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Treatment with 3 cycle pulses of high-dose dexamethasone (HD-DXM) in adults with Primary Immune thrombocytopenia : a prospective randomized clinical trial

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Abbreviations : ITP(Primary Immune thrombocytopenia), HD-DXM(High dose dexamethasone), PDN(Prednisone), IVIG (intravenous immunoglobulin)

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Abstract

Introduction : Primary Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet destruction leading to decreased platelet count and an increased risk of bleeding. For many years, Prednisone (PDN) has been the standard first line treatment in ITP practical guidelines. The current randomized, controlled, clinical trial compared the efficacy of three-pulse high-dose dexamethasone (HD-DXM) regimen versus the conventional treatment with PDN in untreated adult patients with ITP.

Materials and Methods : This was a randomized clinical trial registered in clinical trials.gov(NCT02914054). Eligible patients were randomly assigned to receive PDN or three-pulse regimen of HD-DXM. In the HD-DXM group, 40 mg of DXM was administered intravenously for four consecutive days and then stopped. The treatment course was repeated in 14-day intervals for three pulses of treatment. Patients in the PDN group received 1.0 mg/kg of PDN orally on a daily basis for four consecutive weeks. Baseline parameters and platelet count were compared between the two groups using the Fisher exact test and logistic

regression, respectively. All the patients provided written informed consent before enrollment in the study.

Results : Thirty-six cases were given HD-DXM and 36 patients received PDN as the control group. The overall response rate was higher in the HD-DXM group than in the PDN group without a significant change in complications of corticosteroid therapy ($P < 0.05$).

Conclusion : Treatment with a three-pulse regimen of HD-DXM was an effective therapeutic method for untreated patients with ITP compared with the conventional PDN therapy.

Keywords : Immune thrombocytopenia, Dexamethasone , Autoimmune Diseases

Introduction :

Primary Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet destruction leading to decreased platelet count and increased risk of bleeding. Some mechanisms including autoantibody-mediated platelet destruction, cytotoxic T-lymphocyte platelet lysis, and impaired platelet maturation and production are identified in the pathogenesis of ITP [1,2].

The initial treatment for ITP has not been altered for several years and comprises corticosteroids, intravenous immunoglobulin (IVIG), and anti-D antibody. Corticosteroids are inexpensive and increase platelet count in nearly 75% of patients within one to two days. However, long-term responses are observed in only 25% of patients. The side effects of these medications are common and predictable including hypertension, fatigue, hyperglycemia, and adrenal insufficiency.[3]

Prednisone (PDN) is the standard corticosteroid in the ITP practical guidelines usually given in a dose of 1 mg/kg daily for four weeks and then tapered [4,5]. Dexamethasone was primarily applied in the treatment of relapsing and refractory ITP, and revealed different benefits in treated patients. According to the guidelines, high-dose dexamethasone is recommended as an alternative first line therapy in children and adults with ITP [4,6,7,8].

The current prospective, randomized, controlled clinical trial compared the efficacy and safety of a three-pulse regimen of HD-DXM versus the conventional treatment with PDN in untreated adult patients with ITP.

Materials and Methods :

Study design

The current monocentric, controlled, randomized, clinical trial was approved by the Ethics Committee of Isfahan University of Medical Sciences (IUMS), Isfahan, Iran.Also, this study was registered in clinicaltrials.gov (approval code: NCT02914054).Data were collected from adults referred to Seyed-al-Shohada Hospital (a hematology referral center in Isfahan Province of Iran) with a definite diagnosis of ITP, from September 2016 to November 2017. Written informed consents were obtained from all the patients prior to enrollment.

Inclusion criteria

The inclusion criteria included patients aged 18 years or above, with a new diagnosis of primary ITP formulated according to the international working group (IWG) guidelines [8], other inclusion criteria represented by naïve ITP for three months from diagnosis, and a platelet count of no more than 30×10^9/L or more than 30×10^9/L with the presence of bleeding symptoms according to the grading score of bleeding (Table 1) [9]. Subjects were enrolled from September 2016 to September 2017.

Exclusion criteria

The exclusion criteria were malignancy, pregnancy or lactation, liver or kidney failure, connective tissue disorders, seropositive detection of HIV, hepatitis B or C or any recent viral infections, active infections, diabetes, hypertension, cardiovascular disorders, autoimmune hemolytic anemia, psychosis and osteoporosis. Patients with history of receiving corticosteroid or immunosuppressive medicines three months before diagnosis, and any previous ITP-specific treatments were excluded from the study.

