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A study on high-dose dexamethasone versus prednisolone as frontline therapy in newly diagnosed immune thrombocytopenia in children

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ABSTRACT

Objectives: Treatment for children with newly diagnosed immune thrombocytopenia (ITP) includes corticosteroids, out of which prednisolone is commonly used. High-dose dexamethasone (HD-DXM) treatment for children with newly diagnosed ITP can produce better outcomes than prednisone, as stated by many studies. A few articles compare HD-DXM and prednisolone as frontline therapies in newly diagnosed adult ITP but data on pediatric ITP comparing these two drugs are scarce.

Material and Methods: It was a randomized, prospective, and cohort study. After enrolment, checking the inclusion and exclusion criteria, each child was randomly distributed into two groups; one cohort was treated with HD-DXM in the dose of 40 mg/m^2 (maximum daily dose 40 mg) for 4 days once every 28 days for three cycles; and one with prednisolone in the dose of 2 mg/kg/day (maximum 60 mg/day) for 2 weeks, with quick tapering. A total of 42 children were enrolled, 21 in each cohort.

Results: The overall response (OR) was 42.9% with HD-DXM therapy. The OR and median time to response were similar in both HD-DXM and prednisolone cohorts. There was also no significant difference in incidences of adverse effects between the two cohorts.

Conclusion: Thus, this study confirms that HD-DXM is a safe, effective, and non-inferior option compared to prednisolone as frontline therapy in newly diagnosed ITP in children.

Keywords: Immune thrombocytopenia, Children, Dexamethasone, Prednisolone

INTRODUCTION

Immune thrombocytopenia (ITP) is a disease distinguished as thrombocytopenia with or without bleeding manifestations.[1] At present, available therapies for children with newly diagnosed ITP are IV immunoglobulin (IVIg), corticosteroids, or anti-D Ig. Among corticosteroids, prednisolone is being used as frontline therapy for a long time. The usual dose of prednisolone used was 2 mg/kg for 2 weeks followed by a tapering dose. The usual response rate varied between 50% and 60% in several studies, and the long-term remission rate varied between 10% and 25%.[2-4]

As an alternative, dexamethasone was started as frontline therapy in the newly diagnosed patient of ITP. The usual dose of dexamethasone is used in a high dose of 40 mg/m^2 in 4 days/month. This high-dose dexamethasone (HD-DXM) as frontline therapy in children with newly diagnosed ITP has been used in adults as well as children, but the usefulness was not validated as compared to prednisolone.[4-9] It has been used as a single cycle or multiple cycles. Cheng *et al*. and Bae *et al*. demonstrated its efficacy with a single cycle, whereas Borst *et al*. used it for multiple cycles.[5,8,9]

In studies conducted by Mazzucconi *et al*.,[10] the response rate was 85.6% and there was a significant improvement between the second and third cycles (75.8% vs. 89%, $P = 0.018$) but not between the third and fourth. This suggested that three cycles of HD-DXM may be optimum. With the background of this data, in this study, HD-DXM was used in a dose of 40 mg/m^2/day (maximum daily dose 40 mg), 4 days in a 28 days cycle, for three cycles.

Various theories have been postulated regarding the mechanism of action of HD-DXM in the treatment of ITP. These decrease in IL-18/IL-18BP ratio, shifting monocyte FcγR balance toward the inhibitory FcγR IIb, loss of dendritic cell functions,[11,12] etc.

In light of the above studies, it is evident that HD-DXM is an alternative in the frontline therapy of ITP. However, there are only a few randomized trials available, comparing HD-DXM versus conventional-dose prednisolone as frontline therapy in adult ITP. Data on the comparison of dexamethasone versus prednisolone in children with ITP are far lesser. Thus, this randomized control trial may prove useful in establishing the role of HD-DXM in children with newly diagnosed ITP. The objectives of the study were to assess the efficacy and safety of HD-DXM as first-line treatment in newly diagnosed patients of pediatric ITP and to assess it in comparison to prednisolone.

MATERIAL AND METHODS

Study design and setting

It was a randomized, prospective, and cohort study done in Kolkata, West Bengal. The study began with the enrolment of the patients after checking the inclusion and exclusion criteria. Inclusion criteria were children aged 1–18 years with newly diagnosed primary ITP having platelet count $<30 \times 10^9$/L, or between 30×10^9/L and 100×10^9/L with the presence of bleeding symptoms, who cannot afford treatment with IVIg or anti-D Ig as first-line treatment. Patients who were having secondary ITP; cardiac, pulmonary, hepatic, or renal dysfunction; had taken antiplatelets or NSAIDS within 1 month from the commencement of study; having other bleeding disorders or coagulopathy, were excluded from the study. All procedures performed in this study were by the Ethical Standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was registered at the institutional research ethics board.

