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Comparison of the oxidative stress status of children with ITP in two therapies using methylprednisolone and methylprednisolone along with IVIG

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Abstract

Background: Idiopathic thrombocytopenic purpura (ITP) is a rare and autoimmune disorder determined by an abnormal reduction in the number of platelets. The current study aims to evaluate the oxidative stress status of children with ITP in two treatment methods using methylprednisolone and methylprednisolone with intravenous immunoglobulin (IVIG).

Materials and Methods: This retrospective study was conducted on 60 children with ITP who referred to Baghaei Hospital in Ahvaz in 2021. All the ITP children were equally divided into two groups, 30 receiving methylprednisolone and 30 receiving methylprednisolone and IVIG. The sampling of the patients' blood was done in two stages before and after the start of treatment. Then, malondialdehyde (MDA), superoxide dismutase (SOD), total antioxidant status (TAS), total oxidative status (TOS), catalase (CAT) and glutathione were measured according to the instructions in the commercial kit. The analyses were performed using SPSS software version 23. P value < 0.05 was significant.

Results: The number of platelets after treatment in methylprednisolone and methylprednisolone+ IVIG groups was 133.44 ± 18.93 and 158.76 ± 34.76 (×103/µL), respectively. Itas significantly increased compared to that before the treatment (P = 0.04). The amount of TAC in the group receiving methylprednisolone + IVIG and the methylprednisolone group was 1.64 ± 0.18 and 1.26 ± 0.53 nm, respectively; there was a remarkable difference between the two groups (P = 0.001). Also, SOD, CAT and glutathione in the methylprednisolone + IVIG group were remarkably higher than those in the methylprednisolone group (P < 0.05). Finally, the levels of TOS were lower in the methylprednisolone + IVIG group (19.74 ± 9.93 µmol) than in the methylprednisolone group (26.65 ± 10.64 µmol) (P = 0.01).

Conclusion: A combination of IVIG and methylprednisolone was found to have a greater effect on improving antioxidant status and decreasing the oxidative stress indices of ITP children.

Keywords: Antioxidant, Idiopathic thrombocytopenic purpura (ITP), Intravenous immunoglobulin (IVIG), Methylprednisolone.

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune blood disease associated with defective immune responses, thrombocytopenia, and bleeding (1). It is also called thrombocytopenic purpura because it seems more likely to be related to antibodies against platelets.

Most patients are asymptomatic, while very low platelet counts can develop into bleeding diathesis and purpura (2). In this disorder, instead of platelet function, the total number of blood platelets is affected (3, 4). One of the important diagnostic hematological findings in the blood of

these patients is the reduction of platelets to less than 100x109/L and the production of giant platelets (5). Although the pathogenesis of ITP has not been accurately determined, one of the hypotheses is that oxidative stress can cause this disease (6). In the body, there is normally a balance between the antioxidant system and free radicals. Oxidative stress is a process that occurs due to the imbalance between reactive oxygen species (ROS) or free radicals and the efficiency of antioxidants in the defense systems such as glutathione, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (7). In the pathogenesis of autoimmune diseases, oxidative damage plays a major adverse role. Free radicals and oxidative stress are said to be responsible for the prognosis and pathogenesis of ITP. It should also be mentioned that a decrease in antioxidant capacity and an increase in lipid peroxidation in ITP may play an essential role in the binding of antibodies to membrane lipids and the destruction of platelets (8). In addition, some researchers have shown that the altered proteins associated with oxidative stress have a high ability to stimulate the immune system and cause the production of antibodies for autoimmune diseases (9-12). It has also been noted that elevated oxidative stress can be associated with impaired platelet function (13). Some clinical investigations have found that oxidative stress levels are significantly higher in ITP patients than in healthy individuals (8, 14, 15). According to these pieces of evidence, it seems that changes in the oxidative state of the body in patients with ITP can be of undesirable consequences (15). ITP patients are treated based on platelet count and clinical status so as to increase the platelets and reduce the clinical symptoms. For many years, the first-line treatment has been the use of drugs such as intravenous immunoglobulin (IVIG) or corticosteroids such as methylprednisolone (16-18). So far, however, few investigations have examined the effect of various treatments on the oxidative stress status of ITP patients (19, 20). In the study by Cura et al. (21) in Turkey, it was found that high-dose and short-term oral methylprednisolone is effective in reducing the antioxidant capacity and enhancing the general oxidant status, and it prevents the disease from becoming chronic. Varol et al. (22) also reported that, compared to IVIG, methylprednisolone makes no difference in the rate of the treatment success and its effect on oxidative stress indices. Given the noticeable role of oxidative stress in the pathogenesis of the disease, the choice of a treatment that has the least side effect is very important. Considering the scarcity of research in this field, the present study seeks to determine the oxidative stress status of children with ITP in two treatment methods, using a) methylprednisolone and b) methylprednisolone combined with IVIG.

