (82.10-102.60)	0.053
**Percentage of height for age (%)	97.50 (81.40-107.30)	99.00 (88.90-102.10)	0.385
Carboxylated OC (cOC) ng/mL	15.40 (3.36-22.79)	6.15 (2.89-14.80)	0.076
Uncarboxylated OC (ucOC) ng/mL	8.71 (7.88-8.74)	8.2 (0.31-8.74)	0.163
UCR (ucOC/cOC)	0.56 (0.38-2.54)	0.83 (0.08-2.63)	0.118

* The initial (baseline) values of the patient group
** It indicates that should be percentage of weight and height for their age, according to the scales prepared for Turkish children (8).
*** Mann-Whitney U test
**** Chi-square test

Discussion

The growth of children is not the same at all ages due to features of pre-puberty and puberty. Monitoring the BMI of children is not thorough enough. In our study, we compared the height and weight goals according to chronological ages of the children instead of BMI. The results obtained from by the scale arranged for Turkish children has provided that the physiological increase from growth of pre-pubertal and pubertal children compared with the reference values for a prospective study.

There was no significant difference between the initial and final results of "the percentage of height for age" despite the significantly increased height of pre-puberty and puberty patients (p >0.050). The percentage of height for age, which upon initial measurement had no difference with the control group, showed no significant changes but a slight decrease after using VPA for a year (p>0.050). Our patients have provided the percentages of the height needed according to their age. These results suggested to us that the height growth of patients is not significantly affected by VPA treatment [Table 2].

It has been reported that the weight gain begins, especially in the first 3-6 months of treatment in 44-71% of patients with epilepsy, and is most common to occur when treated with VPA, carbamazepine, or gabapentin [9]. Some anti-epileptic drugs such as Topamax and Levetiracetam are known to cause weight loss [10, 11]. In some adult patients, it is suggested that VPA increases serum leptin levels, lipid accumulation caused by inhibiting to beta oxidation of mitochondrial fatty acids, the result of reducing palmitate connected to albumin to increase long chain fatty acids. It is leads to warning lipogenesis by increasing insulin and made increased appetite by lowering blood sugar [12, 13]. It has been reported that children who received VPA treatment have a 40% risk of weight gain at the onset of puberty [14].

While the values of the weight percentages by age had no difference at the beginning of the study, the values obtained at the end of the study were found significantly higher, particularly in the puberty group, (p = .006). It show that VPA used for one year caused significant weight gain in our patients, similar to other studies discussed above [12- 14] [Table 2].

Table 2. The distribution of initial (baseline) and final values of the study in the pre-puberty and puberty age group

	Pre puberty			Puberty* (n=25)		
* (n=25)	BMV (n=11) (min-max)	FMV (n=11) (min-max)	**P value	BMV (n=14) (min-max)	FMV (n=14) (min-max)	**P value
Height (cm)	111.00 (91.00-118.00)	114.00 (95.00-123.00)	0.003	155.00 (139.00-169.00)	158.00 (145.00-173.00)	0.001
PHA (%)	99.10 (81.40-107.30)	97.00 (81.80-100.00)	0.139	97.45 (93.30-103.50)	97.20 (92.90-103.40)	0.172
Weight (kg)	17.50 (12.00-22.00)	20.00 (15.50-26.20)	0.003	42.60 (828.00-68.50)	49.75 (32.00-70.20)	0.001
PWA (%)	92.80 (64.17-109.80)	93.70 (74.50-113.30)	0.374	85.50 (64.90-122.30)	88.15 (66.60-123.10)	0.006
cOC ng/mL	15.63 (8.42-22.79)	14.43 (7.16-22.81)	0.790	14.86 (3.36-22.76)	11.54 (5.10-22.80)	0.433
ucOC ng/mL	8.71 (7.88-8.73)	8.69 (6.23-8.740)	0.124	8.71 (7.88-8.74)	8.72 (5.85-8.73)	0.562
UCR	0.53 (0.38-1.03)	0.53 (0.20-1.21)	0.139	0.58 (0.38-2.34)	0.72 (0.25-1.70)	0.875
Δ-UCR	0.11 (-0.18-0.36)			-0.04 (-1.32-1.28)		***0.403

* BMV: Baseline Median Values, FMV: Final Median Values,
PHA: Percentage of Height for Age, PWA: Percentage of Weight for Age,
cOC: Carboxylated Osteocalcin, ucOC: Uncarboxylated Osteocalcin,
UCR: ucOC/cOC, Δ-UCR: The difference between UCR1 and UCR2
** Wilcoxon test
*** Mann-Whitney U test

Osteocalcin is a bone matrix protein which is synthesized from mature osteoblasts (Gla proteins). Osteocalcin's primary feature is its calcium binding property that is induced by three vitamin K dependent gamma- carboxyglutamic acid remnants. Osteocalcin's functions as a protein are not definitively known despite its role in the mineralization process [15]. Vitamin K is the cofactor of the five known Gla proteins in the human body. In order for these proteins to function well, the human body requires a sufficient amount of vitamin K supplement [16].

Urine and serum measurements of vitamin K do not provide adequate informa-

tion regarding the tissue levels. The ideal measurement is to directly test the gamma-carboxylation states of the Gla proteins in tissue. cOC, a small Gla protein that is synthesized in bones, and ucOC, that is found in the blood circulation, enables the analysis of the bodies' vitamin K levels. These are the primary indicators of vitamin K levels in bones [17, 18]. Dietary vitamin K is sufficient to the carboxylation of osteocalcin. Metabolic activity and the increase of osteocalcin production during the bone development and the skeleton growth increase the deprivation of vitamin K in bones. In case of inadequate dietary supplement, a subclinical vitamin K deficiency can occur due to the increased need. This increases bone turnover and therefore leads to osteoporosis by hindering children's bone densities from reaching a healthy level. In healthy adults, depending on the amount received, approximately 10-30% of osteocalcin becomes under-carboxylate (ucOC). Research conducted on adults, although unclear in the explanation of pathophysiological mechanism, has indicated that increased levels of ucOC have negative correlation with hip bone mineral density (BMD) and positive correlation with risks of bone fractures [6, 16, 18, 19]. There is very limited research on vitamin K levels and bone metabolisms of children [2-5, 20, 21, 22]. We haven't found any research on vitamin K levels of children who use anti epileptic drug (AED) and its effects on their bone mechanisms.

In the comparison between the pre-treatment levels of the patients and the control group, the cOC, ucOC, and UCR levels were statistically insignificant.

When we examined our patients in groups of pre-puberty and puberty, we observed slight decrease in the pre-puberty cOC and ucOC levels. UCR levels did not change and Delta-UCR had positive levels. It can be inferred from these results that, although statistically insignificant, the vitamin K levels in the bones weren't sufficient to meet the body's need (decrease in cOC), yet the overall vitamin K levels in the body hadn't been worsened (decrease in ucOC, stability in UCR, positive values of Delta-UCR). These results may indicate that, although we lack definitive information on how the VPA affects vitamin K levels in the bones in pre-puberty patients, at least it does not have adverse effects that can be observed in laboratory tests.

In the puberty group, statistically insignificant changes were observed in tests. cOC levels decreased, ucOC levels slightly increased, and UCR levels increased in accordance with that. It was also observed that delta-UCR levels were negative [Table 2]. These results indicate that in cases of the patients who experience puberty phase in which the bone growth is observed to be fast, the vitamin K levels in the body tend to worsen (increase in UCR) and insufficient for the body (decrease in cOC). Thus, the bone metabolism is adversely affected (the negative values of Delta-UCR).

Theuwissen et al. have found that 42 healthy volunteer children had high ucOC levels (3.4-96.9 ng ml) in their vitamin K status study [22]. Van Summeren et al. have found that the cOC, ucOC, and UCR rates in children (app. 31.3 ng/ml, 15.4 ng/ml, and 2.3 ng/ml) are noticeably high. They have discovered a distinctive correlation between bone indicators and these rates, and thus, they have established the suboptimal vitamin K levels in healthy children [3]. The ucOC levels in this study are higher than both the initial levels of the patient group and the levels of the control group in our research (app. 8.6 and 6.8 ng/ml). However, neither in Turkey nor in another country do these indicators have any reference values that are specific to age. The apparent difference in the ucOC levels between ours and that of Van Summeren et al., which share the same research methods, is difficult to comprehend due to the scarcity of research relevant to the topic, the absence of reference values, and the socioeconomic, geographical, and structural differences among societies. However, our cOC rates are similar (14.4 ng/ml). Similar to Van Summeren's research, vitamin K levels in the bodies have been observed to be suboptimal in the healthy children in our control groups and in epilepsy- diagnosed patients who are yet to receive medical treatment.

Kalkwarf et al. have found noticeable variations in ucOC percentages and established a significant correlation between a sufficient state of vitamin K (indicated through ucOC percentage) and decreased bone turnover [23]. In Kalkwarf's research, with a different method from our study, ucOC's proportion to the serum total osteocalcin was measured and considered as the ucOC percentage. Similar to many research studies in the field, we have directly measured serum cOC and ucOC levels with a commercial kit, using ELISA method and comparing them in terms of ng/ml [3, 4, 6, 21]. In our research, increased bone turnover and poor levels of vitamin K has been observed in puberty phase children who received VPA.

O' Connor et al., in their research conducted on 223 healthy girls between the ages of 3 to 16, have compared the percentages of bone indicators, BMD, and ucOC and have found a negative correlation between the BMD values obtained from lumbar vertebrae and ucOC. They have stated that a sufficient vitamin K level is related to increased BMD and such a level reduces bone turnover [5]. Our research exhibits similarities with O'Connor's in terms of research results.

In their research which was conducted through similar methods as ours, Van Summeren et al. has found that UCR levels that are generally thought to be indicators of vitamin K deficiency in the bones, are observed to be high in healthy pre-pubertal children. They have also stated that UCR is correlated in advanced puberty with the exhibited puberty stage, and that UCR levels change in parallel with high growth speed [4]. The relation between UCR and pubertal development has been indicated in previous research as well [3]. Similar to Van Summeren's, in our research, despite the well state of vitamin K levels in pre-pubertal patients, we have observed insufficient levels of vitamin K indicated through increased UCR, decreased cOC, and negative values of Delta-UCR [4]. This situation can be explained through the increased UCR levels induced by an imbalance between the amount of vitamin K metabolically required during growth and the amount received daily, as well as through the imbalance in the originally suboptimal vitamin K state of the body caused by the use of VPA for a year.

As a result of our research, we have concluded that vitamin K levels in pubertal patients are adversely affected and VPA use can contribute to the situation. In general, it has been observed that the use of VPA has greater effect on vitamin K levels in pubertal patients compared to the patients in the pre-puberty group. Use of VPA in children, especially those in the puberty phase when growth occurs faster, can cause decrease in bone development, decrease in body vitamin K levels, hindrance from reaching maximum bone mass, and increased risk of osteopo-

rosis in adulthood. Therefore, vitamin K supplementation may be considered for children who receive VPA treatment. However, this research should be supported by further research with broader participation and a longer study period.

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Competing interests

The authors declare that they have no competing interests.

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LUNG TRANSPLANTATION FOR SILICOSIS

SİLİKOZİSDE AKCİĞER TRANSPLANTASYONU

SILICOSIS

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Öz

Amaç: Silikozis, silika tozu inhalasyonunundan kaynaklanan bir meslek hastalığıdır. Akciğer transplantasyonu açısından, silikozis iyi belgelenmiş bir hastalık değildir. Bu yazıda silikozisden etkilenen hastaların perioperatif seyri ve sonuçları bildirilmektedir. Gereç ve Yöntem: Silikozis tanısı ile 5 hastaya tek akciğer transplantasyonu yapıldı, aynı dönem boyunca akciğer transplantasyonlarının % 6.4'ünü oluşturdu (5/77). Tüm hastalar erkek olup, yaş aralığı 34-41'dir.Beş hastanın ikisi diş teknisyeni, bir tanesi taş ocağı çalışanı, geri kalan iki hasta kot kumlama işçileri idi. Tüm hastalarda istirahat sırasında oksijen ihtiyacı duyan nefes darlığı vardı. Bulgular: Dört hastada sağ, bir hastada sol tek traflı akciğer tranplantasyonu gerçekleştirildi. Tüm hastalara anterior torakotomi uygulandı. Bir hastada sağ ana pulmoner arteri kontrol altına almak için sternuma transvers insizyon yapıldı. Ameliyat sırasında hemodinamik instabiliteye bağlı olarak iki hastada arteriovenöz ekstrakorporeal membran oksijenasyon desteği gerekti. Perioperatif mortalite yoktu. İki olgu ilk 24 saatte ekstübe edildi ve bir hastada uzamış entübasyon nedeniyle trakeostomi açıldı. Üç hasta 9, 21 ve 28. günlerde hastaneden taburcu edildi. Tartışma: Akciğer transplantasyonu, son dönem silikoz için tek küratif tedavi yöntemidir. Native akciğerin pnömonektomisi son derece zor olabilir. Yoğun plevral adezyonlar ve fibrotik hiler lenf düğümleri, preoperatif toraks BT taramasında değerlendirilmelidir.

Anahtar Kelimeler

Silikozis; Akciğer; Trasnplantasyon

Abstract

Aim: Silicosis is an occupational disease caused by inhalation of silica dust. In terms of lung transplantation, silicosis has not been a well-documented disease. This article reports the perioperative course and the outcome of patients affected by silicosis. Material and Method: Single lung transplantation was performed in 5 of 77 patients diagnosed with silicosis, who comprised 6.4% of all lung transplantations during the same period. All the patients were males, with an age range of 34–41 years. Of the five patients, two were dental technicians, one was a quarry worker, and the remaining two patients were jeans sandblasting workers. All the patients had dyspnea that required oxygen during rest. Results: Unilateral lung transplantation was performed in four patients for the right lung and in one patient for the left lung. All the patients were approached by anterior thoracotomy. In one patient, a sternum transverse incision was made to take control over the right main pulmonary artery. Arteriovenous extracorporeal membrane oxygenation support was required for two patients due to hemodynamic instability during the operation. There was no perioperative mortality. Two cases were extubated in the first 24 hours, and tracheostomy was performed in one patient because of prolonged intubation. Three patients were discharged from the hospital on days 9, 21, and 28. Discussion: Lung transplantation is the only curative treatment for end-stage silicosis. Removal of the native lung may be extremely difficult. Dense pleural adhesions and fibrotic hilar lymph nodes must be assessed at the preoperative CT scan of the thorax.

Keywords

Silicosis; ECMO; Lung Transplantation

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Introduction

Silicosis, an occupational disease caused by inhalation of silica dust, results in progressive and permanent lung damage [1]. There is no specific treatment for silicosis, and lung transplantation remains the only option for patients presenting with end-stage lung disease. According to the annual report of the International Society for Heart and Lung Transplantation, silicosis constitutes only 2.2% of patients undergoing lung transplantation [2]. In this article, we report the perioperative course and the outcome of five patients with silicosis who underwent lung transplantation since our program began.

Material and Method

Between July 2009 and July 2015, unilateral lung transplantation was performed in five patients (four patients for the right lung and one patient for the left lung) presenting with end-stage lung disease caused by silicosis. These patients constituted 6.4% (5/77) of the total number of patients who were operated on during the same period. Diagnosis was made by radiological findings on CT scan and history of exposure. The results of spirometry, arterial blood gas values, 6-min walking test, and ventilation–perfusion scintigraphy are presented in Table 1. Echocardiography showed no right side enlargement and tricuspid jet in any of these patients.

Table 1. Characteristics and preoperative evaluation

Patients No	1	2	3	4	5
Gender	M	M	M	M	M
Age	34	38	41	34	43
Occupation	dental prosthesis technician	jeans sandblasting worker	jeans sandblasting worker	dental prosthesis technician	quarrier
Exposure (year)	10	3	4	2	15
İnterval (year)	4	4	6	1	4
FEV1 % (L)	17 (0.61)	37 (1.48)	26 (0.97)	none	27 (0.83)
FVC (L)	42 (1.81)	35 (1.68)	48 (1.48)	none	81 (0.81)
FEV1/FVC	33	81	108	none	100
PaO2 mmHg	49	57	51	57	53
PaCO2 mmHg	45	49	44	51	50
V/Q scan (right/left)	78/22	44/56	47/53	48/52	42/58
6 MWT(meter)	250	170	200	230	310
PASP by RHC (mmHg)	37	none	none	36	80

FEV1, Forced expiratory volume at timed intervals of 1.0 second; FVC, Forced vital capacity; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; V/Q scan ventilation/perfusion lung scan; 6MWT, six-minute walk test; PASP, pulmonary artery systolic pressure;RHC, right heart catheterization

Patients were evaluated and listed for lung transplantation using the consensus committee criteria. However, pleural thickenings suggesting dense adhesions and extensive mediastinal fibrosis were reviewed in more detail for planning of the operation. In only one patient, standard anterior thoracotomy through the fifth intercostal space was the choice of incision that was extended to the contralateral side to split the sternum. Extreme care was undertaken using electro and argon beam cautery to control the bleeding from the chest wall during pneumolysis. However, pleural adhesions necessitate a longer time to remove the native lung, in addition to the hilar dissection that is an obvious challenge for surgeons. Thus, the recipient operation was started at the earliest time point possible to have more time for pneumonectomy and subsequent hemostasis before implantation of the donor lung. None of the patients underwent rethoracotomy due to hemorrhage.

Piperacillin–tazobactam was given as empirical antibiotic therapy for prophylaxis and in the early postoperative period. The antibiotic therapy was changed or was continued based on the donor culture results and postoperative early bronchoscopic findings. Immunosuppression therapy consisted of tacrolimus, mycophenolate mofetil, and steroids. The target whole-blood trough level of tacrolimus was 12–16 ng/mL. Steroid treatment was initiated at the time of graft reperfusion at a dose of 500 mg and then at 1 mg/kg per day during the first week.

Results

The characteristics and preoperative evaluation results of the patients are given in Table 1, and the operation and results are summarized in Table 2.