Study details and participants

After detailed history taking, examination including the analysis of bleeding grade, laboratory evaluation, confirmation of the diagnosis of newly diagnosed ITP, and informed consent, patients were randomly divided into two cohorts by block randomization. A computer-based randomization list was created with a block size of 6. One cohort was treated with HD-DXM in the dose of 40 mg/m^2 (maximum daily dose – 40 mg) for 4 days once every 28 days for three cycles. The other cohort was treated with prednisolone 2 mg/kg/day (maximum 60 mg/day) for 2 weeks, then tapering the dose within the next 2 weeks. Patients were entitled to get any rescue medications (platelet transfusion/IVIg) in case of any major bleeding.

Considering a prevalence of childhood ITP to be around five cases per 1 lac population, based on the previous studies, the expected proportion of patients achieving CR in the prednisolone group is 50% and dexamethasone group is 80%,[10] to achieve a power of the present study of 80%, the minimum sample size required for the study cover around in the present study was calculated as approximately 20 cases in each cohort.

Endpoints

The primary endpoints clarified for this study were the initial response (R) and overall response (OR). The response to treatment was evaluated according to the IWG criteria[13] as follows –

Complete response (CR)

Blood platelet count ≥1 lacs/cmm on 2 times, more than 7 days apart, while not having bleeding symptoms.

Response (R)

Blood platelet count ≥30,000/cmm and a more than 2-fold increase in platelet count from baseline on two occasions, more than 7 days apart while not having bleeding symptoms.

No response (NR)

Blood platelet count <30,000/cmm or a less than 2-fold increase in platelet count from baseline or presence of bleeding.

OR

Number of patients who were maintaining the response at the time of closure of the study.

Follow-up (FU)

It was defined as the time in between diagnosis and the last available assessment.

Relapse

Blood platelet counts <30,000/cmm or bleeding symptoms due to thrombocytopenia after attaining the initial response.

Relapse-free survival (RFS)

RFS was defined as the time interval between the attainment of response and relapse.

Initially, the response was assessed at the end of each cycle of the HD-DXM arm and by day 28 in the prednisolone arm, respectively. After the administration of drugs, in each cohort, the response was defined monthly.

Secondary endpoints included bleeding grades, time to response, and adverse events. The bleeding grade of each patient has been analyzed according to the established ITP-specific bleeding grade[14] and it was assessed at baseline, at the end of three cycles of HD-DXM, and the 28th day of prednisolone. Time to response was defined as the duration from initiation of treatment to the achievement of response. The timeline for primary and secondary endpoints remained up to December 2019.

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 published by the U.S. National Cancer Institute.[15] Adverse effects which were specifically aimed to look for include hyperglycemia, hypertension, secondary infections, gastritis, weight gain, Cushingoid appearance, myopathy, and joint pain. Patients who experienced severe adverse effects were free to stop the allocated intervention and exit the study.

Data collection

Patients were enrolled in this study from January 2018 to June 2019. As a sustained response, denominated as the OR in this study, patients were followed up to December 2019, that is, a minimal of 6 months. Data were taken regarding platelet counts, bleeding symptoms, and adverse effects.

All recorded data were analyzed using standard statistical methods with the help of MS Excel 7.0 and Statistical Package for the Social Sciences, version 20.0 Windows compatible software.

RESULTS

A total of 42 newly diagnosed ITP patients were enrolled for the study, 21 patients each in HD-DXM and prednisolone cohort. No patients died or exit the study. There is no significant difference in age or sex distribution between the two cohorts [Table 1].

Classically, primary ITP is known to occur in the post-convalescence period of viral infections. However, in this study, the observation was different; a history of antecedent viral infection was available in only 7% of cases. All patients enrolled in this study had bleeding symptoms. In each cohort, more than 90% of patients presented with bleeding Grade 1 or 2, and none of the patients presented with life-threatening hemorrhage. The duration of the disease, baseline average platelet count before the intervention, is a confounding factor that may lead to misinterpretation of results. Both these entities were compared statistically, and there was no significant difference. To conclude, patients were divided into two cohorts, which were comparable before therapy in epidemiological, clinical, and hematological aspects. The consort of the study is given in [Figure 1].

Initial response

After the first cycle of HD-DXM, 67% of patients achieved the response(R) and 24% attained CR. At the end of the second cycle, the R was 57%, and CR was attained in 33% of patients. At the end of the third cycle, OR remains the same as 57%; however, CR was attained in 6 children (29%). Nine patients did not respond to the therapy (NR). In the prednisolone cohort, at the end of 4 weeks, OR was attained in 19 patients (90.4%), CR was attained in 9 patients (42.8%), and there was NR in 7 children [Table 2].

