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Original Research Article

Subcutaneous Anti-D versus intravenous methylprednisolone for the treatment of immune thrombocytopenic purpura

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ABSTRACT

Background: Established treatment option for immune thrombocytopenic purpura (ITP) are intravenous immunoglobulin (IVIg), anti-D immunoglobulin' and high dose intravenous methyl prednisolone (HIVMP). The present study was undertaken to compare the efficacy of subcutaneous bolus anti-D over HIVMP in the treatment of ITP.
Methods: A randomized clinical trial was conducted on a total 20 children with ITP, presented with extensive bleeding manifestation and platelet count <20 × 109/L;10 children received single dose subcutaneous anti-D (75 microgram/kg) and 10 children received HIVMP (30 mg/kg/dose) for 3 consecutive days. Patients were monitored for response to treatment and adverse events, platelet count and hemoglobin label were done in all patients at 24-hour, 48-hour, 72 hour, 1st week, 2nd week, 1st month, 2nd month and 3rd month after treatment to observe the change. Response rate define as a platelet count over 20 × 109/L within 72 hours of treatment. All the data were analyzed with the help of SPSS software version 16.0.
Results: By 24 hours of treatment 40% patient of anti-D and 10% patients of HIVMP group had platelet count >20 x109/L, by 72 hours 90% patients of both group achieved complete response (P =1.750). In HIVMP group the rate of remission gradually decreasing but in anti-D group it was persistently remain high. In anti-D group hemoglobin concentration decreased in 80% cases (P=0.023) but rate of decrease was not significant. New hemorrhage or significant extension of hemorrhage did not observe in any group.
Conclusions: A single dose of subcutaneous anti-D raised platelet count in children with ITP more rapidly and effectively than HIVMP (30 mg/kg/dose) with an acceptable safety profile.

Keywords: Anti-D immunoglobulin, High dose intravenous methylprednisolone, Idiopathic thrombocytopenic purpura

INTRODUCTION

Childhood onset immune thrombocytopenia (ITP) has a benign course with spontenious resolution within 6 mounths in 75-80% of the cases. In another 20% it lasts for more than 6 months and usually described as chronic. Even in one third of cases, spontaneous remission can occure later. Therefore, a conservative approach is

advocated and treatment is usually reserved for the minority of patients with very low platelet counts and clinical signs of bleeding. Established treatment options are steroids, intravenious immunoglobulins (IVIG), anti-D globulin (anti-D) and splenectomy.[1-3] Compared to steroids and IVIG, anti-D gains an interest due to its moderate cost and safety profile. Nevertheless, when applied intravenously, anti-D can cause systemic reactions like chills, fever, headache and vomiting, of special concern are the cases of severe haemolysis observed after intravenous application.[3,4] Several authors reported that Subcutenious (SC) bolus anti-D produces largely the same beneficial effect as obtained by IV anti-D. They recommend replacement of IV administration of anti-D by SC administration in ITP.[4,5] Here we report outcomes using subcutaneous anti-D in the treatment of ITP in paediatric patients.

METHODS

This is a prospective intervention type of study carried out in Department of Paediatric Haematology and Oncology in BSMMU during the period of January to December 2010, over one year. Children who were admitted in the Department of Paediatric Haematology and Oncology during the study period with the diagnosis of ITP, were taken as study population. Among them total 20 patients who fulfill the selection criteria, were enrolled in this study. Children were eligible if diagnosed case of ITP made by history, physical examination and confirmed by platelet count and bone marrow morphological examination, age between 1-15 years, platelet count <20 × 109/L, presence of mucosal or extensive cutaneous bleeding and excluded if Rh-negative blood group or splenectomized.

Informed consent was obtained from all participants according to the study protocol approved by the ethical review committee of BSMMU. Patients within the study group were randomized by simple random technique to receive treatment according to protocol, single dose of subcutaneous 75 microgram/kg anti- D or HIVMP 30 mg/kg day/dose for 3 consecutive days.

In anti-D group Baxter preparation of human anti-D immunoglobulin (PARTOBULIN SDF) was used. Single dose of S/C 75 microgram/kg anti-D was given and in HIVMP group Pharmacia Belgium preparation of Methylprednisolone (Solu-medrol) was used. A dose of 30 mg/kg for 3 consecutive days were given. Each dose was given over 1 hour in infusion. Physical examination of all children was done at regular interval. At 24 hrs, 48 hrs and 72 hrs after initiation of treatment platelet count and hemoglobin label were done in all patients to observe the change. Response rate defined as a platelet count over 20 × 109/L within 72 hours of initial treatment. Hemoglobin label decrease up to 1 g/dl is not significant. All investigations were done in the department of Paediatric Haematology and Oncology, BSMMU. Estimations were carried out by SYSMEX automated haematology analyzer and cheeked manually under microscope (Olympus cx21). Thereafter, follow up of patients of both groups were done weekly for 2 weeks and monthly for 3 months. In each follow-up visit through physical examination to find out presence or absence of any skin bleeding or mucosal bleeding and lab investigation including platelet count and hemoglobin label were done.