Table 2. The operation and postoperative evaluation results

No patients	Operation	Extracorporal support	ICU stay (days)	Hos.Stay (days)	Survi
1	Left	-	10	21	41 month
2	Right	A-V /V-V ecmo	14	28	28 month
3	Right	A-V ecmo	19	19	19 day
4	Right	-	4	9	3 month
5	Right	-	10	120	4 month

ICU, intensive care unit; AV, arterio-venous, V-V; veno-venous; ECMO, extracorporeal membrane oxygenation

Patient 1

Single lung transplantation of the left lung was performed in a 34-year-old male patient with a diagnosis of silicosis. This patient was the first successful lung transplantation case in our clinic. His symptoms, which had started 4 years earlier, included cough and shortness of breath. Silicosis was diagnosed based on clinical and radiological criteria. He worked as a dental technician for 10 years and had been exposed to silica particles. He had undergone inpatient treatment at various times since the year of diagnosis. He was admitted several times to the emergency department due to respiratory distress. He also required continuous oxygen support in the last year (5 L/min). The patient's preoperative pulmonary function test showed severe respiratory impairment (FEV1: 0.61 L 17%; FEV1/FVC: 33%; FVC: 1.81 L 42%). Echocardiography of both ventricles showed normal findings. Pulmonary artery systolic pressure (PASP) was measured as 27 mmHg. In the V/Q lung scan examination, the right lung perfusion was 73% and the left lung perfusion was 27%.

The donor was a 13-year-old male. Brain death had occurred as a result of subdural hematoma due to head trauma in a vehicle

accident. The duration of mechanical ventilation was 4 days, and PaO2/FiO2 was 550 mmHg in the arterial blood gas test. Bronchoscopy showed no purulent secretions.

Single lung transplantation was performed with left anterior thoracotomy. Preoperative PASP was measured as 40 mmHg using the Swan-Ganz catheter. The patient tolerated one lung ventilation, and hence there was no need for extracorporeal life support. Ischemia time was 6 h. The length of stay in the intensive care unit (ICU) was 10 days. On the 21st day, he was discharged from the hospital. After 8 months of follow-up, pneumonia was detected in the graft lung. Polymerase chain reaction using throat swabs and bronchial lavage samples showed the presence of H1N1 virus. The patient was treated with oseltamivir. Rejection was excluded using transbronchial biopsy. During the follow-up, several social and educational problems that have a significant effect on the post-transplantation course were identified. The patient showed chronic rejection at the end of the third year because he stopped taking the immunosuppressive drugs for a certain period of time.

Patient 2

A 38-year-old male jeans sandblasting worker was diagnosed with silicosis based on clinical and radiological findings. He was exposed to silica dust for 3 years. Single right lung transplantation was performed 4 years from the time of diagnosis. He required oxygen support at 2 L/min in the last year. Pulmonary function test results were as follows: FEV1: 1.48 L 37%; FVC: 1.68 L 35%; FEV1/FVC: 37%. In the 6-min walking test examination, he was desaturated and walked 170 m with oxygen support. The V/Q scan study revealed respiratory function of 44% in the right lung and 56% in the left lung. Echocardiography examination showed EF measured at 50% and mild suppression of the left ventricular function. PASP was normal. Hence, right heart catheterization was not performed.

The donor was a 24-year-old male who was diagnosed with brain death due to head trauma. The duration of mechanical ventilation was 4 days, and PaO2/FiO2 was 667 mmHg in the arterial blood gas evaluation. Chest radiography and bronchoscopic findings were normal. Right anterior thoracotomy was planned for single lung transplantation. During the operation, arteriovenous extracorporeal membrane oxygenation (ECMO) support was needed because of hemodynamic instability. An ECMO cannula was inserted into the femoral artery. A-v ECMO was converted to v-v ECMO at the end of the operation, and the patient was extubated on the second day. He was extubated from mechanical ventilation on the postoperative third day. He was monitored for 14 days in the ICU and was discharged on the 28th day. Since the patient did not have much familial and social support, he died due to graft rejection on the following 28th month.

Patient 3

A 41-year-old male patient was referred to the lung transplantation clinic due to a diagnosis of silicosis. The patient, who had been diagnosed 6 years earlier, was a jeans sandblasting worker for the past 4 years. He required 4 L/h of oxygen daily and walked 200 m in the 6-min walking test. Pulmonary function test results were as follows: FEV1: 0.97 L 26%; FVC 1.48 L 48%; FEV1/FVC: 108%. The V/Q scan examination showed respiratory function of 53% in the right lung and 47% in the left lung. Echocardiography showed EF measured at 65%, and PASP was 15–20 mmHg. Hence, right heart catheterization was not performed.

The donor was a 27-year-old male who was diagnosed with brain death due to drug intoxication. Mechanical ventilation duration was 7 days, and arterial blood gas test showed PaO2/FiO2 of 549 mmHg. Right anterior thoracotomy incision was scheduled for the lung transplantation. Arteriovenous ECMO support was required in this patient due to cardiac arrest on induction. Femoral artery and vein were used for cannulation. We were not able to wean the patient from the ECMO and he died on the 19th postoperative day due to multiple organ failure. Unfortunately, there was no opportunity for an adequate evaluation of the neurologic status of this patient after the operation.

Patient 4

A 34-year-old male patient was admitted to the emergency room due to sudden onset of dyspnea and pneumothorax detected in both lungs. The patient was referred to the lung transplantation clinic after acute treatment. He had worked as a dental technician for 15 years; silicosis was diagnosed based on clinical and radiological findings. He needed 3 L/min of oxygen daily. Echocardiography results were as follows: EF 65%, PASP 20 mmHg. PASP 36 was measured at the right heart catheterization.

The donor was a 52-year-old male patient. Brain death had occurred in this patient due to cerebrovascular disease. Arterial blood gas test revealed PaO2/FiO2 of 450 mmHg. Bronchoscopy and radiological findings were clear. Single lung transplantation was performed via right thoracotomy. The postoperative course was uneventful. After ICU admission for 4 days, he was discharged on the ninth postoperative day. Bronchus intermedius narrowing was detected on the third month in a routine check-up bronchoscopy. There was no active complaint. Rigid bronchoscopy was planned for bronchial dilation to prevent progression of the narrowing. Active bleeding from the right main bronchus occurred during the operation. Despite the urgent thoracotomy, he died due to asphyxia and bleeding.

Patient 5

The patient was a 45-year-old male with a diagnosis of silicosis and had been followed up for 3 years. He depended on oxygen at 2 L/min daily for the past year. His occupation was ship blasting work for the past 15 years. The pretransplant evaluation results of the pulmonary function test were as follows: FEV1: 0.83 L 27%, FVC 0.81 L 100%; FEV1/FVC: 125%. Arterial blood gas results were measured as pCO2 of 53 mmHg and pO2 of 50 mmHg. He walked 352 m in the 6-min walking test. The V/Q lung scan examination showed right lung perfusion of 52% and left lung perfusion of 48%. PASP was measured at 25 mmHg on echocardiography, 80 mmHg on the right heart catheterization. Ejection fraction was 65%.

The donor was a 57-year-old male who was diagnosed with brain death due to a brain aneurysm. Arterial blood gas test showed PaO2/FiO2 of 392 mmHg. Bronchoscopy and radiological findings were clear. Single right lung transplantation was planned. We believed it would be difficult to perform pulmonary

artery dissection due to the hilar adhesions observed in the patient's preoperative chest CT evaluation. We performed transverse sternal incision in addition to right anterior thoracotomy. Pulmonary arterial bleeding occurred during the operation, and the intrapericardial right pulmonary artery was taken under control. Hemodynamics during the operation were stable. Ischemia time was 5 h. He was extubated 24 h after the operation and was later monitored for 10 days in the ICU. The patient required intermittent CPAP and was again intubated due to respiratory distress on the 15th day. Tracheostomy was performed. Despite being provided the maximum physical and mental support, the patient was extremely reluctant to cooperate with the transplantation team, and his condition never recovered so that he could be discharged from the hospital.

Discussion

Silicosis is a disease that affects not only the lung parenchyma but also the pleural spaces and the pulmonary and mediastinal lymphatics. Clinical expression of this disease varies significantly depending on the intensity and duration of exposure and host defense [3]. Thus, as with any other indications of lung transplantation, it is mandatory to make an individualized decision for silicosis patients.

Compared with other indications of lung transplantation, patients with silicosis resemble those presenting with idiopathic pulmonary fibrosis (IPF) in terms of respiratory mechanics and pulmonary hemodynamics [4]. However, patients with silicosis are relatively young and robust with otherwise good physical condition and remain stable until advanced respiratory failure develops. Thus, patients can still be good candidates for transplantation even if spirometric values are significantly decreased. The right heart performance and pulmonary pressures also remain relatively stable along the course of the disease. Theoretically, the exposure of lungs to silica would be similar in both lungs, but the perfusion scan may reveal a significant difference. This gives important information for surgeons not only about the side to be removed but also about the possible need for perioperative extracorporeal support.

Despite the several postoperative advantages of a silicosis patient, extreme difficulty may be encountered during the removal of the native lung. We believe that this is the most crucial part of patient selection and probably the major determinant of the postoperative course. Excessive bleeding during pneumolysis is unavoidable, and requirement of extracorporeal support for any reason significantly increases blood loss resulting in perioperative hemodynamic instability.

Preoperatively, the CT scan of the thorax must be carefully assessed for dense pleural adhesions and fibrotic hilar lymph nodes. However, our experience shows that preoperative images do not correlate well with perioperative findings. Therefore, we believe that the surgical team must be prepared for the worst scenario when a patient with silicosis is considered for transplantation. We extensively use electro-thermal bipolar tissue sealing system and argon laser during pneumolysis and spend a longer time to achieve hemostasis after the removal of the native lung. Mediastinal dissection of the hilar structures is extremely dangerous in some cases because of fibrosis. Thus, another precaution we took in the present cases is an intrapericardial approach to the main PA for quicker and safer control. The intrapericardial space remains intact despite dense mediastinal fibrosis. When the native lung is removed, the rest of the operation becomes straightforward.

Perioperative heparinization for extracorporeal support increases bleeding and therefore has a negative effect on the postoperative course. However, it seems that ECMO is frequently used for patients undergoing lung transplantation for various indications. In a case series previously reported by Mao et al., four of five patients required ECMO [5]. Although we immediately put one of our patients on ECMO due to cardiac arrest upon induction, compared with the series of lung transplantations, the rate of ECMO use in our experience is still higher. Our experience suggests that those patients who likely require extracorporeal support perioperatively should be listed for transplantation with extreme caution. Regarding the postoperative hemodynamics following a single lung transplantation, we believe that double lung transplantation should be undertaken only in those patients presenting with limited pleuroparenchymal adhesions and mediastinal fibrosis.

In the long term, progressive fibrosis in the contralateral lung results in a refractory dry cough in some patients. Oral codeine is the drug of choice for these patients. Eventually, the contralateral native lung becomes totally fibrotic with zero perfusion without causing any clinical problem.

Depending on the end-stage lung disease, symptoms are worsened by poor living conditions and psychosocial status. In those cases, long-term survival may not be achieved unless these conditions are corrected after successful transplantation of the lung. Our patients, especially jeans sandblasting workers, had poor quality of life. When they applied to our transplant clinic, they had poor nutrition and condition. Immunosuppressive (anti-rejection) drugs are important to protect the transplant organ after lung transplantation. With the other patient who was a dental technician, we were faced with psychosocial problems. In the third year, rejection developed after the discontinuation of immunosuppressive drugs. Long-term survival cannot be achieved based solely on using correct surgical standards; it must also involve correcting poor living conditions and psychosocial situations.

Conclusion

Our limited experience suggests that lung transplantation is an acceptable option for patients with silicosis. However, the perioperative course might be technically challenging for the surgical team and therefore has to be carefully planned. The improvement of living conditions and poor physical condition is required to achieve long-term survival.

Competing interests

The authors declare that they have no competing interests.

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PATIENTS WITH MORTALITY AFTER ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

MORTALİTY AFTER ENDOSCOPİC RETROGRADE CHOLANGİOPANCREATOGRAPHY

MORTALITY WITH ERCP

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Öz

Amaç: Endoskopik retrograt kolanjiyopankreatografi; safra yolları, pankreatik yollar ve periampüller bölge hastalıklarının tanı ve tedavisi için uygulanan nitelikli ama invazif bir işlemdir. Komplikasyonlar için risk faktörleri bilinen veya şüpheli premorbid durumlar, anksiyete ile ilişkili sorunlar ve yetersiz analjezidir. Bu çalışmada, girişimin komplikasyonları ve girişimle ilişkili mortalite incelendi. Gereç ve Yöntem: 2011 ile 2016 yılları arasında rutin monitorizasyon ve standart sedo-analjezi protokolü ile elektif veya acil endoskopik retrograt kolanjiyopankreatografi uygulanan 1471 hasta geriye dönük şekilde incelendi. Girişim sırasında spesifik (cerrahi) ve non-spesifik (kalp-damar, solunum) komplikasyon gelişen ve yoğun bakım ünitesinde ex olan hastalarda yaş, cinsiyet, vücut kitle indeksi, ASA sınıfı, Charlson Komorbidite İndeksi, APACHE II skoru, girişim süresi, kullanılan ilaçlar, komplikasyonlar ve teröpatik girişimler değerlendirildi. Bulgular: Girişim sırasında komplikasyon gelişen ve yoğunbakım ünitesine yatırılan 10 hastanın 7'si (%0,47) ex oldu ve bu hastalarda ortalama Charlson Komorbidite İndeks skoru 3,00±0,81 iken ortalama APACHE II skoru 38,71±4,07 ve beklenen mortalite 88,22±7.23 idi. Tartışma: Endoskopik retrograt kolanjiyopankreatografide, sedason yönteminden bağımsız olarak mortaliteyi artırabilecek risk faktörlerine karşı standart monitorizasyon uygulanmalı ve hasta seçiminde dikkatli olunmalıdır. ASA skorundan ziyade APACHE II skoru ve Charlson Komorbidite İndeksinin kullanılması mortalitenin öngörülmesi açısından daha etkin olabilir.

Anahtar Kelimeler

Endoskopik Retrograt Kolanjiyopankreatografi; Sedo-Analjezi; Monitorlü Anestezi Bakımı; APACHE; Mortalite

Abstract

Aim: Endoscopic retrograde cholangiopancreatography is a high quality but invasive procedure performed for diagnosis and treatment of biliary tract, pancreatic tract and periampullary region diseases. Risk factors for complications include known or unsuspected premorbid conditions, problems related to anxiety and insufficient analgesia. Material and Method: We retrospectively reviewed 1471 patients who underwent elective or emergent Endoscopic retrograde cholangiopancreatography with routine monitoring and standard sedoanalgesia protocol between 2011 and 2016. Patients who had specific (surgical) and non-specific (cardiovascular, respiratory) complications during procedure and admitted to ICU were selected. Age, gender, body mass index, ASA class, comordities, duration of procedure, drugs used, complication and therapeutic interventions were assessed in remaining patient who died in ICU. Results: 10 patients had complications during procedure and internalize at ICU. 7 of them (0,47%) had died. In mortal patients, mean CCI score was 3.00±0.81, while mean APACHE II score was 38.71±4.07 and mean expected mortality was 88.22±7.23. Discussion: In conclusion, one should be careful in standard monitoring and patient selection in addition to physical conditions against risk factors that may increase mortality regardless of sedation method used in Endoscopic retrograde cholangiopancreatography. Using APACHE II score and CCI rather than ASA score can be more effective for prediction of mortality.

Keywords

Endoskopik Retrograt Kolanjiyopankreatografi; Sedo-Analjezi; Monitorlü Anestezi Bakımı; APACHE; Mortalite

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a high quality but complex procedure in the diagnosis and treatment of biliary tract, pancreatic tract, and periampullary region disorders [1]. ERCP involves combined use of X-ray and a long flexible tube, namely an endoscope. The physician can visualize the lumen of the stomach and duodenum through the endoscope and inject dye into the biliary and pancreatic ducts to enable visualization on X-ray [2].

The Ccomplication rate following ERCP varies from 5% to 10% [3]. The Vvast majority of such complications (>90%) are mild or moderate. Nevertheless, and it is important to classify these complications as specific or non-specific in order to prevent and reduce complications [4]. Non-specific complications include those which that could might occur during all any endoscopic procedure,s such as hemorrhage or perforation due to passage of the endoscope, adverse effects caused by drugs used during the procedure, cardiopulmonary events, and desaturation. Specific complications include pancreatitis, sepsis, cholangitis, and hemorrhage and perforation caused by endoscopic sphincterotomy [5].

It is essential to determine risk factors for ERCP complications, which preferentially requires selection of eligible patients (Table 1). The risks can be detected in a timely way by preoperative assessment and appropriate monitorization monitoring [3,6,7].

Table 1. Risk factors for ERCP and complications

1. Anesthesia outside the operating room (physical conditions, monitorization, equipment)
2. Procedure-related (pancreatitis, bleeding, perforation)
3. Patient characteristics (gender, comorbidities)
4. Disease-related (history of pancreatisis, presence of Oddi sphincter dysfunction requiring canullation of pancreatic duct)
5. Difficulty in access to patient, prone position
6. Hyoscine-N-butylbromide

In the previous studies,Previous studies have focused on specific complications and ERCP failure . have been focused; hHowever, there is are fewlimited number of studies on non-specific complications and outcomes.

In our study, we aimed to overview patients with specific and non-specific complications who were admitted to the intensive care unit following ERCP and had a fatal course in our facility.

Material and Method

We retrospectively reviewed 1471 patients who underwent elective or emergent ERCP at a semi-prone position under pharyngeal anesthesia (lidocaine spray) with routine monitoring (including ECG, non-invasive BP, SpO2) and standard sedoanalgesia protocol (midazolam 0.02 mgkg-1; fentanyl, 1 mgkg-1; propofol 1 mgkg-1) between 2011 and 2016 after approval of the local ethics committeetee of Umraniye Training Hospital. We identified 10 patients who developed specific (surgical) and non-specific (cardiovascular, respiratory) complications during the procedure and were admitted to the ICU. Of these, 3 patients who were discharged to the ward after treatment and follow-up in ICU were excluded. Age, gender, body mass index (BMI), ASA class, comorbidities, indication, duration of procedure, drugs used, complications, and therapeutic interventions were assessed in the remaining patients who died in the ICU.

Results

Of 10 patients with complications during the procedure, it was found that one 1 patient died during the procedure in the at ERCP unit and 6 patients died in theat ICU, while remaining the other 3 patients were discharged to the ward after treatment in the ICU. Table 2 presents demographic characteristics, comorbidities, and procedure-related data of the patients who died.

