Original Article

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Comparison of anti-D immunoglobulin and dexamethasone in chronic and persistent forms of pediatric immune thrombocytopenic purpura

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Abstract

Bakcground: The aim of ITP treatment is to prevent intracranial hemorrhage and increase the platelet count rapidly. This study was conducted with the objective of comparing the efficacy of anti-D immunoglobulin (Ig) with dexamethasone in treating childhood ITP.

Materials and Methods: In this randomized prospective control trial, 20 ITP patients (Platelet count<20,000/µl) younger than 16 were selected from those who referred to Dr. Sheikh Children Training and Research Hospital in Mashhad, Iran From February 2013 to January 2014. Patients were divided into two groups according to the type of administered treatment: group A received intravenous dexamethasone 40 mg/m2/ daily for four days. Group B received a single dose of intravenous anti-D Ig 50 µg/kg. The resultant data were then evaluated using SPSS (version 11.5).

Results: In this study, 20 patients [11 girls (55%) and 9 boys (45%)] with the mean age of 5.6±4 years were enrolled. From the total number, 13 (65%) were younger than 5 years old, 4 (20%) aged between 5 and 10, and 3 (15%) were older than 10. There was no significant difference between the two groups regarding sex and age. In both groups the most common symptom was cutaneous manifestations (purpura, ecchymoses) (63.6% vs. 36.4% p=0.325). At enrolment time, the mean disease duration was 28±21 months, ranging from 5 to 132 months. Out of 20 patients, 9 (45%) suffered from chronic ITP, and 11 (55%) were in persistent phase of the disease. No significant difference was observed between the two groups regarding the frequency of chronic and persistent cases (p=0.370). Similarly, the follow-up platelet count four months after the treatment showed no significant difference between the two groups (p=0.241).

Conclusion: The findings of this study did not confirm the priority of dexamethasone over anti-D Ig. The hemolytic side effects of anti-D were negligible compared to dexamethasone.

Key Words: Dexamethasone, Idiopathic, Purpura, RHO(D) antibody, Thrombocytopenic

Introduction

Immune Thrombocytopenic Purpura (ITP) is a benign childhood disease. It was first observed in 1924 in a 16 year old patient (1). ITP is a hemorrhagic disorder with various causes, and presents itself with a remarkable reduction of platelet count and an increase in the number of megakaryocytes in bone marrow. Furthermore, the average life-span of platelets in blood decreases in ITP patients (2). ITP might occur due to lymphoproliferative diseases, drugs or toxins, infections (viral infections, particularly in children), lupus erythematosus, and other underlying disorders (3, 4). ITP usually presents itself with acute petechiae, bleeding, and ecchymoses. ITP is a self-limited syndrome in most cases and usually has a good prognosis (5). Its incidence is estimated to be about 0.25 to 1.5 cases in 10000, and it is more frequent in children aged between 2 and 5 years (3). According to the new definition of ITP in 2009, patients do not achieve spontaneous remission or cannot maintain complete

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response after the end of treatment period in persistent ITP (4). In the chronic form, the disease lasts more than one year, and in the severe form patients continue to show bleeding symptoms despite sufficient treatment, or need additional therapeutic intervention on the occasion of hemorrhagic events (4).

There is evidence that ITP occurs after vaccination against some diseases; particularly measles-mumps-rubella (MMR) and hepatitis (6, 7). An abnormal increase in the number of platelets cleared by reticuloendothelial system, is the main pathology of ITP (8). Recent studies showed that bone marrow megakaryocytes do not produce enough platelets. So, drugs such as thrombopoietin (TPO) receptor agonists (TPO agents) are helpful in treating these patients (6). Patients with the chronic form of ITP have immunoglobulin G (IgG) against platelet membrane glycoproteins Ib/IX and/or GPIIb/IIIa (7). Spontaneous remission happens in most children with ITP: 20%-25% of ITP cases become chronic. According to the International Working Group (IWG) criteria, chronic ITP is defined as the disease lasting for more than a year (8, 9).

Various pharmacological and surgical options have been proposed for the management and treatment of ITP. The fundamental aim of ITP management is to prevent intra cranial hemorrhage (10). Treatment options should be considered in patients with platelet counts below 10000/µl, or in higher counts with evidence of bleeding (11). Intravenous immunoglobulin (IVIG), corticosteroids (CS), and anti-D Ig have been administered in many cases in recent studies, but there is not sufficient evidence as to which treatment provides a superior clinical outcome (9). Some studies reported an equal efficacy of IVIG and corticosteroids in increasing platelet count (12). Preliminary response to CS is dramatic, but this response is sustained only in a small portion of patients (12). Corticosteroids are inexpensive and easy to procure, and can be used orally or intravenously (13). Anti-D Ig is less expensive than IVIG. Moreover, it has a shorter infusion time, fewer side effects, and runs a lower risk of viral infections. Anti- D Ig administration rarely leads to hemolytic or disseminated intravascular coagulation (14). The aim of this study was to compare the efficacy of anti-D Ig with dexamethasone in treating childhood ITP.