Bone marrow aspiration was performed in all patients to exclude any pathologic alterations in lymphoid and myeloid series. Autoimmune markers (antinuclear, antimitochondrial, and anticardiolipin antibodies) and the direct antiglobulin test (DAT) were also checked to rule out any autoimmunity and patients who were positive were excluded from the study.

Therapy schedules and procedures

In the HD-DXM group, 40 mg of DXM was administered in 500 mL normal saline (0.9% saline) intravenously during one hour for four consecutive days and then stopped. This cycle was repeated in 14-day intervals to receive three cycles of treatment. Cell count evaluation was also performed every two months at the last day of the second month after completion of eight months of therapy [10,11].

Patients in the PDN group received 1.0 mg/kg of PDN orally on a daily basis for four consecutive weeks. After achieving responses, the medication was tapered to less than 15 mg daily or terminated over four to six weeks in order to maintain a platelet count of over 30×10^9/L. Cell blood count was assessed every two months up to eight months or until loss of response to treatment[12,13].

In patients without response in both groups, medication was terminated after four weeks and other treatments were considered. Interventions such as platelet transfusion or any hemostatic agents were allowed to prevent severe bleeding.

Randomization

The eligible patients were randomly assigned to either conventional PDN therapy or a three-pulse regimen of HD-DXM. Randomization was conducted via permuted block randomization, where the entire subjects were treated as one block and the allocation ratio was 1:1 to segregate the two groups of the study. Blinding was utilized for statistical analysis and interpretation of results.

Outcome criteria

The primary endpoints included response (R), sustained response (SR), and complete response (CR). Complete response was defined as platelet count $\geq 100\times10^9$/L and absence of bleeding. Response was defined as platelet count $\geq 30\times10^9$/L and at least a two-fold increase of the baseline count and absence of bleeding. No response was defined as a platelet count $< 30\times10^9$/L or less than a two-fold increase in the baseline count or bleeding. The sustained response was defined as response confirmed for at least six consecutive months. Relapse was characterized by platelet count reduction of $<30\times10^9$/L or presence of bleeding symptoms after achievement of response.

The secondary endpoints were bleeding scores and adverse events. Table 1 summarizes the parameters used for the assessment of the bleeding scores before and after each course of medication [10]. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 by the US National Cancer Institute. A comprehensive checklist, including demographic and clinical data, was completed after one month of treatment from all the participants. Adverse events were evaluated and recorded monthly up to the eighth month of follow-up.

Statistical analysis

Baseline parameters were compared between the two groups using Fisher exact test. A logistic regression model was used to calculate the odds ratio for overall, complete, and sustained responses including the baseline parameters. The Mann-Whitney U test was run to compare quantitative parameters and the Freedman test was used to evaluate the differences in response duration in each group. All the analyses were performed with SPSS, version 22.A P-values < 0.05 was considered statistically significant.

Results

Baseline characteristics

Between September 2016 and September 2017, 90 patients were enrolled in the study. Ten of them were excluded because of not meeting inclusion criteria and 80 patients were randomly assigned between the two arms of the study. In the HD-DXM group, three patients did not receive the allocated intervention due to consent withdrawal. Five cases were lost to follow-up including one in the HD-DXM arm and four in the PDN arm. Based on the sample size formula, 36 patients were divided in each group in order to compare platelet count response at 95 % confidence interval, the test power of 80%.

Detailed baseline features of the patients in each group are shown in Table 2. There was no significant difference in baseline characteristics. Bleeding symptoms were generally mild to moderate in both groups, and the skin and mucus membranes were the most common bleeding sites (30.6% in the HD-DXM and 33.4% in the PDN groups) without any significant differences ($P > 0.05$).

Outcomes

Although the difference in mean platelet count between the two groups was not significant at the beginning of the study, three pulses of HD-DXM regimen resulted in a higher mean platelet count compared with PDN during the first year of follow-up at two-month intervals (Table 3).In both groups the mean platelet count increased significantly in comparison with that of the baseline. However, in HD-DXM arm the increase during the first two months of therapy was faster compared with the response in the following months before

reaching a plateau level with no further increase. Otherwise, PDN arm showed a gradual increase in the mean platelet count with a constant slope.