All the data were analyzed with the help of SPSS (statistical package for social science) software version 16.0. For the validity of the study outcome different statistical tests were applied as appropriate (chi square test, t test). A P value <0.05 was taken as significant and confidence interval was set at 95% level.

RESULTS

The demographic characteristics of the patients studied were compared. It showed no significant difference among the parameters between the two groups. After 24 hours of treatment in anti-D treated group 40% of patient had achieved complete response, on the contrary in HIVMP treated group only 10% had complete response.

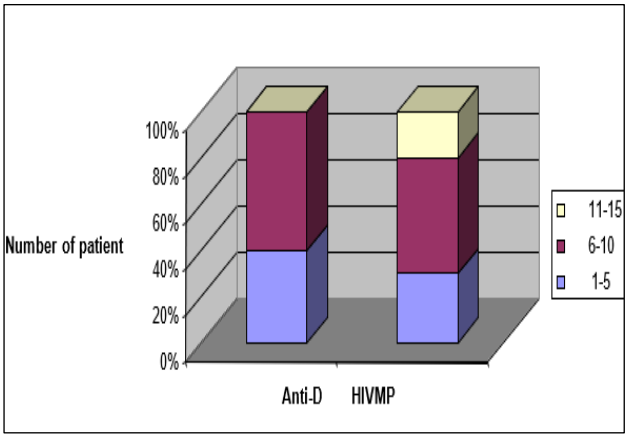

Figure 1: Age distribution of ITP patients among anti-D and HIVMP treated group.

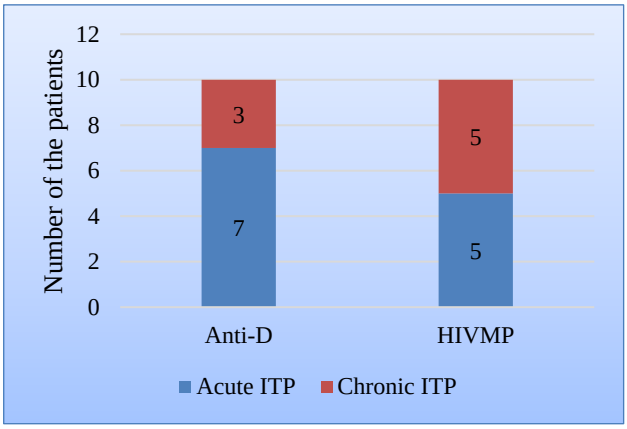

Figure 2: Distribution of ITP patient in anti-D and HIVIG treated group according to clinical pattern.

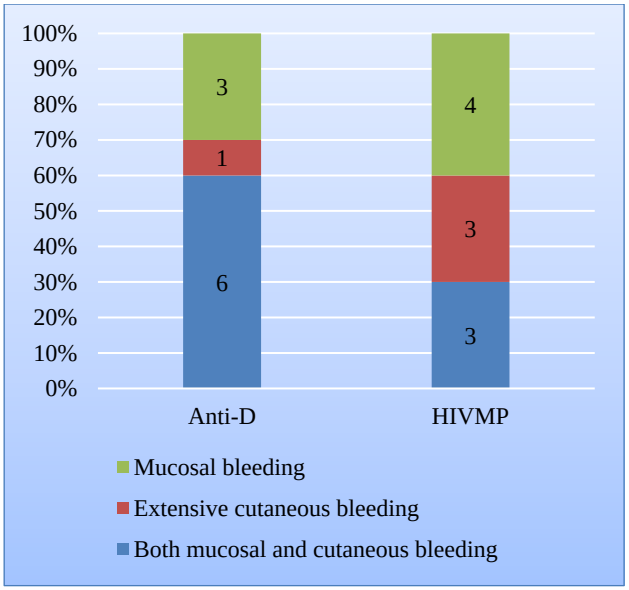

Figure 3: Distribution of ITP patient in anti-D and HIVIG treated group according to bleeding pattern.

The differences of complete response between two groups at 24 hours of treatment were clinically significant. During follow-up it was evident that remission achieved in 80% of anti-D treated group and 100% of HIVMP group during 1st week.

In anti-D group it was maintained persistently but in HIVMP group the rate of remission gradually decreasing and at 3rd month 80% patients in anti-D group and 60% in HIVMP group were in remission.