Materials and Methods

This study was approved by the Ethical Committee of Mashhad University of Medical Sciences (approved No; 2013). It was conducted from February 2013 to January 2014 at Dr. Sheikh Training and Research Children's Hospital in Mashhad, Iran.

Patient selection

Children with chronic and persistent forms of ITP and Rh (+) were enrolled in this study. Except for low platelet count, complete blood count (CBC) was normal; peripheral blood smear (PBS) test was also normal except for the abnormally large-size platelets. Patients with oraganomegaly or lymphadenopathy were excluded. Other exclusion criteria were familial history of hemorrhagic disease, congenital platelet-related disorders, history of life-threatening bleeding, plasma products allergy, contraindication for dexamethasone, connective tissue disorders, Bernard-Soulier and Glanzmann syndrome, and chronic disorders such as diabetes mellitus, kidney and liver disease. Signed written consent form was obtained from the parents of all children before enrolment in the study.

Study design

In this single-blind randomized prospective study, from among those who referred to hematology clinic of Dr. Sheikh Training and Research Children's Hospital from February 2013 to January 2014, 22children with ITP who aged 0 to 16 years old were enrolled. Patients were

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selected by simple random sampling method, and were subsequently randomly divided into two groups. Treatment method was selected by a single researcher randomly picking out cards from a bag (10 cards labeled as anti-D and 10 as dexamethasone). The first group received a single dose of intravenous anti-D Ig 50 µg/kg (Rhophylac, Germany), and the second received intravenous dexamethasone 40 mg/m2/ daily (Caspian, Iran) for four days. Complete blood count was obtained at the beginning of the study and on days 3, 7,14,21,30, 44, 60, It was repeated two times in the next two months. The physician who administered drugs and followed up patients was blind about the treatment method. Complete response (CR) was defined as platelet count above 100000/µl, and response (R) was considered as platelet count above 30000/µl, and good response to treatment was defined as platelet count above 20000/µl.

Statistical analysis

The data were evaluated using SPSS (version 11.5) (SPSS Inc., Chicago, IL, USA). Frequency indexes, and mean and standard deviation were used for data description. X2 or Fisher exact test was used to compare the distribution of variables between the two groups. Differences in platelet and hemoglobin level were assessed by T student test. P value less than 0.05 was considered as significant.

Results

Twenty patients [11 girls (55%) and 9 boys (45%)] with the mean age of 5.6±4 years were enrolled in the study. Out of the total number, 13 children (65%) were younger than 5 years old, 4 (20%) aged between 5 and 10, and 3 (15%) were older than 10. There was no significant difference between the two groups regarding sex and age. Demographic characteristics of patients are summarized in Table I. The most common symptom was cutaneous manifestations (purpura, ecchymoses) in both groups (63.6% vs. 36.4% p=0.325).

At the time of enrolment, mean disease duration was 28±21 months, ranging from 5 to 132 months. Nine children (45%) suffered from the chronic form of ITP, and 11 (55%) from the severe form of persistent phase. These frequencies did not differ between the two groups (p=0.370). Mean platelet count of the two groups were compared in different phases after treatment (Table II).

Mean hemoglobin (Hb) level in Dexamethasone group and Anti-D Ig group in different phases of treatment are compared in Table III.

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Table I: Demographic characteristics of patients in Dexamethasone group and Anti D Ig group

		Dexamethasone	Anti-D Ig	P value
Sex	Male, n (%)	5 (50)	4(40)	0.5
	Female, n (%)	5 (50)	6(60)	
Age groups (years)	5 >	6(46.2)	6(53.8)	0.661
	5-10	3(75)	1(25)	
	>10	1(33.3)	3(66.6)	
Symptoms	Cutaneous, n (%)	7(63.6)	4(36.4)	0.325
	Mucosal, n (%)	3(42.9)	4(57.1)	
	Cutaneous and mucosal, n (%)	0	2(100)	
ITP phase	Persistent n (%)	4(36.4)	7(63.6)	0.370
	Chronic n (%)	6(66.6)	3(33.3)	