Table 3 presents potential confounders (APACHE II score, Charlson Comorbidity Index (CCI), emergency status), surgical and medical complications, and cause and time of death. In our patients, the mean CCI score was 3.00±0.81, while the mean APACHE II score was 38.71±4.07. The Mmean expected mortality was 88.22±7.23.

Discussion

Although ERCP is a minimally invasive procedure, it carries a significant risk due to both anesthetic interventions outside the operating room and the presence of comorbidities and advanced age.

The selection of eligible patients is the most important measure for preventingion of complications. History of acute pancreatitis within prior weeks, previous MI, insufficient endoscopic and surgical experience of the endoscopy operator, history of hypersensitivity against contrast material, poor performance score for surgery, severe cardiopulmonary disorders, bleeding disorders, and anticoagulant use are contraindications for ERCP [8]. In these procedures, which are generally performed with sedoanalgesia protocols, one should be careful in monitorization monitoring forregarding potential complications, including mortality, regardless of sedation method used [9]. In ASA guidelines, standard monitoring includes assessment of hemodynamic, oxygenation, pulmonary ventilation, and consciousness. , and ECG, pulse oximetry, non-invasive blood pressure monitorizationmonitoring, BIS, and capnography are recommended for theise purposes. Several analgesic and anesthetic agents can be used based on the procedure and patient characteristics. ETCO2 monitoringrization reduces risks since access to the respiratory tract is limited in ERCP [10].

It was has been shown that BIS monitorization monitoring is

Table 2. Characteristics of fatal cases

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age [year]	58	86	85	52	95	74	41
Gender [F/M]	M	F	M	M	M	F	F
BMI	29	33	30	34	31	19	24
ASA	2	3	3	2	3	3	2
Number of procedure	1	1	3	3	1	1	1
Duration of procedure	15	30	30	25	20	60	45
Comorbidity	DM, HT, CAD, Smoking	DM, HT, CHF	COPD,HT Smoking	SEPSIS Cholecystitis	DM, CHF, CAD Smoking	DM, HT, CHF AF, OSAS	Hyperthyroidism

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coroner Artery Disease, CHF: Congestive Hearth Failure, AF: Atrial Fibrillation, OSAS: Obstructive Sleep Apnea Syndrome

Table 3. APACHE II, CCI, surgical and medical complications, and cause and time of death in fatal cases

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Mean±SD
Apache II	36	42	38	41	41	42	31	38.71±4.07
Predicted mortality	85.1	93.2	88.4	92.2	38.9	93.2	73.3	88.22±7.23
CCI	3 Severe	4 Severe	3 Severe	3 Severe	4 Severe	2 moderate	2 moderate	3.00±0.81
Emergent	+	+	+	+				
Surgical complication [Pneumothorax]		+	+			+	+	
Respiratory arrest	+			+	+			
Severe dysrhythmia				+	+			
Cause of death	AMI	Sepsis	Sepsis	AMI	AMI	Sepsis	Sepsis	
Time of death	During procedure	Day 12	Day 2	Hour 24	Hour 24	Day 2	Day 14	

more appropriate than scoring systems (Aldrete) in cases where communication with patient is required [11].

In our ERCP unit, standard monitoring with ECG, pulse oximetry, and non-invasive blood pressure monitoring is employed in all patients and a laryngoscope, anesthesia device, oxygen source, defibrillator, emergent drugs, aspirator, and BIS monitorization monitoring are readily available during ERCP. Standard monitoring was performed in all fatal cases who underwent ERCP in our unit, where all physical conditions and equipment are available.

It was has been shown that hypoventilation which couldn't be detected by routine monitoring and clinical assessment was detected by capnography in children who underwent GI endoscopy under conscious sedation [12]. Lack of ETCO2 monitoring is one of the limitations of our study.

According to the WHO, chronological age alone isn't a contraindication for ERCP or a risk factor for ERCP-related complications [13]. It has been reported that frequency of failure, hypoxia, and bleeding due to sphincterotomy is increased by advancing age and that clinicians should be more careful foralert to complications in elder individuals [14], although it was shown that ERCP can be safely employed for diagnostic and therapeutic purposes in elder individuals in addition to infants and, children and elder individuals [15-18]. Elder individuals have a greater tendency to hypoxia, hypotension, and arrhythmia [19-21].

In our study, 4 of the non-survivors were at an advanced age according to WHO criteria. Of these, 3 patients died due to sepsis while one patient died due to acute myocardial infarction.

It is well-known that obesity carries risk due to physiopathological (cardiac and respiratory) changes. Although there is no study evaluating the relationship between sedoanalgesia and BMI, it is obvious that obesity comprisesrepresents an additional challenge in the semi-prone position for the anesthesiologist. In our study, presence of BMI>30 in the 4 patients who died suggests that obesity can be an independent risk factor for mortality in ERCP.

Although female gender comprises is a risk factor for surgical complications, it was reported that the results may change in a larger sample size [4]. There are studies reporting that gender is no risk factor [22,23]. In our study, there was no significant difference in gender (3 female and 4 male). We think that our sample size is too small to draw a conclusion.

Another parameter that may influence on mortality is ASA risk scoring. It is widely used in surgical practice in order to identify risk for sedation and anesthesia; however, it is inadequate to determine risk in ERCP procedures and can be misleading. In our study, 4 of 7 patients had ASA III score with expected mortality of 1.8-4.3 % whereas 2 had ASA II score with expected mortality of 0.27-0.40 %. A Ffatal course despite low expected mortality was attributed to the fact that expected risk in ERCP is more loosely related to specific complications which that aren't included in the ASA scoring [24].

The APACHE II (Acute Physiology and Chronic Health Evaluation) scoring system is based on worste or most critical physiological and laboratory parameters within the first 24 hours. It is used in adults and provides information regarding estimated mortality rate. In our study, among the 7 patients who died, the minimum APACHE II scores ranged from 31 to 42. The was 31 whereas maximum score was 42 among 7 patients died. Mmean APACHE II score was 38.71±4.07 and the mean expected mortality was 88.,22±7.23 (Table 3).

The CCI (Charlson Comorbidity Index) is a scale for assessment ofassessing comorbidity. The index (mild, moderate, severe, and very severe) is calculated by adding scores of each comorbid condition plus an additional one point for every 10 years after 40 years of age. In our study, the CCI was moderate in 2 and severe in 5 cases. The Mmean CCI was 3.00±0.81 among patients. APACHE II and CCI were are considered to be more significant than ASA score as a mortality index in elective ERCP procedures. We think that APACHE II and CCI can providebe more-accurate guiding for prediction of mortality in ERCP procedures.

Repeated ERCP procedures due to failure or indication can comprise a risk for post-ERCP pancreatitis and perforation. In adults, endoscopy accounts for 75% of esophagus perforations. The Ddistal esophagus adjacent to the cricopharyngeal muscle is the most commonly involved portion. On a CT scan, pneumomediastinum, mediastinitis, and contrast material extravasation can be seen. Pleural effusion or pneumothorax may develop within 12-24 hours [5]. In our study, 2 patients underwent repeat ERCP (third procedure)] in emergent conditions. Of these, one patient was admitted to the ICCIU due to intraoperative respiratory distress, diffuse subcutaneous emphysema, and pneumothorax and another patient due to severe dysrhyyhthmia and respiratory arrest. The patient with pneumothorax died due to septic shock in on the hour 48 after the procedure while the patient with respiratory arrest died due to acute myocardial infarction inon the hour 24 [25].

In some studies, it has beenSome studies have reported that complications are associated more strongly with the experience of the endoscopy operator is importantthan with the rather than number of procedures for complicationsthey have per-

formed [26]. It has beenwas reported that an endoscopy operator should complete at least 180 procedures in order to perform ERCP safely [(6]]. Our ERCP unit is an academic clinic providing education and ERCP is performed under the supervision of experienced endoscopy operators.

Hyoscine-N-butylbromide is an anti-cholinergic agent that is widely used to achieve duodenal relaxation during ERCP and may comprise a risk for tachyarrhythmia and anaphylaxis. In a study ofn 1177 cases, ChristensenCristian et. al. evaluated complications of ERCP and reported that Hyoscine-N-butylbromide doses >40 mg areis a risk factor for complications in multivariate analysis [27]. Özaslan et .al. observed ventricular tachycardia, severe hypotension, and reversible AMI after 4 doses (20 mg; IV) of Hyoscine-N-butylbromide [28]. In our study, we also observed AMI after intravenous Hyoscine-N-butylbromide administration (>40 mg) and the patient died.

Infections following ERCP are the most important frequent causes of procedure-related morbidity and mortality. Four of the 7 fatal patients (%0.33%) of total ERCP patients) died due to surgical complication and subsequent sepsis in our study. Tachycardia, hypertension and enhanced sympathetic activity may trigger myocardial ischemia or even AMI in patients at risk. The Rremaining 3 patients (%0.20% of total ERCP patients) died due to severe dysrhythmia and dyspnea followed by AMI (non-specific complication) in our study [5]. Of the 7 fatal cases, 4 were emergent cases. Of these, 2 patients died due to AMI including one patient who died during the procedure. We think that this outcome might be attributed to emergent conditions.

In a review including 21 studies (16,685 patients), 6.85% of patients had specific complications with a mortality rate of 0.33%. In another review including 14 prospective studies (12,973 patients), non-specific complications were assessed. It was found that 1.33% of patients had non-specific complications with a mortality rate of 0.87% [29]. In agreementConsistent with the literature, the mortality rate was 0.47% among the 1471 patients in our study.

In conclusion, one should be careful about standard anesthesia monitoring during the ERCP procedure. In selecting patients, physical conditions should be carefully balanced against risk factors that may increase mortality regardless of sedation method used. In conclusion, one should be careful in standard monitoring and patient selection in addition to physical conditions against risk factors that may increase mortality regardless of sedation method used in ERCP which is an out-of-operating room anesthetic procedure. The patients should be informed about the risks ofregarding mortality and potential complications by taking comorbidities into account. We think that using the APACHE II score and CCI rather than the ASA score can be more effective for predictingon of mortality.

Competing interests

The authors declare that they have no competing interests.

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CHANGES IN MPV, PCT AND OTHER LABORATORY PARAMETERS IN CHILDREN WITH ADENOVIRUS GASTROENTERITIS

ADENOVİRÜS GASTROENTERİTLİ ÇOCUKLARDA MPV, PCT VE DİĞER LABORATUVAR PARAMETRELERİNDEKİ DEĞİŞİKLİKLER

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Öz

Amaç: Enterik adenovirüsler çocuklarda akut ve uzamış ishal nedeni olarak rota virüslerden sonra en sık görülen ikinci viral gastroenterit ajanıdır. Ortalama trombosit hacmi (MPV), trombosit fonksiyon ve aktivasyonu gösteren bir belirteçtir. MPV, farklı inflamatuar ve enfeksiyöz durumlarda, sistemik inflamasyonun şiddetine göre artış ya da azalış gösterebilmektedir. Bu çalışmanın amacı; adenovirüs gastroenteriti olan çocuklarda bazı trombosit indekslerinde ve diğer laboratuvar parametrelerindeki değişikliklerin değerlendirilmesidir. Gereç ve Yöntem: Adıyaman Kamu Hastaneleri Birliği Genel Sekreterliği'ne bağlı ilçe sağlık tesislerinde Ocak 2014 - Aralık 2016 tarihleri arasında akut adenovirüs gastroenteriti tanısı konularak klinikte takibe alınan 5 yaş altı 61 hasta ile 64 sağlıklı kontrol çalışmaya alındı. Bulgular: Adenovirüs gastroenteriti olan 61 çocuğun 29'u kız, 32'si erkek olup hastaların yaş ortalaması 23.70 ±18.8 ay (2-60). Sağlıklı 64 çocuktan oluşan kontrol grubunun ise; 29'u kız, 35'i erkek olup, yaş ortalaması 24,87±14,81 ay (1-54). PCT ile PLT arasında ise pozitif yönde anlamlı ve yüksek derecede korelasyon tespit edildi. WBC, HGB, AST' nin tanısal ayırt ediciliğinin olabileceği tespit edildi. Ayrıca adenovirüs gastroenteritinde PCT'nin ve MPV'nin tanısal ayırt ediciliğinin olmadığı tespit edildi. Tartışma: Adenovirüs gastroenteritli hastalarda MPV değeri kontrol grubu ile karşılaştırıldığında anlamlı olarak düşük bulundu. Bu nedenle MPV'nin adenovirüs gastroenteritlerinde negatif akut faz reaktanı olarak kullanılabileceği düşünüldü.

Anahtar Kelimeler

Ortalama Trombosit Hacmi; PCT; Adenovirus; Gastroenterit

Abstract

Aim: Enteric adenoviruses are the second most common cause of acute and prolonged diarrhea due to viral gastroenteritis after rotaviruses. Mean platelet volume (MPV) is a marker of platelet function and activation. MPV can increase or decrease based on the severity of systemic inflammation in various inflammatory and infectious conditions. The aim of this study was to evaluate the changes in some platelet indices and other laboratory parameters in children with adenovirus gastroenteritis. Material and Method: A total of 61 patients aged under 5 years who were diagnosed with acute adenovirus gastroenteritis in the county healthcare facilities affiliated with the Adiyaman General Secretariat of Public Hospitals between January 2014 and December 2016 and clinically followed-up at the clinic were included in the study together with 64 healthy control subjects. Results: The 61 patients with adenovirus gastroenteritis consisted of 29 females and 32 males with a mean age of 23.70 ±18.8 (2-60) months. The 64 healthy children in the control group consisted of 29 females and 35 males with a mean age of 24.87±14.81 (1-54) months. We found a significant and highly positive correlation between PCT and PLT. WBC, HGB, AST were found to have potential value for the differential diagnosis. We also found that PCT and MPV had no diagnostic value in the differential diagnosis of adenovirus gastroenteritis. Discussion: The MPV value was significantly lower in the adenovirus gastroenteritis patients than the control group. We therefore believe that MPV could be used as a negative acute phase reactant in adenovirus gastroenteritis.

Keywords

Mean Platelet Volume; PCT; Adenovirus; Gastroenteritis

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Introduction

Adenoviruses are double-stranded DNA viruses of the Adenoviridiae family. They have seven types from A to G with more than 50 serotypes and can infect many tissues such as the respiratory system, the eye and the gastrointestinal system [1,2]. Enteric adenoviruses are the second most common cause of acute and prolonged diarrhea due to viral gastroenteritis after rotaviruses. Pediatric gastroenteritis is known to cause severe symptoms and signs such as nausea, diarrhea, electrolyte imbalance and even death, especially in small children and infants [3-5]. Epidemics of adenovirus gastroenteritis can occur as virus excretion continues for a short time after recovery [6].

Mean platelet volume (MPV) is a marker reflecting platelet activation and function and can be easily measured by routine whole blood count devices [7,8]. Platelets are known to have an important role in the pathogenesis of diseases associated with local or systemic inflammation [9,10]. MPV has been shown to increase or decrease in various infectious and inflammatory disorders [11,12]. Changes in MPV and platelet functions have been reported in gastroenteritis cases due to rotavirus, Entamoeba histolytica and non-infectious agents. However, we did not come across any previous studies on the MPV response in adenovirus gastroenteritis. This is the first study in the literature evaluating the effect of adenovirus gastroenteritis on platelet function parameters in laboratory tests performed at intake. The aim of the study was to compare MPV values and other laboratory tests in adenovirus gastroenteritis patients and a control group under the age of 5, and also to investigate whether MPV and PTC values have diagnostic value in adenovirus gastroenteritis.

Material and Method

A total of 125 cases, under the age of 5 years, consisting of 61 patients who had presented to the pediatric outpatient department at the county healthcare facilities affiliated with the Adıyaman General Secretariat of Public Hospitals between January 2014 and December 2016 with a symptom of diarrhea and who were diagnosed with acute adenovirus gastroenteritis and clinically followed-up and 64 healthy control subjects were included in this retrospective, controlled and sectional study. The data in the hospital information management system of adenovirus gastroenteritis patients and the healthy children seen between the above dates were retrospectively reviewed and the results of the laboratory tests conducted at presentation were statistically analyzed. In total, the data of 3397 children under the age of 5 years who presented to the relevant health institution between January 2014 and December 2016 due to diarrhea were reviewed. We excluded patients with a history of drug use (antibiotics or other drugs), anemia, co-infection, chronic disease, and those with no adenovirus on fecal analysis or where other factors were found on macroscopic/microscopic fresh stool analyses or stool culture samples, leaving 61 adenovirus gastroenteritis cases in the patient group. The control group consisted of 64 age-matched healthy children who presented to the same healthcare institution for a routine check. The necessary official permissions and the ethics committee approval were obtained from the relevant institutions before the study. Demographic characteristics, whole blood count (CBC) and C-reactive protein (CRP) values and other biochemical test results at presentation of all children included in the study were evaluated. Our aim was to compare MPV values between the two groups and to investigate the diagnostic value of MPV as a marker in adenovirus gastroenteritis.

We only included the data of the cases where the CBC analysis results were available within 45 minutes of drawing the venous blood. The volume impedance method on the Abbott Cell-Dyn 3700 hematology analyzer system (Abbott Diagnostics Image 3700SL) was used with standard tubes containing a fixed amount of K3-EDTA for the CBC analyses. CRP levels were measured with the turbidimetric experiment method using the Abbott Architect 4000 system and the Abbott 8000 modular system (Abbott Diagnostics, architect c4000 and architect c8000). The constant variables obtained from the study were expressed as mean ± standard deviation and median (minimum-maximum) and the categorical variables as n (%). The chi-square test was used in the analysis of categorical variables. A statistically significant difference in terms of constant variables was being tested between the groups and the compliance of the variables with the normality assumption was checked and appropriate tests were used. The tests used depending on the distribution were the t-test or the non-parametric alternative, the Mann-Whitney U test for independent groups. We used Pearson's correlation test for data with a normal distribution and Spearman's correlation test for those without. ROC analysis was conducted to determine the diagnostic value of the parameters. When a cut-off value could not be identified, the normal limits of the parameters were used and accuracy criteria were obtained from the variable that had been made categorical. A $p < 0.05$ was accepted as statistically significant for the determined differences. The IBM SPSS ver. 20 software program was used for data analysis.

The study was initiated upon approval by the Local Ethics Committee of Fırat University in accordance with the Helsinki Declaration.

