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Evaluation of Mean Platelet Volume Before and After Cobalamin Treatment in Patients with Vitamin B_{12} Deficiency

B_{12} Vitamin Eksikliği Olan Hastalarda Kobalamin Tedavisi Öncesi ve Sonrası Ortalama Trombosit Volümünün Değerlendirilmesi

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ABSTRACT

Purpose: Megaloblastic anemia due to vitamin B_{12} deficiency is common in the population. Vitamin B_{12} therapy may stimulate all cell types in the bone marrow. We investigated whether young, active and large platelets are released into the peripheral blood during vitamin B_{12} treatment and measured the level of mean platelet volume (MPV), an indicator of the presence of these platelets.

Materials and Methods: A total of 204 patients (40 males, 160 females) with vitamin B_{12} deficiency were included in this study. Cobalamin was administered by intramuscular injections. We evaluated the hematologic and biochemical parameters before and after one month of vitamin B_{12} treatment.

Results: The mean age of patients was 40.1 ± 17.4 years. In the pretreatment group, the mean level of vitamin B_{12} was 151.2 ± 34.6 pg/mL, the MPV was 7.8 ± 1.4 fL. In the posttreatment group, the mean vitamin B_{12} level was 638 ± 608 pg/mL, the MPV was 8.3 ± 1.3 fL. The levels of vitamin B_{12} ($P < 0.001$) and MPV ($P < 0.001$) were significantly higher in the posttreatment group than those in the pretreatment group.

Conclusions: After one month of cobalamin treatment in patients with vitamin B_{12} deficiency, the levels of B_{12} and MPV were higher than the pretreatment levels. These results showed that vitamin B_{12} treatment may increases the release of large and active thrombocytes into the peripheral blood; therefore, caution may be needed in patients predisposed to thrombotic diseases.

Key Words: Cobalamin, mean platelet volume, vitamin B_{12}, vitamin B_{12} deficiency.

ÖZET

Amaç: B_{12} vitamin eksikliği toplumda sık görülen bir megaloblastik anemidir. B_{12} tedavisi kemik iliğindeki tüm serileri stimüle edebilir. Biz bu çalışmada B_{12} tedavisi sırasında periferik kana genç, aktif ve büyük trombositlerin salınıp salınmadığını ve bu trombositlerin varlığının iyi bir göstergesi olan ortalama trombosit hacmi (OTH) seviyesini araştırmayı amaçladık.

Materyal ve Metod: Bu çalışmaya 40 erkek ve 160 kadın toplam 204 hasta dahil edildi. Kobalamin intramuskuler (İM) enjeksiyon yoluyla uygulandı. B_{12} tedavisinden önce ve tedaviden bir ay sonra hematolojik ve biyokimyasal testleri değerlendirdik.

Bulgular: Hastaların yaş ortalaması 40.1 ± 17.4 yıl idi. Tedavi öncesi grupta, B_{12} vitamin seviyeleri 151.2 ± 34.6 pg/mL ve OTH 7.8 ± 1.4 fL idi. Tedavi sonrası grupta, B_{12} vitamin seviyeleri 638 ± 608 pg/mL ve OTH 8.3 ± 1.3 idi. Tedavi sonrası grupta B_{12} vitamin ($P < 0.001$) ve OTH ($P < 0.001$) tedavi öncesi gruptan anlamlı yüksekti.
Sonuç: B_{12} eksikliği olan hastalarda İM kobalamin tedavisinin 1. ayı sonunda tedavi öncesi değerlere göre B_{12} ve OTH değerinin arttığı MCV değerinin düştüğü bulundu. Çalışmamızın sonuçları gösterdi ki İM B_{12} tedavisi sırasında büyük ve aktif trombositler perifere daha çok salınabilir; trombotik hastalıklara yatkın olan hastalarda dikkatli olmak gerekebilir.
Anahtar Kelimeler: Kobalamin, ortalama trombosit hacmi, B_{12} vitamini, B_{12} vitamin eksikliği.

