J Surg Med. 2020;4(8):682-684.
DOI: 10.28982/josam.736242

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of mean platelet volume before and after cyclophosphamide treatment in systemic sclerosis associated interstitial lung disease

Sistemik skleroz ile ilişkili interstisyel akciğer hastalığında siklofosfamid tedavisi öncesi ve sonrası ortalama trombosit hacminin değerlendirilmesi

Nurhan Atilla [1], Gözde Yıldırım Çetin [2]

[1] Kahramanmaras Sutcu Imam University Medicine Faculty, Department of Chest Diseases, Kahramanmaras, Turkey
[2] Kahramanmaras Sutcu Imam University Medicine Faculty, Department of Rheumatology, Kahramanmaras, Turkey

ORCID ID of the author(s)
NA: 0000-0003-4127-4924
GYÇ: 0000-0001-9680-7535

Corresponding author/Sorumlu yazar:
Nurhan Atilla
Address/Adres: Kahramanmaraş Sütçü İmam Üniversitesi, Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Kahramanmaraş, Türkiye
E-mail: nurhanatillag@hotmail.com

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University (Date:19.09.2016, number:237). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışmanın onayı Kahramanmaraş Sütçü İmam Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından verildi (Tarih:19.09.2016, Sayı:237). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 8/30/2020
Yayın Tarihi: 30.08.2020

Abstract

Aim: Studies carried out in patients with systemic sclerosis (SSc) have shown that mean platelet volume (MPV) is associated with more advanced stage of SSc. However, the effect of cyclophosphamide (CP) on MPV in systemic sclerosis-associated interstitial lung disease (SSc-ILD) is less clear. In this study, we aimed to investigate the MPV response to CP treatment in SSc-ILD.

Methods: Thirty-eight SSc-ILD patients who responded positively to CP were included in this retrospective cohort study. MPV values before the treatment were compared with third, sixth, and ninth months' values during treatment.

Results: Over the nine-year period, 82 patients were diagnosed with SSc in the rheumatology clinic of our hospital. Forty-three of them had SSc-ILD and all were administered CP treatment for 9 months. Thirty-eight clinically benefited from CP, among which 32 were females (84%) and 6 (16%) were males. The MPV levels in SSc-ILD patients after CP (9.44 fL) were significantly higher than those before CP (7.89 fL) (P=0.001).

Conclusion: Cyclophosphamide treatment causes an increase in MPV in SSc-ILD. MPV, a negative acute phase reactant, is considered an independent risk factor for coronary and peripheral artery diseases. Patients receiving CP should be followed more closely for such diseases.

Keywords: Cyclophosphamide, Mean platelet volume, Systemic sclerosis

Öz

Amaç: Sistemik sklerozlu (SSc) hastalarda yapılan çalışmalar ortalama trombosit hacminin (MPV) SSc ileri evresi ile ilişkili olduğunu göstermiştir. Bununla birlikte, sistemik skleroza sekonder interstisyel akciğer hastalığında (SSc-İAH), siklofosfamid (CP) tedavisinin MPV değeri üzerindeki etkisi bilinmemektedir. Bu çalışmada SSc-İAH'de, CP tedavisine MPV yanıtını araştırmayı amaçladık.

Yöntemler: Bu retrospektif kesitsel çalışmaya CP tedavisinden fayda görmüş 38 SSc-İAH hastası dahil edildi. Tedavi öncesi MPV değerleri ile tedavi sırasında üçüncü, altıncı ve dokuzuncu ayların MPV değerleri karşılaştırıldı.

Bulgular: Dokuz yıllık bir süre içinde hastanemiz romatoloji kliniğinde 82 hastaya SSc tanısı kondu. Hastaların 43'ünde SSc-İAH vardı ve bunların hepsinde 9 ay süre ile CP tedavisi uygulandı. CP'den klinik yarar gören 38 hastanın, 32'si (%84) kadın ve 6'sı (%16) erkek idi. SSc-İAH hastalarında CP tedavisi sonrası MPV düzeyleri (9,44 fL), CP tedavisi öncesine (7,89 fL) göre belirgin yüksek tespit edildi (P=0,001).

Sonuç: Siklofosfamid tedavisi, SSc-İAH'de MPV'de bir artışa neden olmaktadır. Negatif akut faz reaktanı olarak MPV'nin koroner ve periferik arter hastalığı için bağımsız bir risk faktörü olarak kabul edildiği bilinmektedir. Siklofosfamid alan hastalar bu tür hastalıklar için özellikle takip edilmelidir.