Results

The 61 children with adenovirus gastroenteritis (Group-1) consisted of 29 (47.5%) females and 32 (52.5%) males with a mean age of 23.70 ±18.8 (2-60) months. The 64 healthy children (Group-2) consisted of 29 (45.3%) females and 35 (54.7%) males and the mean age was 24.87 ±14.81 (1-54) months. Evaluation of the gender revealed that the female and male ratios were statistically similar between the groups (p=0.803). In this study, there was no statistically significant difference in term of age ratios between the two groups (p=0.312). The MPV value was significantly lower in adenovirus gastroenteritis patients than in the control group (p = 0.048). While WBC and AST values were significantly higher in Group-1 compared to the control group ($p<0.05$), the HGB value was significantly lower (p=0.021). The mean values of the laboratory parameters in the study groups are presented as mean±SD and mean (min-max) in Table 1.

The correlation tests showed a significant but weak positive correlation between PCT and the WBC and BUN values (p=0.001; p=0.036, respectively); a significant and highly positive correlation between PCT and PLT ($p <0.001$); and a significant but weak

Table 1. The disturibution of laboratory parameters of patients and control groups

Parameters	Group 1 Mean±SD Med(Min-Max)	Group 2 Mean±SD Med(Min-Max)	P
PCT (%)	0.26±0.10	0.25±0.06	0.479
	0.24(0.08-0.63)	0.26(0.01-0.38)	
MPV (fl)	8.32±1.92	8.85±0.79	0.048*
	8.30(3.95-13.20)	9.00(7.20-10.50)	
WBC (103 /µL)	9.87±3.28	7.60±1.44	<0.001*
	9.92(3.60-17.60)	7.75(3.94-9.93)	
HGB (g/dL)	11.93±1.32	12.39±0.83	0.021*
	11.80(7.95-14.30)	12.30(11.10-14.30)	
PLT (103 /µL)	307.07±111.10	287.5±59.02	0.224
	286.00(124.00-641.00)	295.00(160.00-381.00)	
CRP (mg/L)	0.57±0.58	0.51±0.88	0.094
	0.38(0.02-2.10)	0.21(0.01-5.67)	
BUN (mg/dL)	16.41±7.01	15.56±5.45	0.449
	17.00(1.86-35.00)	14.00(3.00-26.00)	
KREATININ (mg/dL)	0.40±0.10	0.36±0.11	0.072
	0.40(0.15-0.61)	0.35(0.13-0.59)	
ALT (U/L)	19.78±8.30	21.83±7.90	0.063
	16.00(10.00-44.00)	20.50(9.00-44.00)	
AST (U/L)	36.02±12.45	26.83±9.72	<0.001*
	34.00(19.00-87.00)	26.00(6.00-41.00)	

The data presented as mean ± SD . *P < 0.05 statistical significant
PCT: Plateletcrit. MPV: Mean Platelet Volume. WBC: White Blood Cell Count. Hgb: Hemoglobin. PLT: Platelet Count. CRP: C-Reaktif Protein. BUN: Blood Urea Nitrogen. AST: Aspartat Aminotransferaz. ALT: Alanin Aminotransferaz.

negative correlation between PCT and creatinine (p =0.009) in group-1. We also found a positive correlation between MPV and ALT and a significant but weak negative correlation between MPV and creatinine (p= 0.003; p<0.001, respectively). Correlation test analysis results are presented in Table 2.

Table 2. The relationship of with other blood parameters of PCT and MPV

Parameters	PCT r(p)	MPV r(p)
WBC (103 /µL)	0.28 (0.001)*	-0.13 (0.156)
HGB (g/dL)	-0.10 (0.280)	-0.11 (0.210)
PLT (103 /µL)	0.76 (<0.001)*	-0.16 (0.074)
CRP (mg/L)	0.02 (0.816)	0.06 (0.508)
BUN (mg/dL)	0.19 (0.036)*	0.09 (0.327)
KREATININ (mg/dL)	-0.232 (0.009)*	-0.315 (<0.001)*
ALT (U/L)	0.152 (0.091)	0.26 (0.003)*
AST (U/L)	0.03 (0.706)	-0.12 (0.172)

r: Correlation coefficient. *P < 0.05 statistical significant
PCT: Plateletcrit. MPV: Mean Platelet Volume. WBC: white blood cell count. Hgb: Hemoglobin. PLT: Platelet Count. CRP: C-reaktif protein. BUN: Blood Urea Nitrogen. AST: Aspartat Aminotransferaz. ALT: Alanin Aminotransferaz.

ROC analysis was conducted to identify whether MPV and some other parameters had diagnostic value in adenovirus gastroenteritis. ROC analysis showed PCT (AUC=0.483; p=0.746; 95% CI: 0.379-0.588) and MPV (AUC=0.402; p=0.059 95% CI: 0.296-0.508) did not have differential diagnostic value while WBC (AUC=0.705; p=0.001, 95% CI: 0.609-0.802), HGB (AUC=0,389; p=0.033, 95% CI: 0.287-0.491) and AST (AUC=0.709; p=0.001, 95% CI: 0.620-0.798) did. ROC analysis results for MPV and the other parameters are presented in Figure 1.

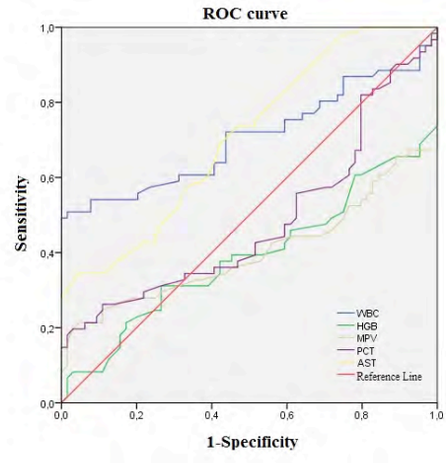

Figure 1. The ROC curve analysis of MPV, PCT and other laboratory parameters

The MPV parameter that was made categorical by using the normal limits in the literature was seen to create a statistically significant difference on cross-tabulation of the groups and accuracy criteria were obtained. We found that the categorical state of the MPV parameter based on its normal limits (7.2-11.1 fl) could be used in the diagnosis and 100% of healthy individuals were classified correctly (sensitivity 39.3%, specificity: 100%, positive predictive value: 100%, negative predictive value: 63.4%). We also determined the relative values for the parameters of WBC (sensitivity 47.5%, specificity: 98.4%, positive predictive value: 96.7%, negative predictive value: 66.3%) and AST (sensitivity 27.9%, specificity: 100%, positive predictive value: 100%, negative predictive value: 27.9%).

Discussion

The MPV value was found to be significantly lower in patients with adenovirus gastroenteritis than in the control group. A positive relationship was shown between MPV and AST. WBC, HGB and AST did not show value for use in the differential diagnosis.

There is no previous study on MPV levels in adenovirus gastroenteritis patients in the literature. We found two studies on MPV levels in rotavirus gastroenteritis, two on MPV levels in patients infected with Entamoeba histolytica and one study on MPV levels in children with infectious and non-infectious diarrhea [13-17]. Mete et al. and Çelik et al. reported decreased MPV values in patients with rotavirus gastroenteritis and suggested using MPV as a negative acute phase reactant [13,14]. Çelik et al. found increased MPV values while Matowick-Karna et al. reported decreased MPV levels in acute gastroenteritis due to Entamoeba histolytica [16,17]. Additionally, Küçük et al. reported the MPV values in patients with acute bacterial diarrhea to be higher than in patients with non-infectious and viral diarrhea [15]. MPV values in children with adenovirus gastroenteritis were found to be lower than in the control group in this study as in studies by Mete et al. and Çelik et al. [13,14]. However, Turhan et al. found MPV values in patients with inac-

tive hepatitis B to be higher than in the control group [18]. Ekiz et al. showed thrombocytopenia and increased MPV in Crimean Congo Hemorrhagic Fever (CCHF) when compared with the control group [19]. Aydemir et al. found a significant increase in the MPV value within the first three days in gram-negative sepsis patients [20].

All these studies demonstrate that MPV can increase or decrease according to the severity of the systemic inflammation in various inflammatory and infectious situations. Although the exact mechanism is unknown, it is believed that MPV can increase in low grade inflammation due to the presence of large platelets in the circulation, whereas it can decrease due to the consumption of these large platelets in the vascular segment of the inflammation area in case of severe inflammation [11-13]. The decrease in the MPV level observed in studies conducted on inflammatory gastrointestinal diseases such as acute appendicitis, acute gastroenteritis, intestinal tuberculosis and inflammatory intestinal disorders can support this hypothesis, but new studies on larger populations and other inflammatory disorders where inflammation markers are also evaluated are required. CD62, CD63, GPIIb/IIIa, PF4 and thromboglobulin are tests that show platelet activation but are not included in routine analyses as they require special equipment and have high cost [21]. However, MPV measurement is a low-cost, highly efficient and useful method showing platelet function and activation that can easily be included in the whole blood count in most medical facilities [7,8]. When all these advantages are considered, MPV can be recommended as a positive or negative marker in inflammatory and infectious diseases.

A significant and strong positive correlation was found between PCT and PLT and a significant but weak negative correlation between PCT and creatinine in Group-1 in the correlation test conducted in this study. Also, a positive correlation between MPV and ALT and a significant but weak negative correlation between MPV and creatinine were found. We found that PCT and MPB had no differential diagnostic value in adenovirus gastroenteritis but WBC, HGB and AST could help the differential diagnosis in the ROC analysis conducted.

A decrease in MPV value was found in children with adenovirus gastroenteritis when compared to the control group in this study. We also found that PCT and MPV had no diagnostic value but WBC, HGB and AST could help the differential diagnosis in adenovirus gastroenteritis. MPV can be used as an acute phase reactant in children with acute gastroenteritis as MPV measurement is an inexpensive and useful test that can easily be performed in most medical facilities.

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Competing interests

The authors declare that they have no competing interests.

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EVALUATION OF p300 AND VEGF EXPRESSION AND MICROVESSEL DENSITY IN PLASMA CELL MYELOMA

MYELOMDA p300 VE VEGF EKSPRESYONU İLE MİKRODAMAR YOĞUNLUĞUNUN ARAŞTIRILMASI

ANGIOGENESIS RELATED PARAMETERS IN MYELOMA

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Öz

Amaç: Çalışmanın amacı plazma hücreli myelom (PHM)'da anjiogenez ile ilişkili parametrelerden vaskuler endotelyal büyüme faktörü (VEGF) ve p300 ekspresyonu ile mikrodamar yoğunluğunu (MDY) araştırmak idi. Gereç ve Yöntem: PHM tanılı 45 hastaya ait parafine gömülü kemik iliği biyopsilerine immünhistokimyasal olarak p300, VEGF ve Faktör VIII ilişkili antijen (MDY'yi hesaplamak için) uygulandı. Histomorfolojik faktörler, klinik ve laboratuvar bulgular ve toplam sağ kalım (TSK), p300 ekspresyonu, VEGF ekspresyonu ve MDY ile korele edildi. Bulgular: Yüksek (≥%50) VEGF ekspresyonu ile diffüz infiltrasyon patterni ve yüksek plazma hücre infiltrasyon oranı arasında anlamlı ilişki saptandı (p=0.014, p=0.002, sırası ile). Yüksek MDY, diffüz infiltrasyon patterni ve artmış CRP düzeyi ile direkt korelasyon göstermekteydi (p=0.026, p=0.015, sırası ile). p300, VEGF ve MDY'ye göre sağ kalanların yüzdesi ve TSK açısından anlamlı bir fark saptanmadı. p300, VEGF ve MDY arasında anlamlı ilişki gözlenmedi. Tartışma: Bulgularımız, kemik iliği infiltrasyon paterni ve neoplastik hücrelerin miktarı ile MDY ve VEGF ekspresyonu arasında anlamlı ilişki olduğunu ortaya koymuştur. p300'ün histomorfolojik prognostik parametreler, MDY, VEGF ekspresyonu ve TSK ile ilişkisi olmadığı saptanmakla birlikte, bildiğimiz kadarıyla bu çalışma, PHM'li hastalarda p300 ekspresyonunun potansiyel prognostik rolünü araştıran ilk çalışma olma özelliği taşımaktadır. Sonuç olarak, anjiyogenez ile myelom hücreleri arasındaki etkileşimin yanı sıra PHM'de artmış kemik iliği anjiyogenezisinin prognostik rolünün daha kapsamlı çalışmalarla aydınlatılması gerekmektedir.

Anahtar Kelimeler

Plazma Hücreli Myelom; p300; CREB; Anjiyogenez; VEGF; İmmünohistokimya

Abstract

Aim: The aim of the study was to evaluate angiogenesis-related parameters including vascular endothelial growth factor (VEGF), p300 expression, and microvessel density (MVD) in plasma cell myeloma (PCM). Material and Method: p300, VEGF, and Factor VIII related antigen (for measurement of MVD) were applied to the paraffin-embedded bone marrow sections of 45 patients with PCM, immunohistochemically. Histomorphologic factors, clinical and laboratory findings, and overall survival (OS) were correlated with p300 and VEGF expression, and MVD. Results: VEGF overexpression (≥50%) was significantly associated with diffuse infiltration pattern and high percentage of plasma cell infiltration (p=0.014, p=0.002, respectively). Higher MVD was directly correlated with diffuse infiltration pattern and increased CRP levels (p=0.026, p=0.015, respectively). No significant difference was noted in percentage of survivors and OS with respect to p300, VEGF, and MVD. No significant correlation was noted between p300 expression, VEGF expression, and MVD. Discussion: Our findings revealed significant association of bone marrow infiltration pattern and quantity of neoplastic cells with MVD and VEGF expression. Although no association of p300 was shown with histomorphologic prognostic parameters, MVD, VEGF expression, or OS, this is the first study investigating the potential prognostic role of p300 expression in PCM, to the best of our knowledge. In conclusion, more-comprehensive studies are needed to further elucidate the interaction between angiogenesis and myeloma cells as well as the prognostic role of increased bone marrow angiogenesis in PCM.

Keywords

Plasma Cell Myeloma; p300; CREB; Angiogenesis; VEGF; Immunohistochemistry

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Introduction

Plasma cell myeloma (PCM) is a haematological malignancy characterized by accumulation of clonal malignant plasma cells predominantly within the bone marrow (BM) [1]. The role of proliferation, apoptosis, and angiogenesis-related defects has been considered in the pathogenesis of PCM, while a very heterogeneous prognosis of the disease necessitates assessment of prognostic factors and prognostic stratification for implementation of individualized targeted therapy [2].

Progressive increase in the bone marrow microvessel density (MVD) is a prominent feature of active PCM, while along with increased angiogenic cytokine expression it has been associated with pathogenesis and progression of PCM as well as survival [1].

Although the exact mechanisms regulating the progressive increase in angiogenesis in PCM remain unclear, expression of proangiogenic molecules such as vascular endothelial growth factor (VEGF) with stimulatory effects on endothelial cell growth and microvascular permeability is considered to drive tumor related angiogenesis and to influence critical steps of myeloma pathogenesis and progression [3-8].

The hypoxic microenvironment of bone marrow in PCM induces tumor angiogenesis via expression of hypoxia-inducible transcription factor 1 alpha (HIF-1 α) that leads to the upregulation of proangiogenetic VEGF and to subsequent increase in the bone marrow angiogenesis and thus growth of myeloma cells [9-11].

In hypoxic conditions, HIF-1 α can also interact with its transcriptional coactivators including p300 and cyclic AMP response element-binding (CREB) protein (CBP), highly homologous proteins that are required for the optimal function of HIF-1α transcription machinery and subsequent angiogenesis. They have also been shown to play a role in tumorigenesis [11-12]. To our knowledge no data exist investigating the potential prognostic role of p300 expression in patients with PCM.

The present study was designed to evaluate angiogenesis-related immunohistochemical parameters including VEGF, MVD, and p300 in newly-diagnosed PCM patients in terms of their potential association with clinicopathological and laboratory parameters, histomorphologic prognostic factors, and survival.

Material and Method

Study population

After obtaining ethics committee approval from Gazi University School of Medicine and informed consents, 76 consecutive patients with newly-diagnosed PCM between 2001 and 2010 at Gazi University School of Medicine were enrolled. 45 of 76 patients [mean (SD) age: 58.6(10.8) years; 62.2% were males] who had available clinical data and paraffin-embedded tissues for the immunohistochemical analysis of p300 expression, VEGF expression, and MVD were included in this study.

Assessments

Data on patient demographics, disease characteristics including clinical stage (I-III), risk group (low, moderate, high), and laboratory findings [serum M protein (IgG, IgA, IgD, kappa, lambda, non-secretory), light chain (kappa, lambda), hemoglobin (g/dL), WBC (e3/IU), platelet count (e3/IU), serum calcium (mg/dL), serum creatinine (mg/dL), β2-microglobulin (g/dL), serum albumin (g/dL), C-reactive protein (CRP; mg/L), lactate dehydrogenase (LDH; U/L), erythrocyte sedimentation rate (ESR; mm/h), proteinuria (g/24 h) and presence of urinary M protein] were retrieved from medical records at initial diagnosis. The clinical stage of the patients was classified according to the Durie and Salmon's criteria [13]. Risk groups were examined according to the classification of Bataille et al. depending on serum CRP and beta-2 microglobulin (β2M) levels [14].

Formalin-fixed paraffin-embedded bone marrow specimens were re-evaluated in terms of histomorphologic factors and immunohistochemical analysis for p300 expression, VEGF expression, and MVD. Demographic, clinical and laboratory parameters, as well as overall survival were evaluated with respect to level of p300 expression, VEGF expression, and MVD.

Histopathological examination

Hematoxylin and eosin- and CD138-stained sections of bone marrow prepared at the time of initial diagnosis were obtained from the archive of the Department of Pathology and re-evaluated for identification of plasmacytic differentiation and immunohistological assessment of plasma cell morphology, the percentage of plasma cell infiltration (<20%; 20-49% and ≥50%), and the histological infiltration pattern.

Plasma cell morphology was cytologically sub-graded according to level of differentiation into low-grade (characterized by predominantly small cells), intermediate-grade (with predominantly cleaved, polymorphous, asynchronous cells), or high-grade (where most tumor cells are plasmablastic) cells as defined by Bartl [15].