INTRODUCTION

Vitamin B12 has a role as a cofactor in DNA synthesis, methylation, neurotransmitter synthesis and in the homocysteine/methionine cycle1. Mental and neural functions may be impaired in patients with vitamin B12 deficiency. Neurological symptoms may occur without any hematological finding in more than 25% of patients with vitamin B12 deficiency, and this deficiency is the major cause of depression in the elderly[2,3]. Development of vitamin B12 deficiency may be associated with being vegetarian, the use of antacids, Helicobacter pylori infection, atrophic gastritis and a history of chronic illness. Also, vitamin B12 deficiency may be caused generally by deficiencies in intrinsic factors released by gastric parietal cells or less frequently by gastrointestinal malabsorption diseases (e.g., celiac disease, large gastric and ileal resection, intestinal blind loops), Diphyllobothrium latum infestation and nitrous oxide intoxication[4-8].

The mean platelet volume (MPV) reflects the size of thrombocytes, and is an important marker of thrombocyte function. MPV follow-up can be done using a low cost routine hematologic test[9]. Large thrombocytes have more granules and a higher thromboxane A2 level. They aggregate more rapidly with collagen and express more glycoprotein Ib and IIb/IIIa receptors than small thrombocytes[10,11]. Thrombocytes secrete many important substances such as mediators of coagulation, inflammation, thrombosis, and atherosclerosis, which increase the incidence of occlusive vascular disease. Previous studies have demonstrated that MPV levels are associated with both arterial and venous diseases[12,13]. During vitamin B_{12} treatment, bone marrow production of granulocytes, erythrocytes and megakaryocytes might be induced, and young and large platelets could be released into the peripheral blood.

MATERIALS AND METHODS

This retrospective study was carried out in the internal medicine department of the Recep Tayyip Erdoğan University School of Medicine. A total of 204 patients diagnosed with vitamin B_{12} deficiency (160 females, 44 males) who had applied to the internal medicine clinic in the hospital were included in this study. The patient complaints included forgetfulness, loss of balance, numbness, and tingling and burning in hands and feet. Patients with serum B_{12} levels less than 200 pg/mL were considered as having vitamin B_{12} deficiency; patients with serum levels equal or higher than 200 pg/mL were considered normal[14].

Cobalamin (Dodex® 1000 µg ampul, Deva Holding, Turkey) was administered once daily for 10 days. After 10 days, it was administered once a week for 4 weeks, then once a month for life[15]. The files of patients taking B_{12} treatment for after first month were retrospectively analyzed, and the hematologic and biochemical results were recorded. This study conformed to the Helsinki Declaration and was approved by the local ethics committee of the Recep Tayyip Erdogan University School of Medicine, Rize, Turkey.

Exclusion criteria for patients were as follows: the presence of folate deficiency, iron deficiency anemia or chronic diseases (such as diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic renal failure and thyroid diseases). Patients were nonsmokers and did not consume

alcohol or use drugs (especially drugs that induce folate deficiency).

Laboratory tests

The hematologic tests such as MPV, Hb, white blood cell count (WBC), mean cell volume (MCV) and platelets (plt) were performed using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The biochemical tests such as fasting plasma glucose, blood urea nitrogen, creatinine, AST and ALT were performed with the photometric assays of the Abbott Architect C16000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA), and the TSH and vitamin B_{12} tests were performed using the chemiluminescent microparticle immunoassay (CMIA) method of the Abbott Architect I 2000 immunology analyzer (Abbott Diagnostics, Abbott Park, IL, USA).

Statistical analysis

The data of this study were analyzed using descriptive and inferential statistics on statistical package for the social sciences software, release 13.0 for Windows (SPSS version 13.0., Chicago: SPSS Inc). Means and standard deviations were computed; Paired *t*-test, Wilcoxon tests, Pearson's correlation test and linear regression analysis were used as appropriate. A significant difference was implied when the P value is < 0.05.

RESULTS

In the pretreatment group, the the MCV was 95.2 ± 10.7 fL, the MPV was 7.8 ± 1.4 fL and the B_{12} was 151.2 ± 34.6 pg/mL. In the post treatment group, the MCV was 85.6 ± 5.0 fL, the MPV was 8.3 ± 1.3 fL and the B_{12} was 638 ± 608 pg/mL. The MPV (P < 0.001) and B_{12} (P < 0.001) were significantly higher in the posttreatment group than in the pretreatment group. The MCV (P < 0.001) was significantly lower in the posttreatment group than in the pretreatment group. The demographic characteristics and the results of hematological parameters are shown in Table 1 and biochemical parameters are shown in Table 2.