Anahtar kelimeler: Siklofosfamid, Ortalama trombosit volümü, Sistemik skleroz

How to cite/Atıf için: Atilla N, Çetin GY. Evaluation of mean platelet volume before and after cyclophosphamide treatment in systemic sclerosis associated interstitial lung disease. J Surg Med. 2020;4(8):682-684.

Introduction

The diagnosis of systemic sclerosis-related interstitial lung disease (SSc-ILD) is based on the presence of various respiratory symptoms, such as non-productive cough, dyspnea, fatigue and bibasilar fine inspiratory crackles at the lung bases on physical examination. Pulmonary function tests and high-resolution computed tomography remain the mainstay for the diagnosis of SSc-ILD [1]. Nonselective immunosuppressors are still the main treatment for SSc-ILD, with cyclophosphamide (CP) most widely used to obtain remission [1].

In our rheumatology clinic, we evaluate our systemic sclerosis (SSc) patients at least monthly. At the control visits, we perform a thorough physical examination, chest X-ray, and obtain a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values. Spirometry and DLCO were performed at three-month intervals, while HRCT was not performed routinely. We usually request HRCT when there is a worsening of symptoms or pulmonary function tests. If the involvement in HRCT is 20% or more in patients diagnosed with SSc-ILD, we switch the treatment to CP. In our clinic, we prefer monthly intravenous CP administration for the management of patients with SSc-ILD. The initial dose is based upon the body surface area and adjusted for renal function, obesity, cachexia, and advanced age. Subsequent doses are based on response to treatment and white blood cell (WBC) counts.

Platelets play a large and complex physiological role in both health and disease, as they contribute to hemostasis, inflammation, tissue repair, and innate and adaptive immunity [2,3]. Increased mean platelet volume (MPV) may reflect either increased platelet activation or increased numbers of large, hyperaggregable platelets. There are reports in the literature that repeatedly document ongoing and chronic activation of platelets and/or their release of biologically of active molecules, which may contribute to vascular, immunologic, and connective tissue pathology in SSc [4,5]. However, responses of MPV and similar inflammatory markers to the CP treatment have not been investigated before. In this study, we aimed to study whether CP treatment influences MPV values.

Materials and methods

Patient selection

All patients diagnosed with SSc-ILD from January 2006 to December 2015 in Kahramanmaras Sutcu Imam University Hospital were retrospectively reviewed. Patients who benefited from CP and received the treatment for at least 9 months were included in the study. Over the nine-year period, 82 patients were diagnosed with SSc in the rheumatology clinic of our hospital. Of these, 43 (52%) had SSc-ILD and all of them were treated with CP, but only 38 (88%) patients benefited from CP treatment. CP was administered intravenously to all patients at a dose of 1000 mg / month. We compared the MPV values immediately preceding the initiation of CP with the third, sixth, and ninth month values after initiation of treatment.

Exclusion criteria included an involvement of less than 20% in HRCT, not benefiting from CP treatment, deterioration in FVC, worsening of dyspnea according to MMRC (Modified Medical Research Council), and radiologic progression. Flow diagram with exclusion criteria is summarized in Figure 1.

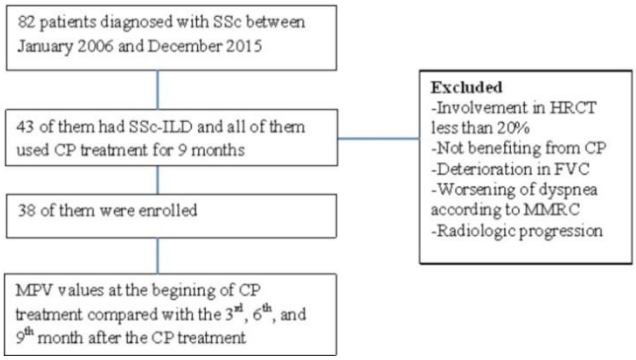

Figure 1: Flow diagram of the study (FVC:forced vital capacity, HRCT: high-resolution computed tomography, SSc-ILD: systemic sclerosis-related interstitial lung disease, CP: cyclophosphamide, MPV: mean platelet volume, MMRC: Modified Medical Research Council Dyspnea Scale)

Ethical approval

Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University. The study was conducted in accordance with the principles of Helsinki Declaration.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 statistics package (SPSS, Inc., Chicago, IL, USA). This was a retrospective cohort study. Descriptive statistics and T test were used to describe the features of the data and analysis of related samples (paired sample T test).