The histological infiltration pattern was classified as interstitial (interstitial or interstitial and sheet-like), nodular (interstitial nodular or nodular), or diffuse (diffuse or sarcomatoid) infiltration pattern [15].

Immunohistochemical analysis

For immunohistochemical staining, 3- to 4-μm thick tissue sections were cut on slides from formalin-fixed, paraffin-embedded bone marrow biopsies of the patients. The slides were deparaffinized for 2 hours in a 60°C oven, and stained for Factor VIII related antigen (vonWillebrand factor Ab-2; 1:100 dilution, clone F8/86, mouse monoclonal, Neomarkers, USA), VEGF (1:50 dilution, clone VG1, mouse monoclonal, IgG1 Kappa, Thermo Scientific, USA), p300 (1:50 dilution, clone Sc-585, rabbit polyclonal, IgG, Santa Cruz, USA), and CD138 antibody (1:40 dilution, rabbit polyclonal, IgG, ThermoFisher Scientific, Rockford, USA) in an automatised stainer (Ventana automated immunostainer Discovery XT, Ventana Medical Systems Inc., Tucson, USA) by using established protocols. Immunostaining was completed with the diaminobenzidine (DAB) detection kit (Ventana), which uses a streptavidin-biotin technique and hematoxylin as a counterstain. Sections of breast invasive ductal carcinoma for p300, angiosarcoma for VEGF, placenta for Factor VIII, and tonsil for CD138 were used as positive controls. For negative controls, the primary antibodies were omitted. Cytoplasmic staining was considered as positive for Factor VIII and VEGF; nuclear staining was considered as positive for p300; and membranous staining was considered as positive for CD138. Each slide was evaluated

under a light microscope (BX53, Olympus, Tokyo, Japan) by two referral pathologists (SS, NA) blinded to the cases.

The measurement of MVD was determined immunohistochemically with Factor VIII. Any positively stained endothelial cell or endothelial cell cluster that was clearly separated from adjacent microvessels was considered as a single, countable microvessel. Slides stained with antibodies to Factor VIII antigen/von Willebrand complex were first scanned with light microscopy under low power (×10 objective) to identify areas with the greatest number of microvessels (hot spots). The microvessels (capillaries and small venules) at hot spots were counted at one high power field (HPF) (x40 objective with eyepiece diameter of 0.65 mm) of the microscope. Then, MVD was counted as the average number of vessels in the three hot spots. Microvessels were identified as endothelial cells either single or clustered in nests or tubes, clearly separated from one another, with or without lumen not exceeding 10 micrometers in transverse diameter. Larger vessels and vessels in the periosteum were excluded. MVD was categorized into two groups based on the number of microvessels including low (<20 microvessels/HPF) and high (≥20 microvessels/HPF) MVD.

The p300 (low expression: <30%; high expression: ≥30%) and VEGF (low expression: <10%; moderate expression: 10-49%; high expression: ≥50%) expressions were evaluated based on the percentage of positive plasma cells.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 15.0. Chi-square (x^2) and Fisher's exact tests for the comparison of categorical data, while numerical data were analyzed using Student t-test and ANOVA. Spearman correlation analysis was used to analyze correlation between immunohistochemical parameters. Survival analysis was made via Kaplan-Meier analysis and comparisons were made via Log-Rank test. Data were expressed as "mean (standard deviation, SD)", minimum-maximum, and percent (%) where appropriate. p<0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Most of the patients had clinical stage II-III disease (82.2%) with intermediate-grade cytology (62.2%), diffuse type of infiltration pattern (44.4%), and plasma cell infiltration of ≥50% (68.9%) and were categorized into the moderate risk group (50.0%) (Table 1).

Overall, mean (SD) MVD score was 23.7(13.2, ranged 3 to 54) microvessels/HPF, while MVD score was <20 microvessels/HPF in 19(42.2%) patients, and ≥20 microvessels/HPF in 26(57.8%) patients (Fig 1).

Mean (SD) extent of VEGF expression was 64.2 (29.2, ranged 5 to 100)%, while VEGF expression was <10%, 10-49% and ≥50% in 3(6.7%), 11(24.4%) and 31(68.9%) patients, respectively (Fig 2).

Mean (SD) p300 expression was 38.7 (31.8, ranged 0 to 90)%; while p300 expression was <30% in 17(37.8%) and ≥30% in 28(62.2%) patients (Fig 3).

No significant difference was noted in patient demographics, clinical stage, histomorphologic prognostic factors, or risk group in terms of p300 expression (Table 1).

Higher (≥50%) than lower (<50%) VEGF expression (85.0% vs. 15.0%, p=0.014) and higher (≥20 microvessels/HPF) than lower (<20 microvessels/HPF) MVD scores (80% vs. 20%, p=0.026) were more likely seen in patients with diffuse type plasma cell infiltration pattern (Table 1).

Higher (≥50%) than lower (<50%) VEGF expression (83.9% vs. 16.1%, p=0.002) was more commonly noted in patients with high (≥50%) percentage of plasma cell infiltration. No significant difference was noted in patient demographics, clinical stage, pattern of plasma cell infiltration, risk group in terms of level of VEGF, and MVD score (Table 1).

Survival

The survival analysis was performed for 42 patients. After median (min-max) 17 months (ranged 2 to 94 months) of follow-up, duration of overall survival was median 65.0 months (ranged 25.9 to 104.1 months) and 29 of 42 (69.0%) patients were still alive at the time of study. (Table 1, Fig 4).

No significant difference was noted in percentage of survivors and median duration of OS with respect to p300, VEGF, and MVD (Table 1, Fig 4).

Laboratory parameters

Higher (≥20 microvessels) than lower (<20 microvessels) MVD scores (78.3% vs. 21.7%, p=0.015) were more likely seen in patients with CRP levels of ≥6 mg/L (Table 2).

None of the laboratory parameters showed a significant change with respect to p300 or VEGF. Apart from CRP, no significant change was observed in laboratory parameters also with respect to MVD (Table 2).

Correlation between p300 expression, VEGF expression, and MVD score

No significant correlation was noted between p300 expression, VEGF expression, and MVD score (Table 3).

Discussion

Our findings revealed association of diffuse plasma cell infiltration pattern with increased VEGF expression and higher MVD scores in patients with PCM. Also, higher percentage of plasma cell infiltration and higher CRP levels were associated with increased VEGF expression and higher MVD scores, respectively. p300 expression was not associated with any of the prognostic factors related to plasma cell infiltration, while none of the angiogenesis-related immunohistochemical parameters was associated with cytological grade or survival.

PCM is the first haematological malignancy in which a significant correlation of angiogenesis with prognosis and survival has been identified [16]. Bone marrow MVD was shown to be significantly increased in PCM compared to monoclonal gammopathy of undetermined significance (MGUS) and also in active versus non-active myeloma [1,17] as well as in stage II–III versus stage I myeloma [3].

The type of infiltration pattern is considered to reflect the stage of disease with identification of interstitial and nodular patterns when hematopoiesis is still preserved, unlike occurence of diffuse inflitration with disease progression that results in the supression of hematopoiesis [18].

Table 1. Demographic and clinical characteristics with respect to p300 expression, VEGF expression, and MVD score categories (n=45)

	p300 expression			VEGF expression				MVD score (microvessel)			Total (n=45)
	<%30 (n=17)	≥%30 (n=28)	p value	<%10 (n=3)	10-49% (n=11)	≥%50 (n=31)	p value	<20 (n=19)	≥20 (n=26)	p value	
Age, mean(SD)	59.8(11.9)	57.9(10.2)	0.593a	51.0(23.3)	64.5(10.8)	57.2(10.1)	0.066b	58.6(11.7)	58.6(0.3)	0.991a	58.6(10.8)
Age group, n(%)											
<50	2(22.2)	7(77.8)	0.447	2(22.2)	1(11.1)	6(66.7)	0.142	3(33.3)	6(66.7)	0.712	9(20.0)
≥50	15(41.7)	21(58.3)		1(2.8)	10(27.8)	25(69.4)		16(44.4)	20(55.6)		36(80.0)
Gender, n(%)											
Female	7(41.2)	10(58.8)	0.961	2(11.8)	4(23.5)	11(64.7)	0.674	9(52.9)	8(47.1)	0.410	17(37.8)
Male	10(35.7)	18(64.3)		1(3.6)	7(25.0)	20(71.4)		10(35.7)	18(64.3)		28(62.2)
Clinical stage, n(%)											
Stage I	5(62.5)	3(37.5)	0.204	1(12.5)	1(12.5)	6(75.0)	0.455	5(62.5)	3(37.5)	0.236	8(17.8)
Stage II-III	12(32.4)	25(67.6)		2(5.4)	10(27.0)	25(67.6)		14(37.8)	23(62.2)		37(82.2)
Plasma cell differentiation, n(%)											
Low grade	6(40.0)	9(60.0)	0.764	1(6.7)	5(33.3)	9(60.0)	0.841	5(33.3)	10(66.7)	0.762	15(33.3)
Intermediate grade	11(39.3)	17(60.7)		2(7.1)	6(21.4)	20(71.4)		13(46.4)	15(33.3)		28(62.2)
High grade	0(0.0)	2(100.0)		0(0.0)	0(0.0)	2(100.0)		1(50.0)	1(50.0)		2(4.4)
Pattern of plasma cell infiltration, n(%)											
Interstitial	5(35.7)	9(64.3)	0.132	3(21.4)	6(42.9)	5(35.7)	0.014	8(57.1)	6(42.9)	0.026	14(31.1)
Nodular	7(63.6)	4(36.4)		0(0.0)	2(18.2)	9(81.8)		7(63.6)	4(36.4)		11(24.4)
Diffuse	5(25.0)	15(75.0)		0(0.0)	3(15.0)	17(85.0)		4(20.0)	16(80.0)		20(44.4)
Percentage of plasma cell infiltration, n(%)											
<20%	2(50.0)	2(50.0)	0.796	1(25.0)	1(25.0)	2(50.0)	0.002	2(50.0)	2(50.0)	0.082	4(8.9)
20-49%	3(30.0)	7(70.0)		2(20.0)	5(50.0)	3(30.0)		7(70.0)	3(30.0)		10(22.2)
≥50%	12(38.7)	19(61.3)		0(0.0)	5(16.1)	26(83.9)		10(32.3)	21(67.7)		31(68.9)
Risk group, n(%)											
Low	3(42.9)	4(57.1)	0.373	1(14.3)	1(14.3)	5(71.4)	0.663	3(42.9)	4(57.1)	0.659	7(25.0)
Moderate	5(35.7)	9(64.3)		1(7.1)	5(35.7)	8(57.1)		5(35.7)	9(64.3)		14(50.0)
High	5(71.4)	2(28.6)		0(0.0)	1(14.3)	6(85.7)		1(14.3)	6(85.7)		7(25.0)
Survival, n(%)											
Survivor	13(44.8)	16(55.2)	0.305	3(10.3)	78(24.1)	19(65.5)	0.153	14(48.3)	15(51.7)	0.236	29(69.0)
Non-survivor	4(30.8)	9(69.2)		0(0.0)	2(15.4)	11(84.6)		4(30.8)	9(69.2)		13(31.0)
Overall survival (month), median (95 %CI)	NA	43(40-43)	0.4626c	NA	NA	65(40-65)	0.6314c	NA	65(40-65)	0.1708c	65(25.9-104.1)

MVD: microvessel density; VEGF: Vascular endothelial growth factor
x2 test, aStudent t-test, b ANOVA, cLog-Rank Test,

High percentage of plasma cells infiltration in bone marrow has been suggested to be a reliable predictor of relapse in PCM patients [19], while advanced grade plasma cell infiltration pattern, reflecting a high tumor burden, has been associated with high plasma cell count and poor prognosis [20].

VEGF activity was shown to be associated with tumor grade and prognosis in PCM, while in vivo inhibition of VEGF-induced angiogenesis by antibodies against VEGF was reported to result in suppression of tumor growth [8,21]. Also, high tumor burden and diffuse pattern of infiltration were reported to be associated with higher MVD along with a highly significant correlation between MVD and histologic grade of tumor, extent of bone marrow infiltration, proliferative activity, and treatment response in patients with PCM [22-24].

Hence, association of diffuse plasma cell infiltration pattern both with increased VEGF expression and higher MVD score and association of the high percentage of plasma infiltration with increased VEGF expression in our cohort seem to indicate the role of angiogenesis in promoting disease progression in PCM and supporting the association of increased angiogenesis with advanced PCM [21].

A high clinical stage/cytological grade in PCM has been associated with higher rate of proliferation, higher intratumoral vascularity, and increased VEFG in the neoplastic cells as well as increased MVD [2,8]. However, unlike other plasma cell related prognostic factors including type of bone marrow infiltration and quantity of neoplastic cells, the morphology of the cells was not associated with any of the angiogenesis-related immunohistochemical parameters in our cohort. This seems to be associated with inability to perform appropriate analysis due to observation of high cytological grade only in 2 patients in the overall cohort.

Table 2. Laboratory findings with respect to p300 expression, VEGF expression, and MVD score categories (n=45)

	p300 expression			VEGF expression				MVD score (microvessel)			Total (n=45)
	<%30 (n=17)	≥%30 (n=28)	P value	<%10 (n=3)	10-49% (n=11)	≥%50 (n=31)	p value	<20 (n=19)	≥20 (n=26)	p value	
Serum M protein											
IgG	10(35.7)	18(64.3)	0.0981	3(10.7)	8(28.6)	17(60.7)	0.6971	11(39.3)	17(60.7)	0.2751	28(62.2)
IgA	2(25.0)	6(75.0)		0(0.0)	2(25.0)	6(75.0)		4(50.0)	4(50.0)		8(17.8)
IgD	0(0.0)	1(100.0)		0(0.0)	1(100.0)	0(0.0)		1(100.0)	0(0.0)		1(2.2)
Kappa	4(100.0)	0(0.0)		0(0.0)	0(0.0)	4(100.0)		3(75.0)	1(25.0)		4(8.9)
Lambda	1(33.3)	2(66.7)		0(0.0)	0(0.0)	3(100.0)		0(0.0)	3(100.0)		3(6.7)
Non-secretory	0(0.0)	1(100.0)		0(0.0)	0(0.0)	1(100.0)		0(0.0)	1(100.0)		1(2.2)
Light chain											
Kappa	12(50.0)	12(50.0)	0.1662	0(0.0)	8(33.3)	16(66.7)	0.0931	12(50.0)	12(50.0)	0.4871	24(54.5)
Lambda	5(25.0)	15(75.0)		3(15.0)	3(15.0)	14(70.0)		7(35.0)	13(65.0)		20(45.5)
Hemoglobin											
≥10.0 g/dL	7(43.8)	9(56.3)	0.8061	1(6.3)	2(12.5)	13(81.3)	0.7461	8(50.0)	8(50.0)	0.5621	16(35.6)
8.5-10.0 g/dL	5(38.5)	8(61.5)		1(7.7)	4(30.8)	8(61.5)		6(46.2)	7(53.8)		13(28.9)
<8.5 g/dL	5(31.3)	11(68.8)		1(6.3)	5(31.3)	10(62.5)		5(31.3)	11(68.8)		16(35.6)
WBC											
<4500 e3/IU	3(37.5)	5(62.5)	1.001	0(0.0)	2(25.0)	6(75.0)	1.001	4(50.0)	4(50.0)	0.6931	8(17.8)
4500-11.000 e3/IU	13(39.4)	20(60.6)		3(9.1)	8(24.2)	22(66.7)		14(42.4)	19(57.6)		33(73.3)
>11.000 e3/IU	1(25.0)	3(75.0)		0(0.0)	1(25.0)	3(75.0)		1(25.0)	3(75.0)		4(8.9)
Platelet count											
<150.000 e3/IU	6(46.2)	7(53.8)	0.5111	1(7.7)	3(23.1)	9(69.2)	1.001	4(30.8)	9(69.2)	0.5102	13(28.9)
150.000-400.000 e3/IU	11(34.4)	21(65.6)		2(6.3)	8(25.0)	22(68.8)		15(46.9)	17(53.1)		32(71.1)
Serum calcium											
<12 mg/dL	15(38.5)	24(61.5)	1.001	3(7.7)	10(25.6)	26(66.7)	0.6711	16(41.0)	23(59.0)	1.001	39(90.7)
≥12 mg/dL	2(50.0)	2(50.0)		0(0.0)	0(0.0)	4(100.0)		2(50.0)	2(50.0)		4(9.3)
Serum creatinine											
<2 mg/dL	15(39.5)	23(60.5)	0.6931	3(7.9)	10(26.3)	25(65.8)	0.7941	17(44.7)	21(55.3)	0.6811	38(84.4)
≥2 mg/dL	2(28.6)	5(71.4)		0(0.0)	1(14.3)	6(85.7)		2(28.6)	5(71.4)		7(15.6)
Beta2 microglobulin											
<3.5 g/dL	9(50.0)	9(50.0)	0.3341	2(11.1)	5(27.8)	11(61.1)	0.7031	11(61.1)	7(38.9)	0.1861	18(62.1)
3.5-5.5 g/dL	2(40.0)	3(60.0)		0(0.0)	0(0.0)	5(100.0)		2(40.0)	3(60.0)		5(17.2)
>5.5 g/dL	5(83.3)	1(16.7)		0(0.0)	1(16.7)	5(83.3)		1(16.7)	5(83.3)		6(20.7)
Serum albumin											
≥3.5 g/dL	11(40.7)	16(59.3)	0.7571	2(7.4)	6(22.2)	19(70.4)	0.8811	12(44.4)	15(55.6)	0.7661	27(60.0)
<3.5 g/dL	6(33.3)	12(66.7)		1(5.6)	5(27.8)	12(66.7)		7(38.9)	11(61.1)		18(40.0)
CRP											
<6 mg/L	5(35.7)	9(64.3)	1.001	1(7.1)	4(28.6)	9(64.3)	1.001	9(64.3)	5(35.7)	0.0151	14(37.8)
≥6 mg/L	9(39.1)	14(60.9)		1(4.3)	6(26.1)	16(69.6)		5(21.7)	18(78.3)		23(62.2)
LDH											
<243 U/L	12(40.0)	18(60.0)	0.7161	3(10.0)	9(30.0)	18(60.0)	0.4431	15(50.0)	15(50.0)	0.0851	30(73.2)
≥243 U/L	3(27.3)	8(72.7)		0(0.0)	2(18.2)	9(81.8)		2(18.2)	9(81.8)		11(26.8)
ESR											
≤20 mm/h	0(0.0)	1(100.0)	1.001	0(0.0)	0(0.0)	1(100.0)	1.001	0(0.0)	1(100.0)	1.001	1(3.3)
20 mm/h	12(41.4)	17(58.6)		2(6.9)	7(24.1)	20(69.0)		13(44.8)	16(55.2)		29(96.7)
Bence Jones proteinuria											
<1 g/24 h	9(37.5)	15(62.5)	1.001	2(8.3)	6(25.0)	16(66.7)	1.001	10(41.7)	14 (58.3)	0.7241	24(64.9)
≥1 g/24 h	5(38.5)	8(61.5)		1(7.7)	3(23.1)	9(69.2)		4(30.8)	9(69.2)		13(35.1)
Urinary M protein											
Negative	4(26.7)	11(73.3)	0.4721	2(13.3)	2(13.3)	11(73.3)	0.3841	5(33.3)	10(66.7)	1.001	15(46.9)
Positive	7(41.2)	10(58.8)		0(0.0)	3(17.6)	14(82.4)		6(35.3)	11(64.7)		17(53.1)