Materials and Methods

Participants

This retrospective study was conducted on 60 children with newly diagnosed ITP. They had referred to the hematology/oncology department of Baghaei Hospital, Ahvaz, Iran, in 2021. Thirty healthy children were also considered as the control group with no family history of ITP, blood abnormalities or autoimmune diseases. The inclusion criterion was platelet count less than 20×10^9/L with an associated risk of severe bleeding (as in extensive bruising, petechiae/purpura, epistaxis, menorrhagia, gingival bleeding, and hematuria).

Experiments and medication

Peripheral smear was performed for all the cases before the treatment. The patients who showed features atypical for ITP

(including marked lymphadenopathy, pancytopenia, or hepatosplenomegaly), or those who had abnormal leukocytes or nucleated red blood cells on peripheral smear underwent bone marrow aspiration and biopsy. Their platelets were measured with a Sismax XP-300 cell counter. Once the subjects met the inclusion and exclusion criteria, sampling was done before and after the treatment; 5 cc of blood was taken from each patient at each stage. Then, the patients were divided into two groups. The first group received methylprednisolone at a dose of 2 mg/kg/day orally, divided into three doses and continued for 3 weeks. The dose was then tapered 25% every 5 days for a total of 5 weeks. The second group took methylprednisolone + IVIG. IVIG was administered at a dose of 0.4 g/kg/day for 5 days along with methylprednisolone.

Assessment of antioxidant/oxidant parameters

Pre- and post-treatment oxidative / anti-oxidative parameters were measured. The serum levels of glutathione peroxidase (GPx), superoxide dismutase enzyme (SOD), catalase (CAT), total antioxidant capacity (TAC), total oxidant status (TOS) and malondialdehyde (MDA) were also measured with the ZellBio kit (ZellBio GmbH, Germany).

Statistical analysis

All the analyses were performed using the SPSS software version 23 (Inc., Chicago, IL, USA). The numerical variables were reported as mean ± standard deviation (SD). The quantitative variables were measured with independent t-tests and ANOVA tests. Paired sample t-tests were also used for within-group comparisons before and after the intervention. P value < 0.05 was considered to be statistically significant.

Ethical considerations

Before the study, written consent was obtained from the individual patients or their parents. The study was approved by the ethics committee of Jundishapur University of Medical Sciences of Ahvaz, Ahvaz, Iran (IR.AJUMS.HGOLESTAN.REC.1399.122).

Results

Hematological parameters before and after the treatment

The number of platelets and the level of hemoglobin in the two groups of patients with ITP were significantly lower than those I the control group, but no considerable difference was observed in terms of the number of white blood cells and hematocrit between the two groups of patients with ITP and the control group. There was also no remarkable difference between the group receiving methylprednisolone alone and the group treated with methylprednisolone + IVIG in terms of hematological parameters (i.e. platelet count, white blood cell count, hemoglobin and hematocrit) before the treatment (P > 0.05). According to the results, after the treatment, the number of platelets and the level of hemoglobin in the two groups of patients with ITP increased significantly, as compared to those before the treatment. Also, the number of platelets and the level of hemoglobin after the treatment were significantly higher in the group receiving methylprednisolone + IVIG than in the methylprednisolone group. However, there was no significant difference between the two groups in terms of the number of white blood cells and hematocrit before and after the treatment. More details are provided in Table I.

Antioxidant/oxidant parameters

Based on the results, after the treatment, the levels of TAC, SOD, CAT and GPx significantly increased in the two groups of the patients with ITP. Also, after the treatment, the levels of TAC, SOD, CAT and glutathione were significantly higher in the methylprednisolone + IVIG group

than in the methylprednisolone group (P < 0.05). However, after the treatment, the levels of MDA and TOC were significantly lower in the group receiving methylprednisolone + IVIG than in the methylprednisolone group (P < 0.05) (Table II).

