IJMSPR

ISSN : 2394-8973
Vol. 1, No. 2, May 2015

International Journal of Medical Sciences and Pharma Research

www.ijmspr.com

Email: editorijmspr@gmail.com or editor@ijmspr.com

International Journal of Medical Sciences and Pharma Research

ISSN 2394-8973 www.ijmspr.com
Vol. 1, No. 2, May 2015

Research Paper

SAFETY, EFFICACY AND TOLERABILITY OF INTRAVENOUS ANTI-D IMMUNOGLOBULIN IN NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA IN CHILDREN

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Objectives: To evaluate the effect of single dose (75 µg/kg) Anti-D in children with newly diagnosed immune thrombocytopenia in terms of its safety, efficacy and tolerability. Methods: This was a prospective study conducted in Dayanand Medical College and Hospital-a tertiary care hospital over a period of 18 months. In this study, nineteen children with newly diagnosed immune thrombocytopenia (10 males, 9 females) were included. Mean age of the children was 4.7 ± 3.2 years. Anti-D was administered as a single intravenous injection in a dose of 75 µg/kg. Main outcome variables taken were Increase in platelet count, fall in hemoglobin, change in AST, ALT, urea, creatinine, sodium and potassium levels and appearance of any adverse symptom. Results: The response rate to Anti-D was 89.4% (n = 17). Mean increase in platelet count was 125.5 ± 86.2 x 10^9 /L at 48 h and 257.5 ± 176.4 x 10^9 /L at day seven. Response at 48 h was seen in 88.2% of the children. Females showed a better response than males (p = 0.05). Anti-D did not have any significant effect on renal or liver function tests and it caused a mean fall of 1.76 ± 1.06 g/dL in hemoglobin. Mild adverse effects developed in 52% children which resolved spontaneously within 12 h. Conclusion: Anti-D shows a good response (89.4%) in children with newly diagnosed ITP with an acceptable safety profile. Adverse effects like fever and chills are common (52%).

Keywords: Anti D, Children, Immune thrombocytopenia, Newly diagnosed

INTRODUCTION

Many studies in the past have demonstrated efficacy of therapy with intravenous immunoglobulin (IVIg), Anti-D or oral prednisolone in immune thrombocytopenia (ITP). However, decision about the treating agent in patients with immune thrombocytopenia has remained controversial and based on individual experience, even among experts (Salama, 1983; Blanchette, 1994; Mohsen, 2006). Among the various options available, the Intravenous rhesus immunoglobulin (Anti-D) seems to be the best especially in India

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where cost can be a major factor for deciding the treatment option. With corticosteroid therapy, slow platelet response and adverse effects are frequently seen. IVIG leads to a rapid rise in platelet count; however, it is very expensive and adverse effects associated with its infusion are common and sometimes troublesome (Soker, 2001; Krishnamurthy, 1994). There is paucity of literature concerning the use of Anti-D (75 μg/kg dose) in newly diagnosed childhood ITP in India. However the literature review has suggested that a dose of 75 μg/Kg is more effective than 50 μg/kg but there are concerns about safety and tolerability of this dose. This study was planned to evaluate the safety, efficacy and tolerability of 75 μg/kg dose in Indian children.

MATERIALS AND METHODS

This prospective study was conducted at a tertiary care centre in North India over a period of 18 months, after approval from the institute's ethics committee. Inclusion criteria included children (≤18 years) with newly diagnosed ITP having platelet count <20 x 10^9/L, Rh-positive blood group, hemoglobin ≥10 g/dL and patients with platelet count ≥20 x 10^9/L but having severe bleeding. Patients with secondary causes of ITP and those who were splenectomized were excluded. A detailed informed consent was taken prior to the study.

Patients were classified as newly-diagnosed ITP as per current consensus definitions if they presented within 3 months from diagnosis (Rodeghiero, 2009). Diagnosis was based on the peripheral blood picture, isolated thrombocytopenia and bone marrow picture suggestive of ITP (cellular marrow showing normal or increased megakaryocytes and all other findings and cell lines as normal). All patients were tested for Anti HBs Antigen, Anti HCV, HIV and Antinuclear Antibody (ANA) to rule out the common secondary causes of ITP.

Anti-D was administered intravenously as a single dose (75 μg/Kg) over 5 minutes. Platelet counts were done on day one, at 48 h and at day seven and then at monthly interval after anti-D administration for six months.

Response was defined as Complete (CR): platelet count ≤100×10^9/L; Response (R): platelet count ≥30×10^9/L and at least twofold increase from the baseline count; and No response (NR): platelet count <30×10^9/L or less than twofold increase of baseline platelet count or bleeding. Time to response was calculated as time taken from starting Anti-D to achievement of CR or R. Loss of complete response (LCR) was taken as platelet count below 100×10^9/L or bleeding. Loss of response (LR) was taken as platelet count below 30×10^9/L or less than twofold increase of baseline platelet count or bleeding.