Data are shown as n(%). CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; MVD: microvessel density; VEGF: Vascular endothelial growth factor; WBC: White blood cell
1Fisher Exact test, 2 Chi-Square Yates Continuity Correction

Table 3. Correlation between p300 expression, VEGF expression, and MVD score.

		p300 expression	VEGF expression	MVD score
p300 expression	r	1,000	-,128	,280
	p	.	,403	,063
	n	45	45	45
VEGF expression	r	-,128	1,000	,208
	p	,403	.	,171
	n	45	45	45
MVD score	r	,280	,208	1,000
	p	,063	,171	.
	n	45	45	45

MVD: microvessel density; r: rho correlation coefficient; VEGF: Vascular endothelial growth factor
Spearman correlation analysis

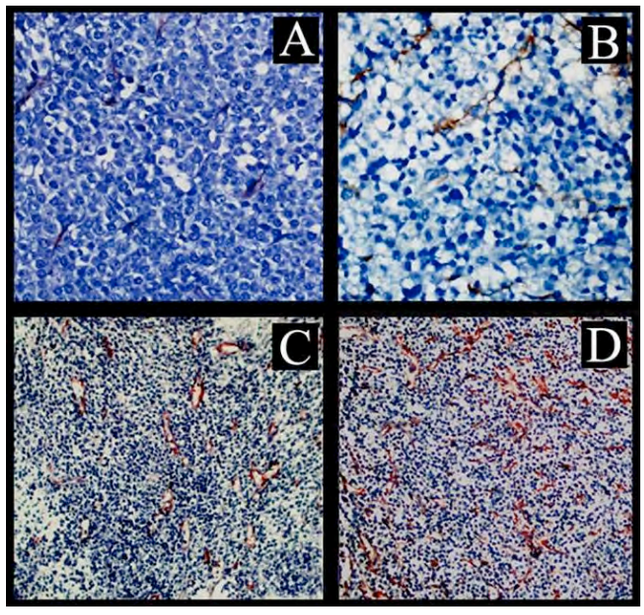

Fig 1. Bone marrow microvessel density (MVD) in PCM cases A-B) <20 microvessel/HPF (Factor VIII related antigen, original magnification x400), C-D) ≥20 microvessel/HPF (Factor VIII related antigen, original magnification x200).

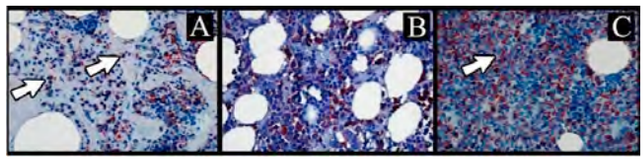

Fig 2. VEGF expression in PCM cases A) <10%, arrows: perinuclear halos in plasma cells (original magnification x400), B) 10-49% (original magnification x400), C) ≥50% (original magnification x400).

Association of higher MVD scores with higher CRP levels in our cohort seems notable given the consideration of both MVD and serum CRP levels as the best variables that predict event-free and overall survival among patients with PCM [22]. This also emphasizes the likelihood of CRP release in response to angiogenic cytokines, given the positive feedback between VEGF and angiogenic cytokines such as IL-6 to promote angiogenesis in proliferating myeloma cells [8].

Providing data on p300 expression for the first time in the literature, our findings revealed high (≥30%) amount of p300 expression in more than half of the patients with PCM, whereas there was no association of p300 expression with clinical or prognostic parameters. Hence, the potential prognostic role

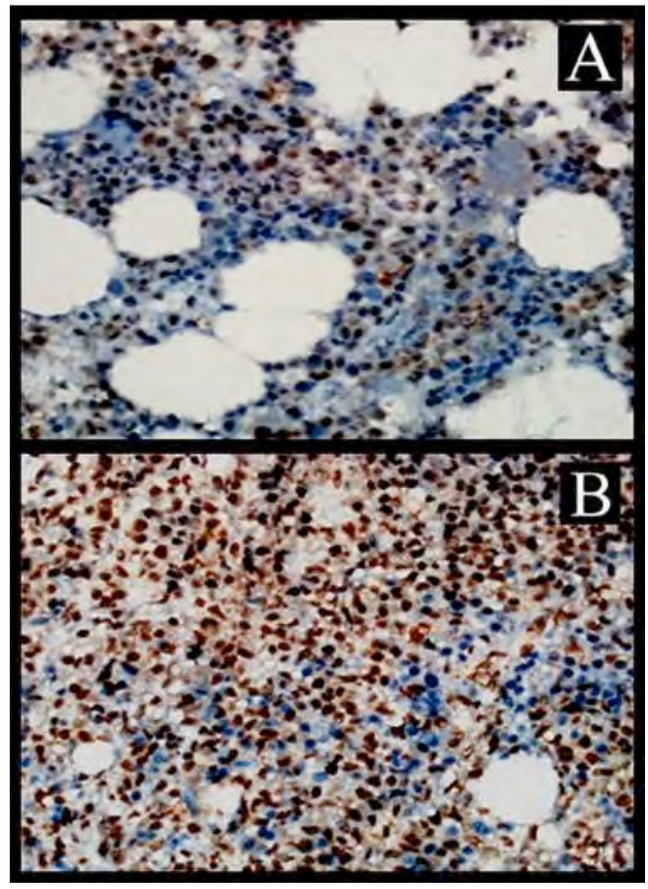

Fig 3. p300 expression in PCM cases A) <30% (original magnification x400). B) ≥30% (original magnification x400).

of increased p300 expression in patients with PCM seems to be justified in larger scale studies. Our findings also revealed no correlation between VEGF expression, p300 expression, and

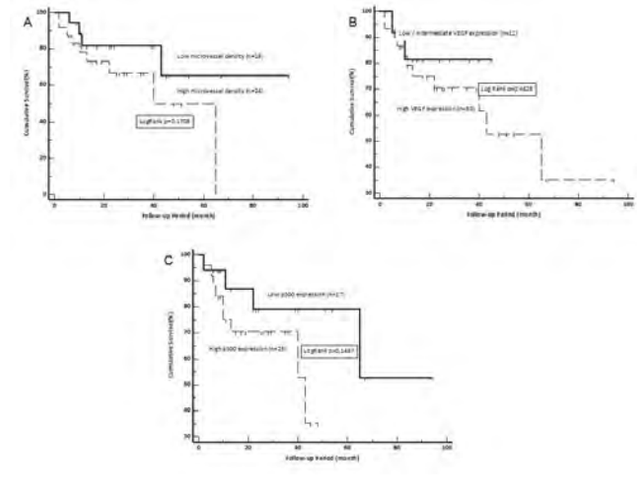

Fig 4. The Kaplan-Meier overall survival curves according to A) MVD B) VEGF expression and C) p300 expression.

MVD. Similarly to our findings, no correlation between the level of bone marrow MVD and plasma levels of VEGF was shown in another study [25]. Besides, high MVD scores were demonstrated in patients both with high and low VEGF expression, indicating the potential role of other angio-regulatory factors in the neo-vascular growth process [8]. Nonetheless, there is inconsistency regarding the correlation of bone marrow angio-

genesis and regulatory factors, and a significant correlation between higher VEGF expression and an increase in the MVD of tumor tissues was also indicated in malignant plasma cell neoplasms [25].

The extent of bone marrow angiogenesis has been reported as a strong indicator of biological potency of malignant clone and a predictor of survival in newly-diagnosed patients with PCM [22-23]. Increased bone marrow MVD was shown to be a significant poor-prognosis factor for survival in patients with newly-diagnosed PCM [6,24].

However, despite a statistically significant relationship between VEGF expression and the OS, expression of VEGF was not considered to be an independent prognostic factor in a past study among PCM patients [8]. Also no significant difference was reported between VEGF-positive and VEGF-negative patients with PCM in terms of overall survival in another study [24]. Bone marrow MVD was not found to be significantly correlated with OS both at diagnosis and prior to transplant [3] and no correlation was noted between baseline bone marrow MVD and PFS and OS in PCM patients [25]. Lack of any association between increased angiogenesis and poorer survival was also reported in another study among patients with advanced PCM [8].

Patients with well differentiated plasma cells and low tumor burden with <50% of bone marrow tumor infiltrates were estimated to have favorable prognosis [18]. However, despite their association with type of bone marrow infiltration and quantity of neoplastic cells, VEGF or MVD had no association with morphology of the plasma cells and had no impact on survival in our cohort. The lack of a statistically significant association of overall survival with VEGF expression and MVD scores in our cohort might be attributed to the potential contribution of angiogenic factors other than VEGF, the small number of cases in study groups as well as in high-grade cytology group along with the influence of different treatment methods and co-morbid disorders.

Conclusions

In conclusion, our findings revealed significant association of bone marrow infiltration pattern and quantity of neoplastic cells but not the morphology of the cells with the angiogenesis-related immunohistochemical parameters. Increased VEGF expression was associated with diffuse type of bone marrow infiltration pattern and high percentage of plasma cell infiltration, while higher MVD score was associated with diffuse type infiltration pattern and increased CRP levels. To the best of our knowledge, this is the first study to date investigating the potential prognostic role of p300 expression in patients with PCM. No association of p300 was shown with histomorphologic prognostic parameters and the angiogenesis-related immunohistochemical parameters and overall survival. Nevertheless, the present study provides the first evaluation and evidence of p300 expression in PCM. Eventually, the interaction between angiogenesis and myeloma cells as well as the prognostic role of increased bone marrow angiogenesis in PCM need further elucidation with larger study groups and longer follow-up.

Competing interests

The authors declare that they have no competing interests.

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CONTENT VALIDATION OF PRESSURE INJURY PREVENTION ALGORITHM: TURKEY CASE

BASINÇ YARASI ÖNLEME ALGORİTMASININ KAPSAM GEÇERLİLİĞİ: TÜRKİYE ÖRNEĞİ

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Öz

Amaç: Basınç yarası önleme algoritması basınç yarası riskinin değerlendirilmesini, derinin değerlendirilmesini ve bakımının yapılmasını, aktivite, beslenme, ıslaklık/inkontinans, destek yüzey yönetiminin sağlanmasını, eğitim verilmesini ve kayıt tutulmasını kapsamalıdır. Bu uygulamaların hepsinin bir arada olduğu basınç yarası algoritmalarının geliştirilmesiyle bakım kalitesinin artacağı belirtilmektedir. Bu prospektif, tanımlayıcı çalışmanın amacı, geliştirilen basınç yarası önleme algoritmasının kapsam geçerliliğini incelemektir. Gereç ve Yöntem: Yıldırım Beyazıt Üniversitesi Ankara Atatürk Eğitim ve Araştırma Hastanesi'nde çalışan yoğun bakım hemşirelerinin tümü araştırmaya davet edilmiştir. Katılımcılardan yazılı izin alındıktan sonra, demografik veriler ve basınç yarası önleme algoritması hakkındaki görüşlerle ilgili veriler toplanmıştır. Katılımcılardan standart kapsam geçerlilik çalışma prosedürleri kullanılarak 101 algoritma karar adımlarının her birinin uygunluğunun değerlendirilmesi istenmiştir. Bulgular: Demografik veri istatistikleri, ortalama uygunluk skorları ve kapsam geçerlik indeksi (CVI) hesaplanmıştır. Davet edilen 96 yoğun bakım hemşiresinden 81'i araştırmaya katılmayı kabul ederek çalışmayı tamamlamıştır (% 84'lük bir yanıt oranı). Katılımcıların yaş ortalaması 28.35 (SS 4.55; aralık 22-41), çoğu katılımcı kadın (% 85.2) ve % 38.3'ü 5 yıldan fazla yoğun bakım deneyimi yaşamıştır. Algoritmanın genel ortalama puanı 3.02 (SS:0.02); kapsam geçerlilik indeksi 0,90 (1.0'dan) puan olarak belirlenmiştir. Tartışma: Basınç yarası önleme algoritması birkaç küçük değişiklikle geçerli ve uygundur. Kapsam geçerliliği yapılan basınç yarası önleme algoritması yoğun bakım hastaları için basınç yarası ve risklerini tanılama ve uygun hemşirelik girişimlerini yapmada hemşirelere yardımcı olabilir. Basınç yarası önleme algoritmasının daha büyük gruplarda uygulanması ve değerlendirilmesi önerilmektedir.

Anahtar Kelimeler

Basınç Yarası; Önleme; Algoritma; Kapsam Geçerlilik Çalışması

Abstract

Aim: Algorithms for preventing pressure injury should include skin care, activity management, nutrition management, moisture/incontinence management, support surface management, registration, and training. Increased quality of care can be observed through algorithms created through a combination of preventive care phases. Material and Method: The purpose of this prospective, descriptive study was to examine the content validity of the pressure injury prevention algorithm incorporating a combination of the preventive care stages and using a larger sample size of intensive care nurses. Material and Method: All of the intensive care nurses working in Yıldırım Beyazıt University Ankara Ataturk Training and Research Hospital were invited to participate in the study. After participants provided written informed consent, demographic variables and opinions on the pressure injury prevention algorithm were collected and participants were asked to comment on and rate the relevance and appropriateness of each of the 101 algorithm decision steps using standard content validation study procedures. Results: Descriptive summary statistics, mean appropriateness scores, and the content validity index (CVI) were calculated. Of the 96 intensive care nurses invited, 81 consented to participate and completed the study (a response rate of 84%). The mean age was 28.35 years (SD 4.55; range 22–41), most participants were female (85.2%), and (38.3%) had >5 years of intensive care experience. The algorithm's overall mean score was 3.02 (SD: 0.02); all except 1 of the 101 steps had a high CVI of 0.90 (out of 1.0). Several minor algorithm modifications were made. Discussion: The pressure injury prevention algorithm is valid and appropriate with the addition of the minor modifications. A construct validated pressure injury prevention algorithm may help nurses identify pressure injury and risks and also help them develop appropriate nursing interventions for intensive care patients. It is recommended that large group studies involving the application and evaluation of the pressure injury prevention algorithm be conducted.

Keywords

Pressure Injury; Prevention; Algorithm; Validation Study

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Introduction

A pressure injury is localized injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of pressure, or pressure in combination with shear [1]. Pressure injury causes physical and psychological trauma by prolonging the healing process, delaying the responsibility of the individual, and increasing the effect of care. At the same time, unnecessary occupation of the hospital bed and increased workload brings additional financial burden to the institution [2,3].

Although pressure injury is an unwanted, preventable condition, it continues to be a worldwide problem despite highly trained staff and advances in medical technology and healthcare [4]. The extent of the problem can be seen by examining the literature. Incidents of pressure injury vary from 4.3% to 30.8% in international studies [5-10]. A multicenter study in Belgium, Italy, Portugal, United Kingdom, and Sweden, approved by the EPUAP (European Pressure Ulcer Advisory Panel) conducted national studies on pressure injury all over the world; 5947 patients were evaluated in 25 hospitals, and the average prevalence of pressure injury was determined to be 18.1%. Italy had the lowest rate at 8.3%, whereas Sweden had the highest at 23% [11]. In Turkey, studies in two different university hospitals found rates of 10,4% and 5,9%, respectively [8,9].

In health services, data on the incidence and prevalence of pressure injury can be used as an indicator for assessing the quality of care provided. Prevention and treatment require an interdisciplinary team with a holistic care approach [12-16]. The nurse's primary role as a member of this team is taking precautions to remove causative factors by evaluating the individuals at risk and factors that may prevent wound healing. Processes that should be followed to prevent the development of pressure injury include the evaluation of risk by skin assessment and preventive skin care like activity management, nutrition management, moisture/incontinence management, support surface management, training and registration with a holistic approach [1,12-19]. Among these methods, providing nursing care is most effective.

Nurses, who play a key role in preventing pressure injury, make numerous daily decisions in clinical practice that directly affect the outcomes of care. They make these decisions with the help of clinical instruments such as algorithms. Algorithms for preventing pressure injury should include skin care, activity management, nutrition management, moisture/incontinence management, support surface management, registration, and training. Increased quality of care can be observed by the use of algorithms, created through a combination of preventive care phases [1,20].

The purpose of this prospective, descriptive study was to examine the content validity of the pressure injury prevention algorithm generated by the combination of the preventive care stages, using a larger sample size of intensive care nurses.

Material and Method

Design. This prospective, descriptive study was constructed to obtain content validation data for the prevention injury prevention algorithm generated by the combination of the preventive care stages.

Sample and setting. All of the intensive care nurses working in Yıldırım Beyazıt University Ankara Ataturk Training and Research Hospital were invited to participate in the study. Sample inclusion criteria were relatively broad to encourage participation by a wide range of providers. Criteria included: licensed nursing, substantive (>1 years) intensive care experience, and/or wound care education. Participants did not receive financial compensation.

A total of 96 intensive care nurses were invited to participate through face-to-face interaction.. If they agreed to participate, they were given a confirmation form, an algorithm, and a study instrument. Volunteers were asked to complete the documents within one week.

Ethical considerations. Institutional permission was obtained from Yıldırım Beyazıt University Ankara Ataturk Training and Research Hospital. Study volunteers were asked to read a consent form and to provide written informed consent. Signed consent forms were collected and the algorithm surveys were distributed. Participants were asked to return consent forms within one week.