Table I: Hematological parameters in the ITP patients before and after the treatment

Variables		Methylprednisolone group (n = 30)	Methylprednisolone + IVIG group (n = 30)	Control group (n = 30)	P-value§	P-value ζ
WBC (10×3/µL)	Before	8.79 ± 1.78	9.11 ± 2.03	8.83 ± 1.97	0.52	0.42
	After	9.01 ± 1.23	8.99 ± 1.38		0.32	0.36
	P-value ŧ	0.47	0.62			
PLT(×10^3/µL)	Before	9.65 ± 1.24$_a$	11.23 ± 4.79$_a$	223.18 ± 63.75	0.01	0.10
	After	133.44 ± 18.93$_{bc}$	158.76 ± 34.76$_{bc}$		0.12	0.04
	P-value ŧ	0.001	<0.001			
Hb (g/dL)	Before	11.47 ± 0.98$_a$	11.13 ± 1.12$_a$	13.65 ± 2.11	0.02	0.28
	After	12.93 ± 1.77$_{bc}$	13.98 ± 2.01$_{bc}$		0.24	0.03
	P-value ŧ	0.03	0.001			
HCT (%)	Before	35.87 ± 6.21	35.11 ± 5.67	36.27 ± 5.03	0.32	0.74
	After	37.56 ± 7.43	35.89 ± 5.92		0.19	0.46
	P-value ŧ	0.21	0.47			

WBC: White blood cell, PLT: Platelet, HCT: Hematocrit, Hb: Hemoglobin, a indicates a significant difference from the control group (P < 0.05), b indicates a significant difference within the group after the treatment compared to before the treatment (P < 0.05), c indicates a significant difference between the two groups after the treatment (P < 0.05)., § : The p-value related to ANOVA test which compares the three groups, ζ: The p-value related to independent sample t-test which compares methylprednisolone and methylprednisolone + IVIG groups, ŧ: The p-value related to paired sample t-test which compares each group before and after the intervention

Table II: Antioxidant/oxidant parameters in the participants before and after the treatment

Variables		Methylprednisolone group (n = 30)	Methylprednisolone + IVIG group (n = 30)	Control (n = 30)	P-value §	P-value ζ
TAC (nm)	Before	1.02 ± 0.36$_a$	1.10 ± 0.23$_a$	1.83 ± 0.48	0.01	0.21
	After	1.26 ± 0.53$_{bc}$	1.64 ± 0.18$_{bc}$		0.41	0.001
	P-value ŧ	< 0.001	<0.001			
SOD (mg/ml/U)	Before	227.92 ± 18.82a	219.39 ± 17.46$_a$	378.92 ± 28.29	0.02	0.54
	After	283.20 ± 13.54$_{bc}$	328.22 ± 19.39$_{bc}$		0.81	<0.001
	P-value ŧ	0.01	0.02			
CAT (g/ml/U)	Before	14.86 ± 2.75$_a$	13.75 ± 3.07$_a$	26.91 ± 3.65	0.001	0.64
	After	18.37 ± 2.81$_{bc}$	22.82 ± 2.39$_{bc}$		0.96	< 0.001
	P-value ŧ	0.02	0.001			
Glutathione(U/µg)	Before	4.12 ± 1.34$_a$	4.78 ± 1.54$_a$	9.07 ± 1.98	0.01	0.14
	After	6.02 ± 1.94$_{bc}$	7.67 ± 1.12$_{bc}$		0.61	0.02
	P-value ŧ	0.03	<0.001			
TOS (µmol)	Before	35.75 ± 11.56$_a$	37.32 ± 8.53$_a$	12.96 ± 5.97	0.001	0.53
	After	26.65 ± 10.64$_{bc}$	19.74 ± 9.93$_{bc}$		0.28	0.01
	P-value ŧ	0.01	0.001			
MDA(nmol/gr)	Before	26.56 ± 8.98$_a$	27.17 ± 11.03$_a$	11.27 ± 4.19	0.01	0.72
	After	19.82 ± 6.92$_{bc}$	13.35 ± 7.12$_{bc}$		0.33	< 0.001
	P-value ŧ	0.001	0.02			

TAC: Total antioxidant capacity, SOD: Superoxide dismutase, CAT: Catalase, TOS: Total oxidant status, MDA: Malondialdehyde, a indicates a significant difference from the control group (P < 0.05), b indicates a significant difference within the group after the treatment compared to before the treatment (P < 0.05), c indicates a significant difference after the treatment between the two groups (P < 0.05). § : The p-value related to ANOVA test which compares the three groups, ζ: The p-value related to independent sample t- test which compares methylprednisolone and methylprednisolone + IVIG groups, ŧ: The p-value related to paired sample t-test which comparee each group before and after the intervention