Safety of Anti-D was also evaluated by monitoring pre-treatment and post-treatment hemoglobin levels, renal and liver function tests including serum ALT, AST, urea, creatinine, sodium and potassium at 48 h and at day seven after Anti-D administration and their comparison with the baseline values. To study the tolerability of Anti-D, all symptoms after administration of Anti-D were recorded and relationship of various parameters to response was also studied.

Patients were followed up for a period of 6 months to monitor the hemoglobin and platelet counts and to evaluate loss of response and recovery of hemoglobin levels.

Student t test was used for statistical analysis and p values were calculated (p value < 0.05 was considered to be significant).

RESULTS

A total of 43 children with immune thrombocytopenia presented to the department, however only 19 children with newly diagnosed immune thrombocytopenia fulfilled all the inclusion criteria and none of the exclusion criteria. Age of the patients ranged from 1.2 year to 14 years (mean ± SD 4.7 ± 3.2 years). Male to female ratio was 1.1:1, with ten males (52.6%) and nine (47.4%) females. Eighteen (94.7%) children presented with skin bleeds, including those who had associated mucosal bleed (n=12). One patient (5.3%) had presented only with mucosal bleed.

Efficacy: At admission platelet count ranged from 2 x 10^9 /L to 20 x 10^9 /L (mean± SD 8.95 ± 5.57 x 10^9 /L). All patients enrolled in the study, showed increase in platelet counts after administration of Anti-D, with a mean increase of 125.5 ± 86.2 x 10^9 /L at 48 h and 257.5 ± 176.4 x 10^9 /L at day seven. Based on the criteria defined earlier, 89.4% children were responders (n=17); and 10.6% were non responders (n=2). Complete response was seen in 16 patients (84.2%). Time to response was 48 h in 15 patients (88.2%) and day seven in two patients (11.8%) (Figure 1 and Table 1).

Among the non responders, one child developed jaundice on day 3 and on subsequent follow up, tested positive for helicobacter pylori. He showed improved platelet counts after receiving eradication therapy for the same. In the second non responder, seven days after Anti-D administration, platelet count increased to 22 x 10^9/L but again showed a fall to 3 x 10^9/L and she continued to have bleeding manifestations. This patient was given methylprednisolone following which she showed increase in platelet count to 51 x 10^9/l.

Tolerability: After Anti-D administration, 52% children developed adverse effects. Common adverse effects observed were fever and chills (26.3%). fever alone (10.5%), only chills (5.3%), nausea (10.5%), vomiting (10.5%), headache (5.3%), myalgia (5.3%) and jaundice (5.3%). All these symptoms were mild and resolved within 12 h without any specific treatment (Table 2).

Safety: Mean fall in hemoglobin was 1.76 ± 1.06 g/dL with a range of 0 to 3.5 g/dl. Nine patients (47.4%) had a significant fall, i.e., more than or equal to 2 g/dl. In two children, hemoglobin decreased to < 8 g/dL and they were advised blood transfusion. After Anti-D administration 50% of the patients showed complete hemoglobin recovery by day seven. Rest of the patients showed recovery in hemoglobin levels by one month (Figure 2).

Table 1: Increase in Platelet Count Among Patients

Time	Platelet count (x10^9/l)		*p*-value
	Mean ± SD	Change from baseline	
Baseline	8.9 ± 5.5	–	–
48 hrs	134.7 ± 88.6	125.7	0.00417
Day 7	266.7 ± 176.6	257.7	0.00591