Results

The basic demographic findings of the patients are presented in Table 1. There were 32 females (84%) and 6 males (16%). Their mean age was 50.5 (13.6) years. Age at the onset of SSc was 34.2 years, mean disease duration (years) was 4.1 (4.2) years, mean pulmonary artery pressure (PAP) value was 24.4, scl-70 value was positive in 52%, antinuclear antibody (ANA) was positive in 89%, concomitant esophageal dilatation was present in 5 patients (13%), concomitant cardiomegaly was present in 7 patients (5.4%), and 8 patients had pleural thickening (21%).

Table 1: Sociodemographic characteristics of the study population

Age (years), mean (SD)	50.5 (13.6)
Gender (F/M)	32/6
Age at onset of SSc (years)	34.2
Disease duration (years), mean (SD)	4.1 (4.2)
Mean PAP	24.4
Scl-70 +/-	24/14
ANA +/-	34/4
Esophageal dilatation +/-	5/33
Cardiomegaly +/-	7/31
Pleural thickening +/-	8/30

SD: standard deviation, F: female, M: male, PAP: pulmonary artery pressure, ANA: antinuclear antibody

We found that the posttreatment MPV values were significantly higher than those before the treatment (P=0.001). The mean MPV levels of SSc-ILD patients before CP (7.89 fL) were significantly lower than those after 3 months (9.44 fL), 6 months (9.51 fL), and 9 months (9.48 fL) of treatment (P=0.001) (Figure 2).

According to the results in Table 2, there is a positive and significant relationship between the values before CP and 3 months (t= -10.957, P=0.001), 6 months (t= -12.34, P=0.001), and 9 months (t= -11.28, P=0.001) after treatment).

Table 2: Comparison of the difference between before and after CP treatment (CP: cyclophosphamide, MPV: mean platelet volume)

Before CP	MPV values After CP		t	*P*-value
7.89	3th month	9.44	-10.95	0.00
	6th month	9.51	-12.34	0.00
	9th month	9.48	-11.28	0.00

Discussion

To the best of our knowledge, this was the first study which showed the effect of CP on MPV in SSc-ILD patients. Our results showed that MPV values significantly increased after CP administration.

Cyclophosphamide is an alkylating agent of the nitrogen mustard type, which is used to treat cancers and autoimmune disorders such as SSc-ILD [6]. It is the most recommended agent in SSc-ILD, but the changes in blood parameters related to CP treatment in SSc-ILD is still unknown.

Platelets are small cells which include various granules, a microtubular system and an active membrane [7]. It is known that these granules produce and secrete many bodies which play an essential role in atherosclerotic coronary artery disease, atherothrombosis, coagulation, and inflammation processes [8]. On the other hand, MPV, which represents platelet volume, is one of the most studied parameters indicating the level of inflammation. Larger size platelets are more active metabolically and enzymatically than small ones. In other words, increase in MPV increases the risk of thrombosis [9]. The mean platelet volume may play a significant role in atherosclerotic and thrombotic pathways [10]. Aksoy et al. [11] found that low MPV values were associated with bone marrow aplasia after cytotoxic chemotreatment, splenomegaly, reactive thrombocytosis, and high-grade inflammation.

Systemic sclerosis, especially SSc-ILD, is a systemic inflammatory disease which leads to secretion of various pro-inflammatory cytokines, some of which cause secretion of hematopoietic cells into the circulation by affecting the maturation of hematopoietic cells in the bone marrow. Conditions associated with a high degree of inflammation (active inflammatory bowel disease, rheumatoid arthritis, FMF attack) are usually related to low MPV values [12]. In remission or anti-inflammatory drug use, MPV values remain high [13]. Patients included in our study were considered to have high degree inflammation, because all had active ILD. Some of the recent studies associated with rheumatologic disorders have investigated the potential relationship between MPV levels and disease activity in rheumatoid arthritis, ankylosing spondylitis, and synovitis with osteoarthritis. Previous studies have demonstrated decreased MPV levels in active patients with rheumatic diseases in contrast to the healthy population and inactive SSc patients [14-16]. In their study consisting of 596 patients with various rheumatic diseases, Sahin et al. [17] found a negative correlation between MPV and CRP, ESR. In another study involving 76 SSc patients and 45 healthy volunteers, Soydinc et al. [18] found that the mean MPV levels of SSc patients were significantly higher than those of the control group. On the other hand, as expected in any systemic high-grade inflammatory response, they found MPV levels decreasing in clinically active SSc patients. In this study, the authors compared the MPV values of patients with and without lung involvement. MPV values, regardless of CP usage in patients with lung involvement, were 9.42, lower than in patients without lung involvement (9.51). However, this result was not statistically significant. In our study, when we assessed SSc-ILD patients, MPV values were 9.07 and similar to the previous report.