The initial response was higher in the HD-DXM arm than the PDN arm (69.4% vs 30.6%, P=0.001), although there was no significant difference in the incidence of complete response between the two arms (HD-DXM 22.2% vs PDN 8.3%, P>0.05). In HD-DXM, more patients reached sustained response after the eight months follow-up (88.9% vs 66.6%, P<0.05). The logistic regression model was employed to evaluate the response rate in both groups in order to control other parameters such as age, gender and bleeding scores (Table 4).

As shown in Table 5, after 3 courses of HD-DXM, the most common adverse events reported include hypertension and hyperglycemia. Nevertheless type and incidence of the disease were not significantly different between the groups (P>0.05). There were no reports of bleeding complications in either group during the one year follow up after treatment as bleeding symptoms initially were generally mild to moderate. Other complications such as insomnia and mood disorder were reported by fewer patients and did not indicate any difference in accordance with either arm of the study or the type of treatment. Most of the adverse events were mild and usually resolved spontaneously after treatment was completed. No patient exited from the study because of adverse complications of therapy.

Discussion

The main goal of the initial ITP treatment is to overcome the risk of bleeding and achieve a persistent response, especially after discontinuing treatment, without any further treatments, and thus, prevent long-term adverse events such as infections or metabolic alterations. Glucocorticoids are the cornerstone of ITP treatment [4,7]. Based on recent guidelines, most patients are currently treated with PDN (1.0 mg/kg/day for two to four weeks orally) as the first-line treatment. An initial response rate of 50%-60% is estimated using this approach, but the long-term response rate without any other therapies is very low (10%-25%) [4].

Although there is no consensus on the optimal dosage of glucocorticoids as well as the type and duration of administration, the major concern is represented by the potential side effects of corticosteroids. Glucocorticoid toxicity is generally related to both the average dosage and cumulative duration of administration, though, for most toxicities, no threshold dose and duration is established [14]. Controversy exists over the relative safety of low-dose glucocorticoid use (≤10 mg/day of PDN or equivalent) in chronic conditions. Several large retrospective reviews showed that long-term glucocorticoid use, even in low doses, is a significant independent predictor of numerous serious adverse effects and that risk is both dose- and time-dependent [15,16].

Administration of immunosuppressive agents for patients with ITP often increases the risk of infection. A study on 152 patients with ITP, conducted by Portielje et al. showed that the administration of immunosuppressive treatment significantly increased the mortality and morbidity rates in patients [17]. Low doses of PDN (5 to 10 mg/day) or high doses of corticosteroids are used in short-term courses to sustain an adequate platelet count in refractory patients with ITP. Experiences on this therapy showed more toxicity [18].

PDN protocol has been the standard of treatment-naïve adult patients with ITP [4,7,19,20]. However, recent studies proposed pulses of HD-DXM regimen (40 mg/day for

four days) as an alternative treatment [10,11,13,21,22,23,24]. Other studies suggested that repeated pulses of HD-DXM regimen may be better to induce long-term remission than a single-pulse regimen [12,21,25,26]. In the study conducted by Din et al. (2015), sixty-one patients with ITP received 40 mg/day of DXM in three four-day pulses with 14-day intervals. It was revealed that treatment with a three-pulse of HD-DXM regimen with low-dose DXM maintenance was an effective method for previously untreated ITP patients [25]. In our trial the administration route of dexamethasone was intravenous without any maintenance dose in order to compare the effects and complications of intravenous administration with previous studies [9,12].

The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) ITP Working Party planned the first pilot monocentric study aimed to evaluate the efficacy, safety, and tolerability of HD-DXM as a first-line therapy in previously untreated adult patients with ITP, utilizing a six-pulse regimen. The initial response rate was very encouraging (about 90%) and the long-term response was about 68% (25/37, with 20 CR) in all the evaluated patients (median follow-up: 26 months).After that, the GIMEMA ITP Working Party planned a multicenter pilot study in order to obtain a better compliance, feasibility, and satisfactory efficacy through modifying the regimen used in the first study by reducing the number of courses (four instead of six) and their intervals (14 days instead of 28 days). The GIMEMA experience showed a persistent response after four treatment courses in about 67% of adult patients and suggested 3 courses of HD-DXM may be the optimal regimen and should be evaluated in the future trials [10].

Mithoowani et al. (2016) did a systematic review and meta-analysis of randomized trials to compare between HD-DXM pulses and PDN regarding to platelet responses.[27] From 5 trials included in that study except Din et al [25] other trials compared 1 to 2 cycles of HD-DXM with PDN. The study found no differences in overall platelet count responses at 6 months as opposed to the findings of our study which was similar to Din et al trial showed more durable platelet responses with 3 cycles of HD-DXM pulses. The study showed similar findings in fewer toxicities and higher initial responses with HD-DXM.