Instrumentation. The data collection survey comprised an instrument consisting of a 10-item demographic data form, a 6-item evaluation form for the pressure injury prevention algorithm, and the content validation questionnaire containing 101 statements matched to each of the 101 decision steps of the pressure injury prevention algorithm. The content validation survey asked participants to review the entire algorithm and to then read the statements related to each of the decision steps and rate their level of agreement with the relevance (appropriateness) of the item. A 4-point rating scale was used as per Lynn [21] and Waltz, Bausell (22): 4 = very relevant and appropriate; 3 = relevant but needs minor alteration; 2 = unable to assess relevance without revision; 1 = not relevant/appropriate. For each statement, participants were asked to add written comments for the changes they proposed.

Data collection procedures. Following an overview of the ethical considerations and a brief oral introduction about the history of the algorithm development and purpose of the study, participants signed and returned the consent forms. Each participant received the algorithm and the questionnaire. Participants reviewed the algorithm and then provided validation ratings and narrative comments. All participants completed and returned the survey within one week.

Data analysis. The questionnaire data were coded and entered into SPSS® Version 21.0 for analysis. Descriptive summary statistics were calculated for all demographic variables and the evaluation form for the pressure injury prevention algorithm. The Content Validity Index (CVI) and mean scores were calculated for each of the 101 individual algorithm components. CVI was calculated by grouping very relevant/relevant (ratings 3 and 4) and not relevant/unable to assess relevance (ratings 1 and 2). The proportion of items rated 3 and 4 was used to calculate the CVI; validity was indicated by a score of >0.70 (scale 0 to 1.0) [23,24].

Results

Participant characteristics. Of the 96 providers invited, 81 consented to participate and completed the study (a response rate of 84%). The majority (85.2%) of participants were female and

their mean age was 28.35 years (SD 4.55; range 22–41). Of the participants, 59.3% had a baccalaureate degree and 3.7% a masters degree. Thirty-one (38.3%) had 5 or more years of intensive care experience. Twenty-two (27.2%) encountered more than 5 patients weekly who had or were at risk for pressure injury.

Quantitative analysis. The calculated average item appropriateness score for the entire algorithm's decision points was 3.02, with an overall CVI of 0.90 (out of 1.0). Suggestions were made for five decision points/steps. Four participants suggested that the use of support surfaces should be explained. Two participants suggested that priority should be given to enteral feeding. Four participants suggested that the severity of the edema and the gode drop status should be added. Four participants suggested that the phrase "follow the age of 65 and above" should be added in front of "especially". Two participants suggested that the value of prealbumin should be added. Otherwise, quantitative data analysis found that the algorithm components and inherent decision processes are appropriate.

All participants gave written answers about the evaluation of the pressure injury prevention algorithm. Analysis of general answers produced themes such as comprehensive, feasible, necessary, and helpful in making clinical decisions about the strengths of the algorithm. Negative themes included complexity and taking a long time in practice.

Table 1. Study participant data (N = 81)

Nurses' Characteristics	N	%
Gender		
Male	12	14.8
Female	69	85.2
Age (in years)		
20-30	57	70.4
31-40	23	28.4
41-50	1	1.2
Professional degree		
Masters	3	3.7
Bachelor	48	59.3
Years of intensive care experience		
10–14	2	2.5
5–9	29	35.8
1-4	50	61.7
Average number of weekly patients treated who are at risk for or who have pressure injury		
≥5	22	27.2
3-4	16	19.8
1–2	43	53.1
Source of pressure injury education		
Wound care nurse	4	9.5
Conference	3	7.1
Journal	7	16.7
In-service training	28	66.7

Discussion

The best evidence-based practices for preventing pressure injury are approved by the European Pressure Ulcer Advisory Panel (EPUAP) and the National Pressure Ulcer Advisory Panel (NPUAP) under skin care, activity management, nutrition management, moisture/incontinence management, support surface management, training, and registration. Pressure injury prevention algorithms should include these approaches [1]. In this study, the content validation of the algorithm created by the combination of preventive care stages was done. To the author's knowledge, this is the first study in Turkey to examine the content validity of the Pressure Injury Algorithm generated by the combination of the preventive care stages.

Table 2. Content validation results: individual item score averages and content validity index (CVI)a

Item #/Decision statement/step	N	Average	SD	CVI
1. Assess the skin.				
(Within the first 8 hours after being admitted to the clinic)	81	4	0.00	1
1.a Color (Normal, Pale, Cyanotic, Jaundice, Redness)	81	4	0.00	1
1.b Moisture (Normal, Dry, Wet)	81	4	0.00	1
1.c Heat (Normal, Cold, Hot)	81	4	0.00	1
1.d Structure (Smooth, Rough, Thin, Thick, Flexible, Nervous, Sensitive, Susceptible to scratches)	81	4	0.00	1
1.e Edema (Yes,No)	81	3.62	0.58	0.95
1.f Turgor (Normal, Abnormal)	81	4	0.00	1
1.g Localized pain (Yes, No)	81	3.89	0.32	1
1. h Lesion (Yes, No)	81	4	0.00	1
2. Non-intact skin	81	4	0.00	1
2.a Follow the inflammation.	81	4	0.00	1
2.b Follow skin damage related to moisture.	81	4	0.00	1
2.c Follow the induration.	81	4	0.00	1
2.d Follow the partial and full-thickness skin loss.	81	4	0.00	1
3. Intact skin	81	4	0.00	1
4. Evaluate daily risk with holistic factors.	81	4	0.00	1
4.a Follow the Weight/BMI.	81	4	0.00	1
4.b Follow the fever.	81	4	0.00	1
4.c Follow age 65 and above.	81	3.37	0.58	0.95
4.d Follow the edema.	81	4	0.00	1
4.e Follow the Diastolic pressure <60mmHg.	81	4	0.00	1
4.f Follow the protein level.	81	4	0.00	1
4.g Follow the albumin level.	81	3.75	0.49	0.98
4.h Follow the hemodynamic instability.	81	4	0.00	1
4.i Follow the reduced activity level.	81	4	0.00	1
4. j Follow the comorbities.	81	4	0.00	1
5. Evaluate pressure-injury risk with a valid assessment (Braden, Norton vs.).	81	4	0.00	1
6. Evaluate change in each situation and daily risk with risk assessment tool.	81	4	0.00	1
7. Not at risk+Braden >18	81	4	0.00	1
7.a Daily; Continue skin assessment.	81	4	0.00	1
7.b Daily; Continue to use the Braden scale.	81	4	0.00	1
8. Yes, at risk + Braden≤18	81	4	0.00	1
9. Pressure injury	81	4	0.00	1
9.a Yes	81	4	0.00	1
9.b No	81	4	0.00	1
10. * Set the stage. *Use the template behind the algorithm to determine the stage.	81	4	0.00	1
10.a Stage II Pressure Injury	81	4	0.00	1

10.b Stage III Pressure Injury	81	4	0.00	1
10.c Stage IV Pressure Injury	81	4	0.00	1
10.d Unstageable Pressure Injury	81	4	0.00	1
10.e Deep Tissue Pressure Injury	81	4	0.00	1
10.f Mucosal Membrane Pressure Injury	81	4	0.00	1
11. Tell stoma and wound care nurse.	81	4	0.00	1
12. Stage I Pressure Injury	81	4	0.00	1
13. Perform preventive care.	81	4	0.00	1
14. Skin Care	81	4	0.00	1
14.a Keep the skin clean and at normal moisture.	81	4	0.00	1
14.b Clean the skin with a Ph stabilizing product.	81	4	0.00	1
14.c Protect skin with barrier product.	81	4	0.00	1
14.d Do not rub skin strongly, do not massage.	81	3.86	0.34	1
14.e Evaluate the pressure regions in contact with the medical device at least twice a day.	81	4	0.00	1
14.f Ensure that the sheets are kept clean, stretched, and dry.	81	4	0.00	1
15. Activity Management	81	4	0.00	1
15.a Change position at least every 2 hours.	81	4	0.00	1
15.b Give 30° right side, back side, 30° left side respectively.	81	4	0.00	1
15.c If there is no objection, give a supine position.	81	4	0.00	1
15.d Do not rotate to the area of redness.	81	3.93	0.24	1
15.e Prevent the individual from rubbing the skin while positioning.	81	4	0.00	1
15.f Do not position medical devices so they will cause pressure.	81	4	0.00	1
15.g Support the body region where medical devices are located.	81	4	0.00	1
15.h Do not give 90° side position - semi-seated position.	81	4	0.00	1
15. i Support the extremities.	81	4	0.00	1
16. Nutrition Management	81	4	0.00	1
16.a Provide the diary / nutrition nurse to organize the daily diet together.	81	4	0.00	1
16.b Provide individual nutrition (enteral/parenteral).	81	3.64	0.53	0.98
16.c Evaluate the daily nutritional status.	81	4	0.00	1
16.d Follow the weekly albumin / CRP values.	81	4	0.00	1
16.e Evaluate the state of dehydration.	81	4	0.00	1
17. Moisture/Incontinence Management	81	4	0.00	1
17.a Minimize skin contact with urine / feces.	81	4	0.00	1
17.b Avoid excessive skin moisture.	81	4	0.00	1
17.c Use barrier products.	81	4	0.00	1
18. Support Surface Management	81	4	0.00	1
18.a Use a support surface for individuals in need.	81	3.56	0.50	1
18.b Use a support surface that matches the characteristics and risk factors of the individual.	81	3.40	0.59	0.95
19. PRESSURE INJURY STAGING	81	4	0.00	1
20. Stage 1 Pressure Injury				
Non-blanchable erythema of intact skin	81	4	0.00	1
20.a Intact skin with non-blanchable redness of a localized area usually over a bony prominence.	81	4	0.00	1
20.b The area may be painful, firm, soft, warmer, or cooler as compared to adjacent tissue.	81	4	0.00	1
20.c Darkly pigmented skin may not have visible blanching.	81	4	0.00	1
21. Stage 2 Pressure Injury				
Partial-thickness skin loss with exposed dermis.	81	4	0.00	1
21.a Partial-thickness loss of skin with exposed dermis.	81	4	0.00	1
21.b The wound is superficial.	81	4	0.00	1
21.c The wound bed is red-pink in color and has no yellow, brown necrotic tissue.	81	4	0.00	1
21.d It can also be seen as bulbs filled with solid or explosive liquid.	81	4	0.00	1
22. Stage 3 Pressure Injury				
Full-thickness skin loss	81	4	0.00	1
22.a Full-thickness loss of skin.	81	4	0.00	1
22.b Subcutaneous tissue can be seen in the wound bed, but bones, tendons, and muscles are not affected.	81	4	0.00	1
22.c Slough and/or eschar may be visible.	81	4	0.00	1
22.d Undermining and tunneling may occur.	81	4	0.00	1
23. Stage 4 Pressure Injury				
Full-thickness skin and tissue loss	81	4	0.00	1
23.a Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer.	81	4	0.00	1
23.b Slough and/or eschar may be visible.	81	4	0.00	1
23.c Undermining and/or tunneling often occur.	81	4	0.00	1
24. Unstageable Pressure Injury				
Obscured full-thickness skin and tissue loss	81	4	0.00	1
24.a Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar.	81	4	0.00	1
25. Deep Tissue Pressure Injury				
Persistent non-blanchable deep red, maroon, or purple discoloration	81	4	0.00	1
25.a Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration, or epidermal separation revealing a dark wound bed or blood filled blister.	81	4	0.00	1
25.b The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue.	81	4	0.00	1
26. Mucosal Membrane Pressure Injury	81	4	0.00	1
26.a Mucosal membrane pressure injury is found on mucous membranes with a history of a medical device in use at the location of the injury. Due to the anatomy of the tissue these injuries cannot be staged.	81	4	0.00	1

a Rating scale scores: 4 = very relevant and appropriate; 3 = relevant but needs minor alteration; 2 = unable to assess relevance without revision; 1 = not relevant (appropriate). PU=pressure ulcer; CVI range = 0–1; CVI >0.70 = generally valid

The study provided content validation data and an overview of strengths and areas of challenge. CVI (0.90 out of 1.0) of the pressure injury prevention algorithm for use in adults were strong, suggesting the components were appropriate to the purpose of the instrument. Suggestions were recived for five decision point/steps; support surfaces should be explained, priority should be given to enteral feeding, the severity of the edema and the gode drop status should be added, the phrase “especially” should be added in front of “follow the age of 65

and above", and the value of prealbumin should be added. Otherwise, quantitative data analysis found that the algorithm components and inherent decision processes are appropriate.

Following a careful review of all results, several minor algorithm modifications were made. The severity of the edema was added to the pressure injury prevention algorithm with the recommendation of "The severity of the edema and the gode drop status should be added". "Especially" was added in front of the phrase "Follow the age of 65 and above" by the participants' suggestions. "Firstly enteral then parenteral" was added to the pressure injury prevention algorithm by the participants' suggestions. The value of prealbumin was added to the pressure injury prevention algorithm based on the participants' suggestions.

face management. Thus, we undertook the establishment of a more comprehensive pressure injury prevention algorithm. As a result, necessary arrangements were made and the algorithm was prepared in its final form (see Figure 1/2).

Participants comments were generally supportive and positive. The few negative comments were used to tweak the structure of the algorithm to support its effectiveness.

Limitations

The pressure injury algorithm was designed to focus on adults and cannot be suggested for safe use in pediatric and/or neonatal populations.

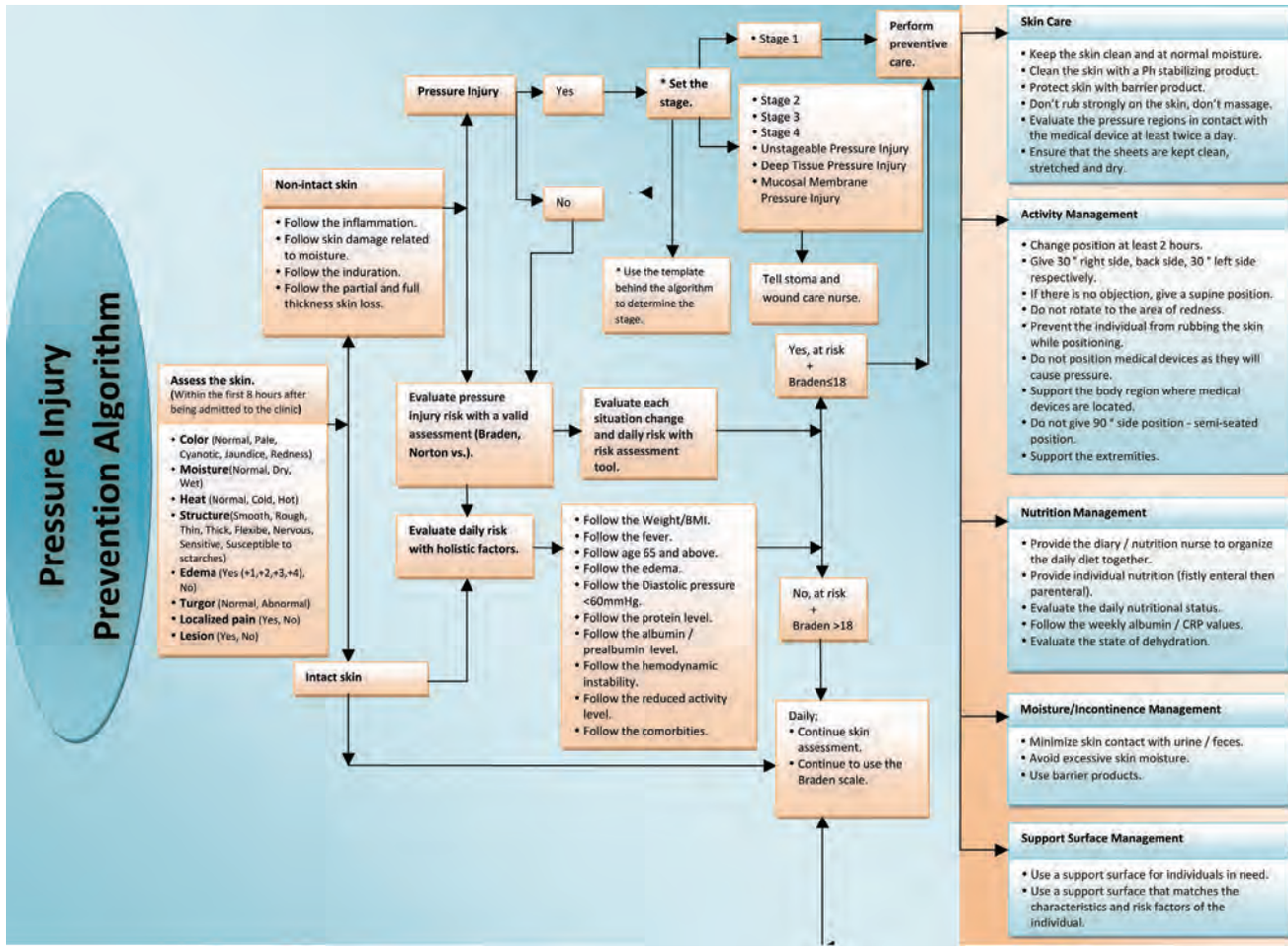

Figure 1. Pressure Injury Prevention Algorithm.