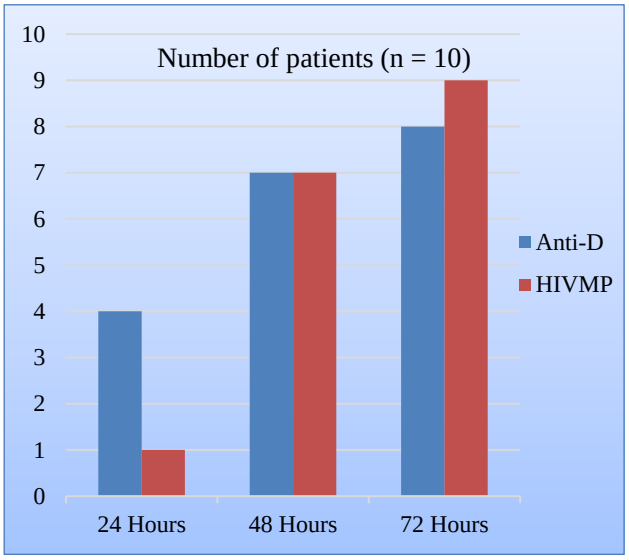

Figure 4: Response of patients in anti-D and HIVMP treated group within 72 hours of treatment.

It was seen that in anti-D group, the baseline mean platelet was 8.80 (±1.69) and after 24 hour of treatment it was 26.90 (±29.13), after 48 hour and 72 hour it was 50.60 (±34.04) and 69.80 (±48.14), the difference was found to be highly significant, overall P value 0.005.

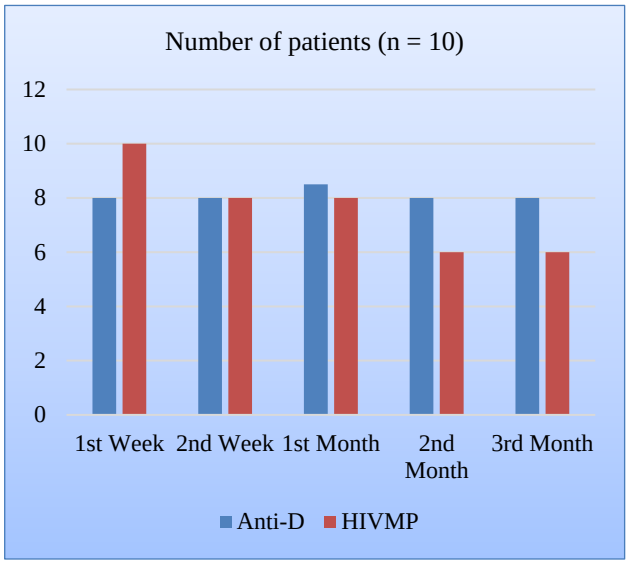

Figure 5: Overall rate of remission in patients during follow-up.

It was also found that in HIVMP group, baseline mean platelet was 10 (±5.44) after 24 hour of treatment it was 13.30 (±7.51) and after 48 and 72 hours it was 39.50 (±21.48) and 59.20 (±33.36) respectively, overall P value was highly significant 0.001.

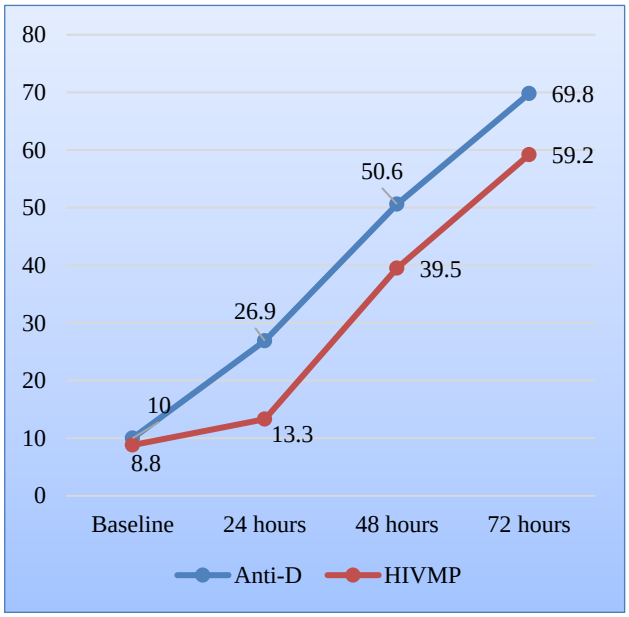

Figure 6: Mean platelet in both anti-D and in HIVMP group at baseline, at 24-hour, 48 hour and at 72 hours of treatment.

Significant rise of average mean platelet was found in both anti-D group and HIVMP group but in anti-D group the mean of platelet was much higher.

It was found that during follow-up period mean platelet count was persistently remain high in anti-D group, which was highly significant (P = 0.008). Haemolysis accompanied by drop in hemoglobin concentration is a predictable event after administration of anti-D in pediatric patients with ITP.