The results of the current study suggested that a three-pulse HD-DXM regimen was more effective than the conventional treatment with PDN. It resulted in both a higher overall response and a more sustained response during the eight month follow-up. In contrast with other studies [12,25], complete response was not significantly higher in the HD-DXM group than in PDN group. However, the findings suggest that a three-pulse HD-DXM regimen could be better to achieve sustained response and overall response without the burden of long-term corticosteroid consumption.

Study strengths and limitations

In the current study, both groups were matched by the baseline characteristics including age, gender, and bleeding score, which was the strength of this study. The limitation of the current study was that the size of each group did not allow comparing the results of different pulses of HD-DXM treatment with a single course of treatment. Follow-up for more than one year could also increase the efficacy of comparison between the two groups. In our study bleeding symptoms of patients were mild to moderate and patients with bleeding score of 3 or 4 were not included. Another study enrolled patients with more severe bleeding symptoms found that bleeding was more effectively controlled with HD-DXM and accompanied with fewer bleeding events [12].

Conclusion

In summary, the current randomized, clinical trial showed that a three-pulse HD-DXM regimen was more effective and resulted in more sustained responses than the conventional PDN therapy, without an increase in the rate of complications. As a result of the current study, a three-pulse HD-DXM regimen could become the preferred choice for the treatment of ITP. More studies are required to compare the efficacy and safety of different courses of HD-DXM.

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Table 1: Grade and score of bleeding symptoms[8]

Grade	Bleeding symptom
0	Absent
1	Petechiae
2	Ecchymoses with minor blood loss
3	Major mucous hemorrhage without sequelae
4	Major blood loss with sequelae or death

Table 2: Baseline characteristics in both arms

Characteristics		PDN. (n=36)	HD-DXM. (n=36)	P value
Sex	**Male**	12(33.3%)	18(50%)	0.232†
	Female	24(66.7%)	18(50%)	
Age; year		39.80±17.12	39.36±11.65	0.900††
Bleeding score				
0		24(66.7%)	25(69.4%)	
1		10(27.8%)	10(27.8%)	0.838†††
2		2(5.6%)	1(2.8%)	

Data shown mean ± SD or frequency in N(%). P value >0.05
†: Significance level of Fisher's exact test
††: Significance level of Mann-Whitney test
†††: Significance level of Chi-square test

Table 3: Comparison of mean platelet count in 2 months interval between each arms.

Platelet count, $\times 10^9$/L	PDN. (n=36)	HD-DXM. (n=36)	P value†
Baseline	10.00	11.00	0.804
After 2 month	20.50	36.00	0.001
After 4 month	29.50	61.50	0.002
After 6 month	35.00	100.00	0.001
After 8 month	36.00	104.00	0.009
P value††	0.001	<0.001	

Data shown Median.

†: Significant level of comparison mean platelet count between two groups by Mann-Whitney test.

††: Significant level of comparison mean platelet count by passing time (baseline-after 8 month) in each group by Friedman test.

Table 4 : Comparison of response rate of platelet count in each arms of the study.

Response	PDN. (n=36)	HD-DXM. (n=36)	OR (95% CI)	P value†
Initial response*	11(30.6%)	25(69.4%)	5.68(2.05-15.76)	0.001
Complete response**	3(8.3%)	8(22.2%)	3.05(0.74-12.62)	0.124
Sustained response***	24(66.7%)	32(88.9%)	4.17(1.19-14.60)	0.025

*: Initial response = platelet count over 30×10^9/l after one month from treatment.

**: Complete response =platelet count over 100×10^9/l after one month from treatment.

***: Sustained response = platelet count over 30×10^9/l for at least 6 month from treatment.

†: Significance level calculated from logistic regression model with control of other parameters such as age, gender and bleeding score.

Table 5 : Comparison of complications in each arms of the study.

Adverse events, n(%)	PDN. (n=36)	HD-DXM. (n=36)	P value†
Hypertension	5(13.9%)	3(8.3%)	0.710
Hyperglycemia	2(5.6%)	1(2.8%)	0.555
Insomnia	0(0%)	4(11.1%)	0.115
Mood disorders	0(0%)	2(5.6%)	0.493
Weight gain	1(2.8%)	0(0%)	0.314
Cushingoid appearance	3(8.3%)	0(0%)	0.239

†: Significance level of fisher exact test