The most crucial difference of our study from other studies is that we evaluated the relationship between CP treatment and MPV values. We found posttreatment MPV values significantly higher than those prior to treatment. Similarly, Gasparyan et al. [16] compared MPV values before and after TNF-α in 21 patients with rheumatoid arthritis. They found a statistically significant increase in MPV values after TNF-α administration (7.7 (0.9), 7.8 (1.1), and 8.4 (1.1) fL at baseline, 2, and 12 weeks, respectively).

The elevated level of MPV might increase the risk of arterial and venous thromboembolism. Therefore, physicians should be alert for thrombus in patients receiving CP treatment. It should also be remembered that MPV is not specific to the disease, and that the results may vary depending on many factors. Therefore, the changes in MPV level may be influenced by the other factors.

Limitations

Our study contains several limitations, one being its retrospective nature, the other, including results from a single center, and a relatively small sample size.

Conclusions

Our study shows that CP has led to the rise of MPV levels. However, further studies which are covering larger groups are required to verify our findings.

References

1. Cappelli S, Bellando Randone S, Camiciottoli G, De Paulis A, Guiducci S, Matucci-Cerinic M. Interstitial lung disease in systemic sclerosis: where do we stand? Eur Respir Rev. 2015;24(137):411-9.
2. Gear AR, Camerini D. Platelet chemokines and chemokine receptors: Linking hemostasis, inflammation, and host defense. Microcirculation. 2003;10:335–50.
3. Weyrich AS, Lindemann S, Zimmerman GA. The evolving role of platelets in inflammation. Thromand Hematol. 2003;1:1897-905.
4. Friedhoff LT, Seibold JR, Kim HC, Simester KS. Serotonin induced platelet aggregation in systemic sclerosis. Clin and Exp Rheu. 1984;2:119-23.
5. Postlethwaite AE, Chiang TM. Platelet contributions to the pathogenesis of systemic sclerosis. Cur Opin in Rhe. 2007;19:574-9.
6. Giraud B, Hebert G, Deroussent A, Veal GJ, Vassal G, Paci A.Oxazaphosphorines: new therapeutic strategies for an old class of drugs. Expert Opin Drug Metab Toxicol. 2010;6(8):919-38.
7. Eren R, Doğu MH, Koç A, Altındal Ş, Yokuş O, Suyanı E. The association of mean platelet volume and platecrit and bone marrow fibrosis in patients with essential thrombocythemia: A cohort study. J Surg Med. 2019;3(2):176-9.
8. İnanır M. An investigation of platelet parameters in smoking patients with coronary slow flow detected during coronary angiography. J Surg Med. 2020;4(4):281-4.
9. Abanoz M. Predictive value of plateletcrit in the diagnosis of lower extremity deep vein thrombosis. J Surg Med. 2020;4(2):148-51.
10. Bıyık İ, Aslan MM, Keskin F. Association between platelet indices and missed abortion. J Surg Med. 2019;3(8):549-52.
11. Aksoy S, Kilickap S, Hayran M, Harputluoglu H, Koca E, Dede DS. Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. Int J Lab Hematol. 2008;30:214-9.
12. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators of Inflammation. 2019;2019:14.
13. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17:47-58.
14. Balbaloglu O, Korkmaz M, Yolcu S, Karaaslan F, Beceren NG. Evaluation of mean platelet volume (MPV) levels in patients with synovitis associated with knee osteoarthritis. Platelets. 2014;25(2):81-5.
15. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint, Bone, Spine. 2008;75:291-4.
16. Gasparyan AY, Sandoo A, Stavropoulos-Kalinoglou A, Kitas GD. Mean platelet volume in patients with rheumatoid arthritis: The effect of anti-TNF-α treatment. Rheumatology International. 2010;30:1125-9.
17. Sahin A, Yetisgin A, Sahin M, Durmaz Y, Cengiz AK. Can Mean Platelet Volume be a Surrogate Marker of Inflammation in Rheumatic Diseases? West Indian Med J. 2015;65:165-9.
18. Soydinc S, Turkbeyler IH, Pehlivan Y, Soylu G, Goktepe MF, Bilici M et al. Mean Platelet Volume Seems To Be a Valuable Marker in Patients with Systemic Sclerosis Inflammation. 2014;37(1):100-6.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.