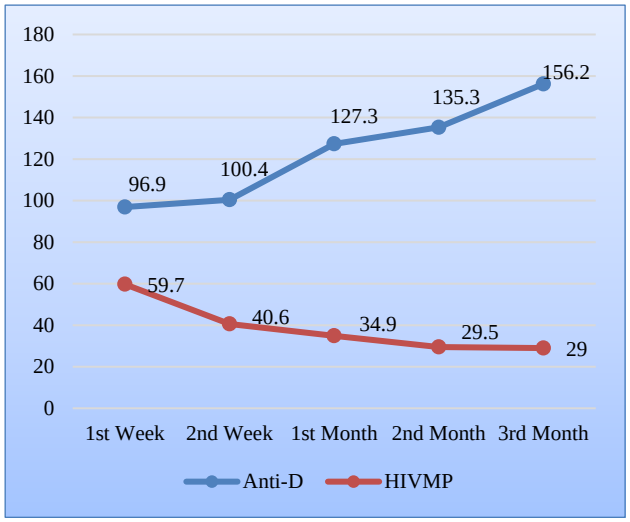

Figure 7: Mean platelet values during follow-up.

Decrease level of hemoglobin was found in 80% of patients in anti-D group and in 20% of patients of HIVMP group, the difference was found to be significant (P = 0.023). None of the patient was given red blood cell transfusion. The decline in hemoglobin concentration was not associated with patient's age or sex and was not predicted by the degree of rise in platelet count after anti-D treatment.

Table 1: Adverse effects observed among the patients treated with anti-D and HIVMP group.

Adverse effects	Anti-D (n=10)	HIVMP (n=10)	P value (Chi-square)
Decrease level of hemoglobin	8	2	Chi-square: 7.467 Degree of freedom (df): 2 P-value: 0.023 (significant)
Fever	1	1	
Headache	0	4	

Table 2: Overall decrease of mean level of Hemoglobin in anti-D and HIVMP group.

Duration	Anti-D (n=10)	HIVMP (n=10)	P value (paired test)	S/NS
Base line	10.53	10.29	0.692	NS
24 hours	10.37	10.46	0.884	NS
48 hours	9.94	10.58	0.401	NS
72 hours	9.92	10.37	0.561	NS
1st week	10.24	10.34	0.873	NS
Overall	10.20±1.10	10.41±1.00	0.743	NS

S: Significant; NS: Not Significant

New hemorrhage or significant extension of hemorrhage, taken as severe adverse event and not observer in any group.

DISCUSSION

In the present study we compare the efficacy of single dose subcutaneous anti-D with HIVMP for the treatment of ITP and also compare side effects. Significant rise of platelet was found in both anti-D and HIVMP group. A single dose subcutaneous anti-D raised platelet count more rapidly and effectively than HIVMP. Mean platelet value remained persistently high in anti-D group but in HIVMP group the rate of remission was gradually delimiting. Decrease level of hemoglobin was found significantly more in anti-D group New hemorrhage or significant extension of hemorrhage, taken as severe adverse event and not observer in any group.

Present study shown that after 24 hours of treatment in anti-D group 40% of patient had complete response, on the contrary in HIVMP group only 10% had complete response. Anti-D is more effective in children in the treatment of ITP, but the mechanism of action is not fully understood.[6] The outcome measures of rate and degree of platelet rise, a single dose anti-D, 75 mg/kg, is effective and similar to single dose of IVIg, 0.8 gm/kg. The platelet count was significantly higher for the anti-D group and nearly equal to IVIg.[7]

Hemolysis accompanied by drop in hemoglobin concentration is a predictable event after administration of anti D in paediatric patients with ITP.[8] Some degree of hemolysis is quite commonly seen with anti-D treatment due to its mechanism of action.[9] Decrease level of hemoglobin which indicates hemolysis, found in most of the patients of anti-D group then HIVMP group, diffrence was found to be significant (P = 0.023). Hemoglobin decline is an expected adverse event associated with anti-D treatment.[7] When change of mean hemoglobin, at base line, 24-hour, 48 hour and 72 hour of therapy were compared the difference was found to be not significant (P = 0.160 and 0.349).

The limitation of the present study was small sample size. Studies related to treatment of ITP mostly had small sample size. In the study conducted over 1 year, sample size was only 12.[5] In a study by Kjaersgraard conducted over 4-year sample size was 45.[10] In another study conducted over 1-year sample size was 8.[11] It correlates with our study. Follow-up study can be carried out involving large number of patients.

CONCLUSION

Significant rise of platelet was found in both anti-D and HIVMP group. A single dose subcutaneous anti-D raised platelet count more rapidly and effectively than HIVMP with an acceptable safety profile. Follow-up study can be carried out involving large number of patients and

implementation of anti-D in the treatment of ITP is preferable, but it should be given in hospital setting and under strict supervision to handle the adverse effect (hemolysis) if occurs.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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