Note: P value <0.05 considered to be statistically significant

Figure 1: Platelet Counts on Follow up

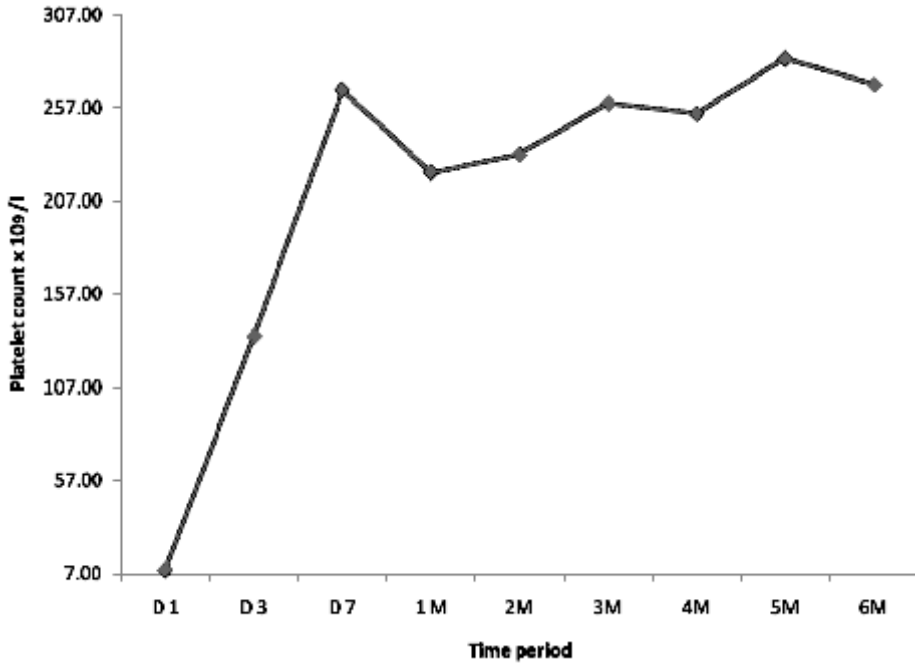

Figure 2: Hemoglobin Levels on Follow up

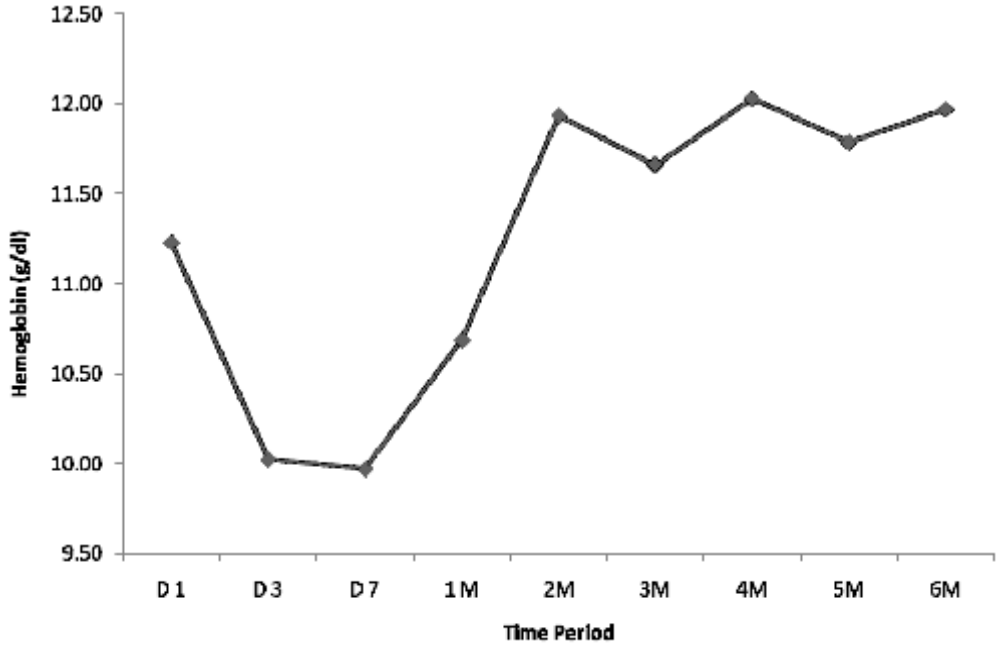

Table 2: Adverse Effects Related to Anti-D Administration

Adverse effects	Number	Percentage (%)
Fever with chills	5	26.3
Fever	2	10.5
Chills	1	5.3
Nausea	2	10.5
Vomiting	2	10.5
Headache	1	5.3
Myalgia	1	5.3
Jaundice	1	5.3

During the study, renal function tests including serum urea, creatinine and serum electrolytes and liver function tests, i.e., AST and ALT levels were monitored before administration of Anti-D, after 48 h and at day seven. No significant change was seen in renal or liver functions after Anti-D administration ($p > 0.05$).

Relation of response to various other parameters was also studied such as age, gender, blood group, presenting complaints, duration of complaints, pre-treatment level of hemoglobin and platelets, and the fall in hemoglobin levels. Of all the parameters studied, significant difference between response and mean increase in platelets was seen in relation to gender of the patient. It was observed that female children showed greater increase in platelet count as compared to males ($P = 0.05$ on day three and 0.03 on day seven).

Follow up: Out of nineteen patients enrolled in the study, fourteen had regular follow up for four months and eleven patients completed follow up for six months. Out of these, two children (18.1%) showed a fall of platelet count to < 50 x 10^9/L. One child had loss of response after one month and the second child after 5 months of Anti-D administration. Three children (27.2%) had loss of complete response (fall of platelet count to < 100 x 10^9/L) at one month, two month and 4 months. All of these patients had spontaneous increase in platelet counts later on.