Correlation analysis indicated positive correlations between MPV with Hb (r = 0.152, P = 0.002) and B_{12} (r = 0.156, P = 0.002); positive correlations between WBC and B_{12} (r = 0.120, P = 0.016), Hb (r = 0.155, P = 0.002) and plt (r = 0.213 P < 0.001); and negative correlation between age and Hb (r^2 = 0.044, P = 0.002).

A linear regression analysis was performed in which MPV was used as the dependent variable and Hb, MCV, plt, WBC and B_{12} were used as the independent variables. We found that plt (β = -0.443, P = 0.001), WBC (β = 0.123, P = 0.007) and B_{12} (β = 0.123, P = 0.006) were independently associated with increased MPV. We found that Hb (β = 0.085, P = 0.059) and MCV (β = 0.035, P = 0.430) were not independently associated with increased MPV.

Table 1. The main characteristics and hematological parameters for the two groups.

N = 204	Before treatment (mean ± SD)	After treatment (mean ± SD)	P value
Age (year)	40.1 ± 17.4		
Gender (M/F)(N)	44/160		
WBC (x109/L)	6.6 ± 1.7	6.9 ± 2.0	0.014
Hb (g/dL)	12.5 ± 1.9	12.8 ± 1.5	0.004
MCV (fL)	95.2 ± 10.7	85.6 ± 5.0	0.001
Platelet (x109/L)	269 ± 79	261 ± 67	0.013
MPV (fL)	7.8 ± 1.4	8.3 ± 1.3	0.001

Abbreviations: M, male; F, female; WBC, white blood cells; MCV, mean cell volume; MPV, mean platelet volume.

Table 2. The biochemical parameters for the two groups.

N = 204	Before treatment (mean ± SD)	After treatment (mean ± SD)	P value
FPG (mg/dL)	90.6 ± 27.2	90.9 ± 25.6	0.763
BUN (mg/dL)	27.6 ± 9.3	27.6 ± 9.4	0.894
Creatinin (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.086
AST (IU/L)	18.2 ± 5.6	18.9 ± 7.1	0.395
ALT (IU/L)	17.0 ± 9.1	17.7 ± 10.2	0.307
Vitamin B12 (pg/mL)	151.2 ± 34.6	638 ± 608	0.001

Abbreviations: FPG, fasting plasma glucose; BUN, blood urea nitrogen.

DISCUSSION

Our study demonstrated elevation of B_{12}, Hb, WBC and MPV levels after IM injection of cobalamin in patients with vitamin B_{12} deficiency. The MCV level was significantly decreased posttreatment, as compared to pretreatment with vitamin B_{12} therapy. A strong relationship was found between the increased MCV level and vitamin B_{12} level. Vitamin B_{12} deficiency may have hematologic, neurologic, gastrointestinal and cardiovascular symptoms[16-20]. These symptoms range widely from mild sensory neuropathy, macrocytosis and combined degeneration of the spinal cord to serious conditions such as pancytopenia. In this study, patients with B_{12} deficiency had mild symptoms such as fatigue, forgetfulness, numbness and tingling in hands and feet.

Vitamin B_{12} deficiency is associated with neuropsychiatric disorders, as the level of homocysteine is increased due to the lack of Vitamin B_{12}[21,22]. Additionally, low vitamin B_{12} levels are related to breast cancer, vascular mortality and coronary atherosclerosis[19,20]. Moreover, it has been associated with osteoporosis, deafness, neural tube defects, and an increased risk of infection[22-24]. Vitamin B_{12} deficiency without anemia is a common condition, seen especially in the elderly[4,25]. The incidence of neurological symptoms without hematologic findings is increased in vitamin B_{12} deficiency because folate masks the hematological effects in vitamin B_{12} deficiency. While a normal peripheral blood smear in patients with vitamin B_{12} deficiency may appear initially, macrocytic anemia, isolated thrombocytopenia, neutropenia and pancytopenia may be seen in advanced cases[26,27]. Vitamin B_{12} deficiency impairs the DNA repair and replication mechanisms, which can lead to ineffective erythropoiesis and macrocytic anemia. None of our cases had pancytopenia or thrombocytopenia related to vitamin B_{12} deficiency.