Table II: The comparison of mean platelet count in Dexamethasone group and Anti D Ig group over a four-month period after treatment

Treatment phase	All patients		P value	Chronic ITP		P value
	Dexamethasone (mean ±SD)	Anti-D Ig (mean ±SD)		Dexamethasone (mean ±SD)	Anti-D Ig (mean ±SD)	
Before treatment (*10^9)	7.8±5.4	13.5±3.8	0.015	5.5±3.6	11.3±6.5	0.108
Third day(*10^9)	85±65	85±72	0.929	76±54	110±79	0.476
Seventh day(*10^9)	74±53	120±102	0.498	77±67	71±61	0.749
After 2 weeks (*10^9)	114±83	40±26	0.252	51±27	29±21	0.258
After 3 weeks (*10^9)	55±33	35±25	0.200	64±35	14±12	0.054
After 4 weeks (*10^9)	47±22	29±17	0.053	52±18	13±9	0.013
After 6 weeks (*10^9)	33±15	30±23	0.710	39±16	9±7	0.021
After 8 weeks (*10^9)	28±10	20±12	0.159	27±11	8±3	0.028
After 3 months (*10^9)	26±14	18±13	0.222	21±12	6±3	0.091
After 4 months (*10^9)	16±9	14±9	0.655	19±12	9±7	0.241

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Table III: The comparison of Mean Hb level between Dexamethasone group and Anti-D group over a three-week period after treatment.

	Dexamethasone (mean ±SD)	Anti-D Ig (mean ±SD)	P value
At the beginning	12±0.9	11.6±1.6	0.210
Third day	12.4±0.89	11.9±1.1	0.275
Seventh day	12.8±0.69	11.8±1.2	0.054
2 weeks after treatment	12.6±0.68	11.8±1.4	0.124
3 weeks after treatment	12.2±0.96	11.6±0.79	0.2

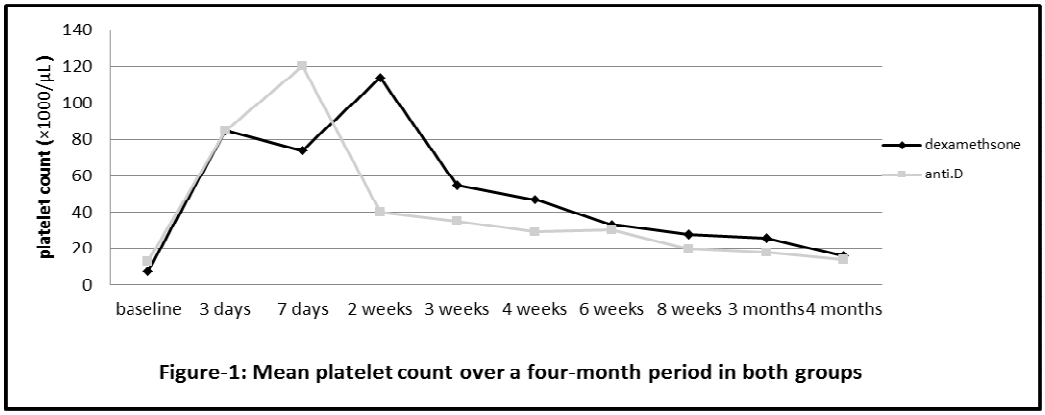

Figure1. The follow up platelet count of patients treated with dexamethasone and Anti-D Ig over a four-month period

Discussion

Preventing intracranial hemorrhage and rapidly increasing platelet count are the two main aims of ITP treatment (15). Despite therapeutic strategies, 45% of the patients in the present study suffered from chronic ITP and 80% of children in anti-D group, and 70% of those in dexamethasone group had platelet counts lower than 20000 at the end of the follow-up period (p=0.65). No adverse events were observed during the study. Hb levels were lower in Anti-D receivers but this difference was not statistically significant during treatment and follow-up period (P>0.05). The findings in this study, in line with El Alfy's, indicated the safety of Anti-D Ig with intravascular hemolysis (16). Although the mean hemoglobin level was lower in patients who received intravenous Anti-D Ig, no Hb drop below 20% was noted. No serious hemorrhagic event, such as intracranial hemorrhage, was noted in either group, in this study. The results of this study indicated that three patients (30%) in Anti-D group and 4 (40%) in dexamethasone group reached complete response after three days of treatment. CR frequency was observed after one week (3 patients vs. 2 patients), after two weeks (1 patient vs. 0), and after three weeks (1 patient vs. 0) in dexamethasone and anti-D groups, respectively. Mean time for conversion of complete response to response was 6.03± 3 days for dexamethasone group and 2.1±1 days for Anti-D patients.