DISCUSSION

In our study, 89.4% children showed increase in platelet count to > 30 x 10^9 /L at the end of 48 h. Mean increase in platelet count in the present study was 125.5 ± 86.2 x 10^9/L at 48 h and of 257.5 ± 176.4 x 10^9 /L at day seven.

This response was better than the studies conducted in the past. In a study by Shangholi *et al*, the response rate of Anti-D (75 µg/Kg) was 76% (Salama, 1984). Tarantino *et al* used 50 µg/Kg dose and reported a response rate of 80-90% after 72 h (Tarantino, 2006). In a study by Naithani *et al.* a dose of 50 µg/Kg was used and response rate was 70% (Krishnamurthi, 1994). Scardavou *et al* and Blenchette *et al* reported an increase in platelet count to more than 20 x 10^9 /L in 72% and 82% patients respectively, by using 25 µg/Kg of Anti-D repeated on two consecutive days (Tarantino, 2006; Bussel, 2006).

In the study by Tarantino *et al* (50 µg/Kg dose), mean increase at 24 h was approximately 35.9 x 10^9 /L and at 72 h, it was 55.6 x 10^9 /L (Sacaradavov, 1997). In another study using 75 ìg/Kg dose by Shangholi et al, mean increase in platelet count at 48 h was 30.3 x 10^9 /L, and at day seven it was 104.6 x 10^9 /L (Salama, 1984). This data suggests that increasing the dose of Anti-D improves its response.

Various studies show that by increasing dose of Anti-D, fall in hemoglobin tends to be more (Scaradavov, 1997; Soker, 2001). In our study,

mean fall in hemoglobin was 1.76 ± 1.06 mg/dL. This fall is comparable to the results of other studies. Bussel *et al* reported a fall in hemoglobin of 1.9 g/dL by using 10-30 ìg/Kg dose of Anti-D (Andrew *et al.,* 1992).[1]Andrew *et al.* reported mean decrease in hemoglobin to be 1.3 g/dL using a dose of 25-55 µg/Kg (Naithani *et al.,* 2009). Scardavou and Alfy reported mean decrease in hemoglobin to be 0.8 g/dl using doses of 20-60 µg/Kg and 50 µg/Kg respectively (Bussel, 2007; Tarantino, 1999). In another study by Shangholi et al, using 75 µg/Kg dose of Anti-D, fall in hemoglobin was noted to be 1.1 g/dL (Salama, 1984).

Our study also collaborates that the degree of fall of hemoglobin is not related to response to Anti-D or to absolute increase in platelet count. This observation is possibly based on the hypothesis that although the primary mechanism of action of Anti-D is believed to be immunologic blockade of Fc receptors within the reticuloendothelial system, other immunomodulatory effects are also possible. Fall in hemoglobin level associated with Anti-D administration shows a spontaneous recovery (50% of the patients showed complete hemoglobin recovery by day seven while rest of the patients showed recovery by one month) and may need no intervention.

Anti-D was well tolerated by most children. Minor adverse effects observed were fever and chills (26.3%), nausea and vomiting (10.5%), headache and myalgia (5.3%) and jaundice (5.3%). Adverse effects were similar to those reported in previous studies but incidence was more (as compared to 2-11% in the previous studies using doses ranged from 25-75 µg/kg) (Scaradavov, 1997; Andrew *et al.,* 1992; Bussel, 2007; Krishnamurthi, 1994; Panzer, 1986). This suggests that incidence of these adverse effects is possibly dose related and. Other contributing factors towards a higher incidence of adverse reactions may be demographic or genetic predisposition. But even at this higher dose, adverse events were usually well tolerated and resolved spontaneously within 12 h. Still one needs to be watchful for these adverse effects and must prepare the parents for the same.

Not much work has been done in past to determine safety of Anti-D especially in 75 µg/Kg dose, in terms of its possible effect on renal functions and liver functions. Results of our study showed that Anti-D does not have any significant impact on renal as well as liver function.

In our study, the relationship of various parameters with response was evaluated. Of all the parameters studied, it was observed that female children respond better to Anti-D treatment as compared to males and show greater increase in platelet count. However this is a small sample size study and the results need to be confirmed in a large randomized multicentric study.

The strengths of this study include that it addressed all parameters, i.e., safety, efficacy and tolerability of Anti-D in children, and application of appropriate statistical analysis. Limitations of the study are its small sample size and being a unicentric study.

CONCLUSION

Treatment with a single dose (75 µg/kg) of Anti-D in children with newly diagnosed ITP provided an overall response rate of 89.4% within 48 h and showed an acceptable safety and tolerability profile.

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