In most cases, low levels of complete blood count were accompanied by elevation of MCV, an indicator of macrocytosis. In patients with vitamin B_{12} deficiency, hypercellularity and a decrease in the myeloid/erythroid ratio are observed in bone marrow. Additionally, megaloblastic changes and abnormal mitotic figures are seen in erythroid precursor cells, most granulocytic cells appear larger than normal, giant band cells and metamyelocytes are observed and megakaryocytes are reduced without changes in their normal morphology[28]. Cobalamin treatment given to patients with vitamin B_{12} deficiency accelerates hematopoiesis, causes a 50% reduction in serum LDH, and induces the disappearance of megaloblastic changes in the erythroid series in bone marrow by 48 h. Reticulocytosis is observed in the first week of treatment, recovery from thrombocytopenia and neutropenia occurs by the second week, improvement in anemia with decreased MCV is observed by the third week and a reduction in the number of neutrophil lobes is observed by the fourth week[15,28,29]. A previous study achieved normal Hb levels and decreased MCV during the first month of treatment in 54% of the patients[30]. In our study, the complete blood count was increased while MCV values were decreased in patients after

the first month of IM cobalamin treatment. Thus, a response to cobalamin treatment was observed.

Increased MPV levels are associated with some diseases such as myocardial infarction, venous thromboembolism and stroke[31,32]. MPV is a good indicator of an increased number of young and large peripheral platelets. This increase in large peripheral thrombocytes elevates the level of peripherally released aggregated substances, which can lead to increased peripheral arterial and venous occlusive diseases. A previous study demonstrated that the MPV value in a megaloblastic anemia group was higher to that in the non-megaloblastic anemia group[33]. This finding suggested that increase in large and active thrombocytes in the peripheral blood was found in patients with megaloblastic anemia. The level of MPV for vitamin B_{12} deficiency is unknown in literature. However, thrombocytopenia may develop in patients with vitamin B_{12} deficiency due to ineffective megakaryopoiesis[28]. If deep thrombocytopenia developed due to vitamin B_{12} deficiency, the MPV value of the deficiency group than control group would be decreased.

The presence of thrombocytopenia in patients with vitamin B_{12} deficiency and the improvement in thrombocyte value with cobalamin treatment show the stimulation of megakaryopoiesis by vitamin B_{12}. In another study, patients with vitamin B_{12} deficiency treated with oral and IM cobalamin demonstrated markedly increased MPV values[30]. Our study supports the idea that cobalamin therapy stimulates megakaryopoiesis in bone marrow, leading to the release of young, large and active thrombocytes into the peripheral blood.

The vast majority of patients with vitamin B_{12} deficiency in our clinic had B_{12} levels of 203–270 pg/mL, and most of them had no obvious complaints. Patients with vitamin B_{12} levels below 203 pg/mL were considered as having vitamin B_{12} deficiency[14]. Values below 135.4 pg/mL represented a serious deficiency. The majority of our cases did not have serious levels of B_{12} deficiency. In severe B_{12} deficiency, thrombocyte levels may be lower before treatment and, secondary to cobalamin treatment, large and active thrombocytes may be released into the peripheral blood. For this reason, it is important to administer cobalamin treatment with care in arterial or venous thrombosis patients who have B_{12} deficiency. On the other hand, the comparison between pretreatment and posttreatment thrombocyte counts revealed a higher pretreatment thrombocyte level. The pretreatment level of MPV was lower than the posttreatment level, and thrombocyte levels might not increase after treatment. However, elevated MPV levels indicate a release of large and active thrombocytes into the peripheral blood. Thus, the risk of thrombosis might increase during cobalamin treatment.

Limitations to this study

The limited number of subjects in our study may not reflect the general population. Serum homocysteine levels are expected to increase in patients with vitamin B_{12} deficiency; however, the homocysteine levels were not evaluated before or after treatment in the present study. In patients with vitamin B_{12} deficiency, the increased homocysteine levels before treatment may increase the risk of arterial and venous thrombosis as well as high levels of MPV posttreatment. On the other hand, the strong association between posttreatment vitamin B_{12} and MPV levels brings to mind the question of whether the MPV level is increased in normal subjects having high levels of vitamin B_{12}, which may be associated with the role of vitamin B_{12} in DNA synthesis. The results of this pilot study suggest that further studies on this subject are required.

CONCLUSION

In the present study, high MPV values were found after cobalamin treatment in patients with vitamin B_{12} deficiency. The release of young, large

and active thrombocytes into the peripheral blood is increased during vitamin B_{12} treatment. Therefore, the elevated level of these thrombocytes might increase the risk of arterial and venous thromboembolism.

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Running Title: Cobalamin treatment on MPV

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