Salama firstly proposed a hypothesis about the role of Anti-D Ig in treating ITP patients (17). He confirmed the efficacy of rhesus antibodies (anti-Rho antibody) in

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blockading the reticuloendothelial system (RES) which influences platelet destruction and increases platelet count in immune thrombocytopenia (18, 19). In this study, the highest platelet count was observed on the 7th day in Anti-D group, and on the 14th day in dexamethasone patients. In this study 90% of children in dexamethasone group and 70% in Anti-D group, had platelet counts above 20000/µl (good response to treatment) during the first six weeks after drug administration ($p>0.05$).

In children with chronic ITP, the average platelet count was significantly higher in dexamethasone group in weeks 4, 6 and 8 after treatment. However, this difference did not last until the end of follow-up period. It seems that although platelet count rose in the first week after dexamethasone injection, this increasing trend did not continue in the next months. So, its efficacy is not superior to anti-D. A study in Egypt showed that repeated doses of anti-D Ig can raise platelet count in a sustained manner (16).

Age more than 10 years old, female gender, negative history of viral infection, and positive history of autoimmune disorders are the main risk factors for chronic ITP (20). However, gender and age did not show any associations with the chronic form of the disease in this study. This might be due to the rather small sample size in this study (only 9 children had chronic ITP).

The most prevalent feature was cutaneous manifestations in these patients, all of S.faihi patients also had cutaneous bleeding (21). The mean age of children in this study was 5 years old. Children in this age range are assumed to have a lot of physical activities and are, therefore, more susceptible to traumas that lead to hemorrhagic events (21).

Cheng showed that although a four-day course of high-dose dexamethasone is effective in adults with ITP, about 50% of patients experienced relapse (22). Mashhadi concluded that with single-dose dexamethasone treatment, only 10% of ITP patients experience relapse (23). This rate was higher in the present study: platelet cut off point was 20000/µl in this study, whereas in Cheng and Mashhadi reported it to be 30000/µl. Moreover, patients in this study were younger than those studied by Cheng and Mashhadi.

Mean time needed to increase platelet count up to 20000/µl after injection was 5.2±1.8 and 5.2±2.5 days in dexamethasone and Anti-D groups, respectively ($p=0.923$). Yetgin showed that administration of Anti-D Ig with an attack dose of 75 µg/kg, could prevent hemorrhagic events within two hours after injection (24).

Kumar concluded that hospital charges did not vary between patients treated with Anti-D Ig and IVIG, and that many cases needed re-treatment (25). The cost effectiveness of these drugs was not evaluated. In this study, the number of children was too small to allow a definitive conclusion. Another limitation of this work was short follow up duration and the mere assessment of the hemolytic side effect of Anti-D.

Conclusion

The results of this study indicated that dexamethasone is not more effective than Anti-D Ig. Moreover, the findings indicated that anti-D hemolytic side effects were negligible. On the other hand, the prophylactic effect of dexamethasone occurred more rapidly and lasted longer than that of Anti-D Ig.

Conflict of interest

There was no conflict of interest.

References

1. Hachisuga K, Hidaka N, Fujita Y, Fukushima K, Kato K. Can we predict neonatal thrombocytopenia in offspring of women with idiopathic thrombocytopenic purpura? Blood res. 2014; 49(4): 259-64.