Discussion

The present investigation was performed to compare the oxidative stress of ITP children in two treatment methods including the use of methylprednisolone alone and the use of methylprednisolone plus IVIG. Based on our results, the number of platelets and the level of hemoglobin after treatment were significantly higher in the methylprednisolone + IVIG group than in the methylprednisolone group. WBC count and hematocrit level were not markedly different between the two groups. Moreover, the levels of TAC, SOD, CAT and glutathione after treatment in the methylprednisolone + IVIG group were remarkably higher than those in the methylprednisolone group. The levels of TOS were also lower in the methylprednisolone + IVIG group compared to the methylprednisolone group. According to previous reports, oxidative stress is involved in ITP pathogenesis (23), and it is likely to increase due to systemic inflammation and platelet destruction (21). Akbayram et al. (8) found that the levels of TAC, MDA, TOS and oxidative stress in patients after treatment did not significantly change compared to those before the treatment.

Contrary to our findings, Varol et al. (22) showed the decrease of the oxidative stress index in methylprednisolone and methylprednisolone + IVIG groups after the treatment; however, the difference was not statistically significant between the two groups. Moreover, the total antioxidant capacity in the methylprednisolone and methylprednisolone + IVIG groups was not significantly different. This is while, in the present study, the level of TAC in the group receiving methylprednisolone + IVIG was remarkably higher than that in the methylprednisolone group. Also, the total oxidative status was lower in the prednisolone + IVIG group than in the methylprednisolone group. The discrepancy between these two studies may be due to the difference in the sample size, the measuring method, and the kits for measuring the oxidative stress indicators. Cura et al. (21) evaluated the effect of the short-term use of high-dose methylprednisolone on the state of oxidative stress in ITP patients. As it was demonstrated, oxidative stress was higher in ITP patients than in healthy children, but treatment with methylprednisolone caused a notable reduction in its levels in the patients. These results are similar to our findings. Further in line with the present study, Cura's team showed an increase in the mean level of the total antioxidant status as well as a decrease in the mean level of the total oxidant status and the oxidative stress index after one week of using high doses of methylprednisolone in ITP children. Koyuncu et al. (24) demonstrated that high-dose methylprednisolone is more efficacious than IVIG to increase the platelet count. A combination of IVIG and methylprednisolone may accelerate the increase of platelets, so it can be a suitable option in cases of urgent need for a rapid rise in platelet counts. In a similar context, Ancona et al. (25) showed that both IVIG and methylprednisolone can significantly increase platelet counts, somewhat more with IVIG. However, they stated that the higher platelet count induced by IVIG may not justify the additional cost and potential risks of this agent. These findings are similar to the results of the present

research. Previous studies have shown that a considerable decrease in the number of platelets is the main characteristic of ITP disease. Although ITP pathogenesis is not well identified, in general, the causes of thrombocytopenia in this disease include 1) the reduction of platelet production to in a congenital or acquired form, 2) broken platelets inside an enlarged spleen or other organs, and 3) the increased destruction of natural platelets due to immune or non-immune causes (26). Similar to our findings, in the research by Eshagh-Hosseini et al. (19), age and gender were not remarkably different between the IVIG group and the methylprednisolone + IVIG group A randomized controlled trial conducted by Godeau et al. (27) showed that administering IVIG with methylprednisolone had better outcomes than methylprednisolone, thus advisable as a front-line treatment for adult ITP. The results of that study are in line with our findings, with the difference that the statistical population in Godeau's study consisted of adults. The mechanism of IVIG is to block and modulate macrophage-activating Fc receptors in the reticuloendothelial system (28). There are several limitations in the present investigation. First, the sample size was small. Second, this is a retrospective study. Also, the background knowledge to use was poor because, to date, there have been very limited published data on comparing treatments with methylprednisolone and methylprednisolone plus IVIG.

Conclusion

Our findings showed that, compared to methylprednisolone, treatment with methylprednisolone + IVIG had a greater effect on improving the platelet count and antioxidant status of ITP patients with ITP. The results also indicated that a combination of IVIG with methylprednisolone is more beneficial than methylprednisolone alone to decrease the oxidative parameters in ITP patients. That is, methylprednisolone + IVIG treatment is preferable in the case of such patients. These results should be applied with caution because this survey was hospital-based rather than population-based.

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Conflict of interest

The authors declare no conflict of interest.

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