Since the support surface is not used in the institution, no information was reported on this issue. So the participants suggest explaining the support surfaces. Algorithms aren't comprehensive, but are ideal to identify appropriate management strategies, to communicate a complex set of conditional expressions, and to help translate research into clinical practice [25]. The other content validation study participants indicated they were pleased with the easy-to-follow steps and were interested in algorithmic guidelines, but that they would require more detail in some action steps [26]. In this study, an algorithm was created that includes a combination of preventive care stages such as skin care, activity management, nutrition management, moisture / incontinence management, and support sur-

Conclusion

In conclusion, strategies for preventing pressure injury include skin care, activity management, nutrition management, moisture/incontinence management, support surface management, registration, and training. Increased quality of care can be observed through the use of algorithms that were created through a combination of preventive care phases. In this study, the content validation of the algorithm created by the combination of preventive care stages was determined. The results of the study of content validation involving 81 intensive care nurses were similar to results in the literature. The algorithm's overall mean score was 3.02 (SD: 0.02). All except 1 of the 101 steps had a high CVI (average 0.90), indicating that the pressure injury pre-

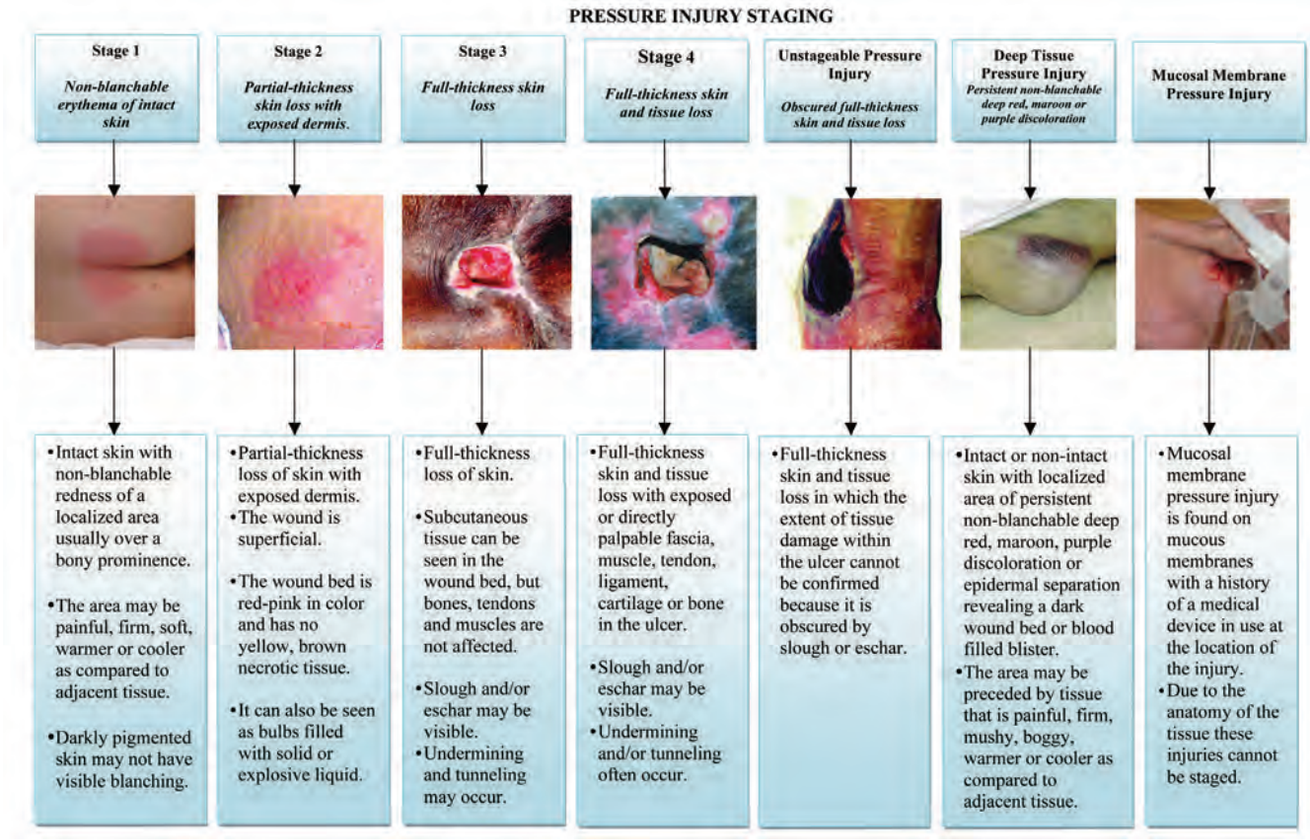

Figure 2. Pressure Injury Prevention Algorithm-Pressure Injury Staging

vention algorithm is valid and appropriate with the addition of the minor modifications. A construct validated pressure injury prevention algorithm may help nurses identify pressure injury and risks and also help them develop appropriate nursing interventions for intensive care patients. We recommend carrying out large-group studies involving the application and evaluation of the pressure injury prevention algorithm.

Competing interests

The authors declare that they have no competing interests.

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ANTIBACTERIAL EFFECTS OF VARIOUS CHEMICAL AGENTS ON AGGREGATIBACTER ACTINOMYCETEMCOMITANS

FARKLI KİMYASAL AJANLARIN AGGREGATİBACTER ACTİNOMYCETEMCOMİTANS BAKTERİSİ ÜZERİNDEKİ ANTİBAKTERİYEL ETKİLERİNİN ARAŞTIRILMASI

ANTIBACTERIAL EFFECTS OF CHEMICAL AGENTS ON AGGREGATIBACTER ACTINOMYCETEMCOMITANS

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Öz

Amaç: Periodontal hastalıklar kronik, enflamatuvar ve enfeksiyöz karakterde hastalıklardır. Bu sebeple periodontal tedavi hastalığa neden olan periodontopatojen bakterilerin eliminasyonunu hedefler. Bu araştırmanın amacı, doğal kimyasal ürünler olan asetik asit, sodyum bikarbonat ve sodyum klorürün Aggregatibacter actinomycetemcomitans üzerindeki etkilerinin araştırılmasıdır. Gereç ve Yöntem: Bu araştırmada Aggregatibacter actinomycetemcomitans (ATCC 33384TM) suşu test edilmiştir. Asetik asit, sodyum bikarbonat ve sodyum klorür, %5 konsantrasyonda distile suda dilüe edilerek uygulanmıştır. Negatif kontrol olarak distile su, pozitif kontroller olarak penisilin, tetrasiklin, siprofloksasin ve %0,12'lik klorheksidin, kullanılmıştır. Test ajanlarının antimikrobiyal etkileri, disk difüzyon, minimal inhibitör konsantrasyon ve minimal bakterisidal konsantrasyon testleri ile araştırılmıştır. Bulgular: Antibakteriyel etkinliği en fazla olan antibiyotik siprofloksasin bulunmuştur. Penisilin, A. actinomycetemcomitans üzerine orta seviyede etki göstermiştir. Klorheksidin penisiline benzer bir etki göstermiştir. Asetik asit, klorheksidin ve penisilinden daha kuvvetli bir inhibitor etki sağlamıştır. Sodyum bikarbonat ve tuz antibakteryel etki sağlamamıştır. Tartışma: Asetik asit anti-bakteriyel bir metabolittir ve aynı zamanda sirke olarak günlük tüketimi vardır. Periodontal patojen bakteriler üzerindeki antibakteriyel etkisi sayesinde, periodontal tedaviye yardımcı olabilir. Gargara, diş macunu, jel veya irrigasyon ajanı şeklinde preparatları hazırlanarak klinik kullanıma uygunluğunun test edilmesi gereklidir.

Anahtar Kelimeler

Aggregatibacter Actinomycetemcomitans; Agresif Periodontitis; Ağız Sağlığı; Asetik Asit

Abstract

Aim: Periodontal diseases are chronic, inflammatory, and infectious diseases. Therefore, periodontal treatment aims to eliminate periodontopathogenic bacteria causing periodontal diseases. The aim of the present study was to evaluate the effect of commonly-used products such as acetic acid, sodium bicarbonate, and sodium chloride on periodontopathogenic bacteria, Aggregatibacter actinomycetemcomitans. Material and Method: In the present research, effects on Aggregatibacter actinomycetemcomitans (ATCC 33384TM) were tested. Acetic acid, sodium bicarbonate, and sodium chloride were used in 5% concentration dissolved in distilled water. The negative control agent was distilled water and the positive control agents were chlorhexidine, penicillin, tetracycline, and ciprofloxacin. The antibacterial efficacy against bacteria was tested via disc-diffusion method, minimum inhibitory concentration test, and minimum bactericidal concentration tests. Results: The most antibacterial efficacy was found in ciprofloxacin. Penicillin had moderate effect and chlorhexidine provided a similar efficacy. Acetic acid provided an inhibitory effect higher than penicillin and chlorhexidine against Aggregatibacter actinomycetemcomitans but lower than tetracycline and ciprofloxacin. Sodium bicarbonate and sodium chloride showed no inhibitory effect. Discussion: Acetic acid is commonly consumed in the form of vinegar. Due to its antibacterial efficacy against Aggregatibacter actinomycetemcomitans, it can be useful as an adjunct to periodontal treatment. Further studies to evaluate clinical use of acetic acid as mouthwash, dentifrice, gel, and/or irrigation agent are necessary.

Keywords

Aggregatibacter Actinomycetemcomitans; Aggressive Periodontitis; Acetic Acid; Oral Care;

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Introduction

Periodontitis is the chronic inflammatory and infectious disease of periodontium primarily caused by dental plaque [1]. There are two forms of the disease: chronic periodontitis (CP) and aggressive periodontitis (AgP) [2]. In both forms, bacterial accumulation initiates an inflammatory process and host-bacterial interactions determine the disease course [3]. In AgP, both the bacterial component of dental plaque and the response to these bacteria is different from CP, resulting in a more rapid and severe disease course [2]. AgP lesions are usually associated with a certain bacterial strain called Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans) [4, 5]. Because of these differences between the diseases, the treatment modalities are also different. CP generally responds well to conventional periodontal treatment while AgP requires additional applications such as chemotherapeutic agents [6]. These chemotherapeutics include mainly antibiotics and antiseptics such as chlorhexidine. However, long-term use of these agents causes adverse effects like antibiotic resistance, suppression of regular oral microbiota, and fungus superinfection. Therefore, naturally-derived agents that do not cause these adverse effects might be beneficial.

Antibiotics act by disrupting genetic materials, cell wall, or metabolism [7]. Chlorhexidine, on the other hand, acts by binding cationic chlorhexidine molecules to the cell wall [8]. Most of the bacteria are sensitive to the environmental changes. Thus, changes in temperature, pH, pressure, and/or humidity can also inhibit bacterial growth. For instance, acidic compounds increase pH and most bacteria cannot grow in an acidic medium. Acetic acid is an organic compound with a pH 2.4 and is used in many households as vinegar. Sodium bicarbonate is a food additive that increases pH due to its alkalinity. Acetic acid has been shown to have antibacterial efficacy by various studies [9] while sodium bicarbonate has been shown to exhibit antifungal properties [10, 11]. As for sodium chloride, bacterial growth requires certain amounts of sodium chloride and concentration in the growth medium influences bacterial growth. High concentrations of sodium chloride in an environment might provide antibacterial efficacy by causing lysis [12].

Acetic acid, sodium bicarbonate, and sodium chloride are commonly-used products that, due to their chemical structures, might exhibit antibacterial properties against periodontopathogenic bacteria. Therefore, the aim of the present study was to evaluate the effect of these products on A. actinomycetemcomitans cell culture via the Kirby-Bauer test, also called the disc-diffusion test.

Material and Method

Acetic acid (Sigma, St. Louis, Missouri, USA), sodium bicarbonate (Sigma, St. Louis, Missouri, USA), and sodium chloride (Sigma, St. Louis, Missouri, USA) were used as test materials. Penicillin, ciprofloxacin, tetracycline, and chlorhexidine (CHX) were used as positive controls and distilled water was used as a negative control. All solutions except CHX were prepared as 5% dilutions of each material in distilled water. 0.012% CHX was used. The antibacterial efficacy of test materials was tested via the Kirby-Bauer (disc-diffusion) method and minimum inhibitory concentration and minimum bactericidal concentrations were also determined.

Disc-diffusion method [13]

The bacterial species used in this study was A. actinomycetemcomitans (ATCC 33384TM). The antimicrobial activity was determined with the disc-diffusion method. First, nutrient agar (NA) was prepared and 108 CFU/mL of bacteria was added to 100 mL NA solution. Then, bacteria was inoculated to the petri dish containing Mueller-Hinton agar (MHA) medium, which does not include any indicator or inhibitor. 38.0 g/L MHA was sterilized by autoclave (121°C, 15 min). After cooling to 45-50 °C 5% defibrinated sheep blood was added. 20 mL of blood-enriched MHA was poured into sterile petri dishes. The blank discs (6 mm diameter, Oxoid) were impregnated with 20 mL of each test compound dissolved in distilled water (105 µg/disc) and placed on the inoculated agar. The inoculated plates were incubated at aerobic conditions with 36°C for 24 h. After incubation, the growth inhibition zones were measured via a millimetric scale. The procedure was repeated two more times and the arithmetic mean of the three measurements was recorded as one inhibition zone. The results are shown in Table 1.

Table 1.

Materials	A. actinomycetemcomitans		
	Inhibition zones	MIC values	MBC values
Penicillin	10 mm	MIC was not detected in 50-0.0243 dilutions.	X
Tetracycline	17 mm	MIC was not detected in 50-0.0243 dilutions.	X
Metronidazole	X	X	X
Ciprofloxacin	48 mm	3.905 µl/ml	3.905 µl/ml
Chlorhexidine 0.12%	11 mm	MIC was not detected in 50-0.0243 dilutions.	X
Sodium bicarbonate	X	X	X
Acetic acid	12 mm	7.81 µl/ml	1000 µl/ml
Sodium chloride	X	X	X

MIC tests

MIC values of test materials against A. actinomycetemcomitans were determined with a micro-well dilution method (Figure 1). Tryptic soy broth (TSB) was used in MIC tests. TSB; 20 gr

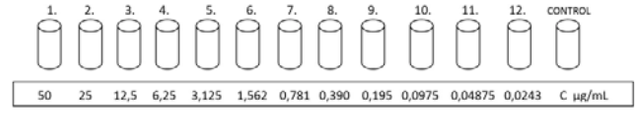

Figure 1. Minimum inhibitory concentration test protocol.

tryptone (Sigma, St. Louis, Missouri, USA); 5 gr soytone (Sigma, St. Louis, Missouri, USA); 5 gr NaCl; and 950 ml distilled water were mixed to form a 30 gr/L solution that was then sterilized with autoclave (121°C, 15 min). After cooling to 47°C, 5.0 µg/mL hemin and 0.5 µg/mL vitamin K1 were added and gently mixed. The inoculum of microorganisms was prepared using 12 h broth cultures, and suspensions were adjusted to 0.5 McFarland standard turbidity. Test compounds and the positive control agents dissolved in distilled water were first diluted to the high-

est concentration tested (1000 mg/ml), and then serial two-fold dilutions were made (concentration range 7.8–1000 mg/ml) in sterile 10-ml test tubes containing TSB. 96-Well plates were prepared by dispensing 95 ml of TSB and 5 ml of the inoculum into each well. Then, 100 ml of compound solutions were added. Wells containing 195 ml of TSB without compound and 5 ml of the inoculum were used as negative control. The final volume in each well was 200 ml. The 96-well plates were incubated at 368 for 24 h. The assay was performed in triplicate.

MBC tests

Samples were taken from MIC test tubes and inoculated on petri dishes containing MHA. The lowest concentration inhibiting bacterial growth was recorded as MBC.

Results

Against A. Actinomycetemcomitans the most effective antibiotic was ciprofloxacin and second was tetracycline. The antibacterial effects of penicillin, CHX, and acetic acid were similar. There was no inhibitory effect observed in sodium bicarbonate and sodium chloride. Chlorhexidine, penicillin, and tetracycline did not exhibit antibacterial effect on MIC test tubes with the studied concentrations from 0. The results are shown in Table 1.

Discussion

The present study evaluated any possible antibacterial effects of the commonly-used products vinegar, sodium bicarbonate, and salt against one of the etiological factors of aggressive periodontitis, A. actinomycetemcomitans. Results demonstrated that the major ingredient of vinegar, acetic acid, has a strong antibacterial efficacy while neither sodium bicarbonate nor salt had an inhibiting effect.

Treatment of aggressive periodontitis is one of the most challenging practices for clinicians. There are no established protocols and guidelines for effective and complete treatment of the disease [14]. The most accepted treatment measures combine conventional mechanical, nonsurgical, and surgical treatments with diverse adjunctive anti-infective therapies such as antiseptics and antibiotics [15]. As A. actinomycetemcomitans can invade gingival tissues and is generally related to AgP lesions, systemic and/or local antibiotics are usually recommended as adjuncts to conventional treatment. However, there are certain disadvantages of chemotherapeutic therapy. These are bacterial resistance, adverse systemic effects of systemic antibiotics, cost of local antibacterial agents, and alteration in regular oral microbial components [16]. The present study evaluated the effectiveness of acetic acid, bicarbonate, and salt as antiseptic and antibacterial agents that are natural products with low side effects.

Most of the bacterial species in the oral cavity are anaerobic and/or facultative anaerobic bacteria [17]. These bacteria obtain their energy from phosphorylation at the substrate level and produce metabolic end products such as long, medium, and short chain fatty acids [18]. These by-products inhibit metabolism and growth of other bacterial cells and even the host defense mechanism [19, 20]. Acetic acid is a short chain fatty acid (SCFAs) produced by bacteria as an end metabolite. Periodontopathogenic bacteria, A. actinomycetemcomitans, Porphyromonas gingivalis, and Fusobacterium nucleatum, produce SCFAs as metabolic products [21]. Recently acetic acid has been reported to inhibit the growth and biofilm formation of the strongly pathogenic bacterium Pseudomonas aeruginosa [22]. Changes in local tissue concentrations of SCFAs are related to the metabolism of the dysbiotic microbiota and infectious diseases such as periodontitis alter the concentrations of these molecules. In the present study, 5% acetic acid exhibited more antibacterial efficacy than CHX and penicillin against A. actinomycetemcomitans. In contrast, Huang et al. reported that acetic acid had no significant antibacterial effect on A. actinomycetemcomitans [23].

Other than acetic acid, sodium bicarbonate is also known as an antimicrobial agent especially effective on fungus. Research has shown that bicarbonate inhibits growth of C. albicans [24]. Nonetheless, sodium bicarbonate was found to be ineffective as an antibacterial agent [10]. Likewise, our present results found no inhibitory effect of sodium bicarbonate on A. actinomycetemcomitans. Another household agent tested in this study was sodium chloride. Bacteria usually do not require sodium ions for growth, and high concentrations of salt inhibit bacterial growth (except halophilic or halotolerant species). However, antibacterial tests showed that no inhibition zone was observed with a 5% concentration of salt.

Conclusions

Among the tested molecules, only acetic acid showed antibacterial effectiveness against A. actinomycetemcomitans. Acetic acid is a commonly-used product and has no side effects with low doses such as a 5% concentration. Due to its biological properties, use of acetic acid as an irrigation agent and/or mouthwash might be beneficial as an adjunctive agent to periodontal therapy.

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Competing interests

The authors declare that they have no competing interests.

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