2. Kowalczyk M, Rubinstein PG, Aboulafia DM. Initial Experience with the

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Use of Thrombopoetin Receptor Agonists in Patients with Refractory HIV-Associated Immune Thrombocytopenic Purpura A Case Series. J Int Assoc Provid AIDS Care. 2015; 14(3): 211-6.
3. Rohmer B, Valla FV, Baleydier F, Launay V, Dommange-Romero F, Pondarré C. Newly Diagnosed Immune Thrombocytopenic Purpura in Childhood: Successful Implementation of a Limited Intervention Strategy in the Setting of Pediatric Emergency Care. J Pediatr. 2015; 166(2): 480-2.
4. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009; 113(11): 2386-93.
5. Farah RA, Hage P, Al Rifai A, Afif C. Immune thrombocytopenic purpura associated with brucellosis. Case report and review of the literature. J Med Liban. 2010; 58(4): 241-3.
6. Cecinati V, Principi N, Brescia L, Giordano P, Esposito S. Vaccine administration and the development of immune thrombocytopenic purpura in children. Hum Vaccin Immunother. 2013; 9(5): 1158-62.
7. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. J Pediatr. 2010; 156(4): 623-8.
8. Coppo P, Veyradier A, Monge M. Acquired idiopathic thrombotic thrombocytopenic purpura: arguments for an autoimmune disease. Presse medicale (Paris, France: 1983). 2006; 35(12 Pt 2): 1876-86.
9. Journeycake JM. Childhood immune thrombocytopenia: role of rituximab, recombinant thrombopoietin, and other new therapeutics. Hematology Am Soc Hematol Educ Program. 2012; 2012(1): 444-9.
10. Son DW, Jeon IS, Yang SW, Cho SH. A single dose of anti-D immunoglobulin raises platelet count as efficiently as intravenous immunoglobulin in newly diagnosed immune thrombocytopenic purpura in korean children. J Pediatr Hematol Oncol. 2008; 30(8): 598-601.
11. Mantadakis E, Farmaki E, Thomaidis S, Tsalkidis A, Chatzimichael A. A case of immune thrombocytopenic purpura after influenza vaccination: consequence or coincidence? J Pediatr Hematol Oncol. 2010; 32(6): 227-9.
12. Celik M, Bulbul A, Aydogan G, Tugcu D, Can E, Uslu S, et al. Comparison of anti-D immunoglobulin, methylprednisolone, or intravenous immunoglobulin therapy in newly diagnosed pediatric immune thrombocytopenic purpura. J Thromb Thrombolysis. 2013; 35(2): 228-33.
13. Shahgholi E, Vosough P, Sotoudeh K, Arjomandi K, Ansari S, Salehi S, et al. Intravenous immune globulin versus intravenous anti-D immune globulin for the treatment of acute immune thrombocytopenic purpura. Indian J Pediatr. 2008; 75(12): 1231-5.
14. Blanchette VS, Price V. Childhood chronic immune thrombocytopenic purpura: unresolved issues. J Pediatr Hematol Oncol. 2003; 25: S28-33.
15. Ou CY, Hsieh KS, Chiou YH, Chang YH, Ger LP. A comparative study of initial use of intravenous immunoglobulin and prednisolone treatments in childhood idiopathic thrombocytopenic purpur. Acta Paediatr Taiwan. 2005; 47(5): 226-31.
16. El Alfy MS, Mokhtar GM, El-Laboudy MA, Khalifa AS. Randomized trial of anti-D immunoglobulin versus low-dose intravenous immunoglobulin in the treatment of childhood chronic idiopathic thrombocytopenic purpura. Acta Haematol. 2006; 115(1-2): 46-52.
17. Salama A, Kiefel V, Amberg R, Mueller-Eckhardt C. Treatment of autoimmune thrombocytopenic purpura

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with rhesus antibodies (anti-Rh0 (D)). Blut. 1984; 49(1): 29-35.
18. Adly AAM, Ragab IA, Ismail EAR, Farahat MM. Evaluation of the immature platelet fraction in the diagnosis and prognosis of childhood immune thrombocytopenia. Platelets. 2015; 26(7): 645-50.
19. Alavi S, Aryan Z, Ghazizadeh F, Arabi N, Nikougoftar M, Ebadi M. The immunophenotype of bone marrow lymphocytes in children with immune thrombocytopenic purpura. Pediatr Hematol Oncol. 2014; 31(6): 548-54.
20. Heitink-Pollé KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood. 2014; 124(22): 3295-307.
21. Sfaihi L, Kassar O, Medhaffar M, Kamoun T, Hadiji S, Aloulou H, et al. Primary immune thrombocytopenia in childhood: a regional study in the south of Tunisia. Tunis Med. 2014; 92(3): 219-23.
22. Cheng Y, Wong RS, Soo YO, Chui CH, Lau FY, Chan NP, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. N Engl J Med. 2003; 349(9): 831-6.
23. Mashhadi MA, Kaykhaei MA, Sepehri Z, Miri-Moghaddam E. Single course of high dose dexamethasone is more effective than conventional prednisolone therapy in the treatment of primary newly diagnosed immune thrombocytopenia. Daru. 2012; 20(1): 1.
24. Yetgin S, Aytaç S, Olcay L, Tunç B, Özbek N, Aydinok Y. Evaluation of the effects of and earliest response rate to anti-D treatment in children with chronic idiopathic thrombocytopenic purpura: a pilot study. Turk J Pediatr. 2010; 52(2): 126.
25. Kumar M, Vik TA, Johnson CS, Southwood ME, Croop JM. Treatment, outcome, and cost of care in children with idiopathic thrombocytopenic purpura. Am J Hematol. 2005; 78(3): 181-7.

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