Long-term response: In the HD-DXM cohort, after the third cycle, the platelet count of patients was followed up monthly until the study closure. Total cumulative FU periods were 187 months. Finally, at study closure, OR was attained in 9 patients (42.9%), 12 patients did not respond to therapy (57.1%). Out of 12 patients who did not attain response, 8 patients (43%) ever responded, but 4 patients (14%) responded at some point in time but relapsed thereafter. CR was attained in 7 patients (33.3%).

In the prednisolone cohort, patients are also followed up months after the 28-day cycle. Total cumulative FU periods were 199 months. Finally, at study closure, OR was attained in 14 patients (66.7%), seven patients did not respond to therapy (33.3%). All patients who received prednisolone responded to it, but these seven patients failed to maintain the response, that is, relapsed. CR was attained in all 14 patients who attained response (66.7%) [Table 2].

Table 1: Comparison between the two cohorts at baseline.

Properties	High-dose dexamethasone (*n*=21)	Prednisolone (*n*=21)	Significance test	*P*-value
Age (Mean±SD) (Years)	8.2±3.94	8.6±3.93	tdf40=0.33 SE=1.2144	0.744
Sex	Male (%) – 12 (57.1) Female (%) – 9 (42.9)	Male (%) – 11 (52.4) Female (%) – 10 (47.6)	Chi-square$_{df1}$ 0.096	0.757
Duration of disease (mean±SD) (Days)	17.1±12.16	18±10.28	t_{df40}=0.26 SE=3.4747	0.797
Baseline platelet count (Mean±SD)	12,190.5±7186.6	11,666.7±4943.0	t_{df40}=0.28 SE=1901.7801	0.784

Table 2: Responses in high-dose dexamethasone and prednisolone cohort.

Response	High-dose dexamethasone (*n*=21)			Prednisolone (*n*=21)		
	CR	OR	NR	CR	OR	NR
Initial response (%)	6 (29%)	12 (57.1%)	9 (42.9%)	9 (42.8%)	19 (90.4%)	2 (9.6%)
Long-term response (%)	7 (33.3)	9 (42.9)	12 (57.1)	14 (66.7)	14 (66.7)	7 (33.3)

OR: Overall response, CR: Complete response, NR: No response

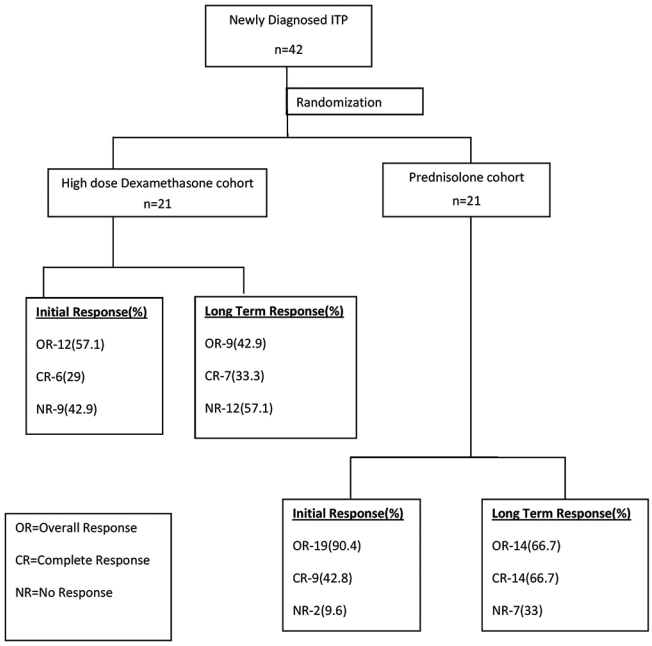

Figure 1: Consort of the study.

Bleeding symptoms

There is a significant improvement in bleeding symptoms in both cohorts. At the end of three cycles of HD-DXM, 71% of patients had no bleeding symptoms. After 4-week course of prednisolone, 76% of the patient has no bleeding symptoms. In both arms, no patient required rescue treatment for control of bleeding.

Comparison between two groups:

Response

After obtaining the final response, CR, OR, and relapse rate of each cohort, they were compared statistically. In the comparison, there is no significant difference in OR and CR. The median time to response was similar (14 days) in both two cohorts [Table 3].

Relapse

The relapse rate was 30% in the HD-DXM arm and 33.3% in the prednisolone arm. If it is expressed in the number of episodes, it comes as 5.4/100 person-months in the HD-DXM arm and 3.6/100 person-months in the prednisolone arm. There is no significant difference in the relapse rate between the cohorts [Table 3].

RFS

Mean RFS was 11.48 months in the HD-DXM arm and 14.09 months in the prednisolone arm. The statistical comparison revealed that there is no significant difference regarding RFS in the two cohorts [Figure 2].

Safety

No significant adverse effect occurred in any of the cohorts, which required discontinuation of the study. No death occurred in either of the two arms. The adverse effect in the HD-DXM arm in this study was observed in 28% of patients, whereas it was observed in 24% of the patients in the prednisolone arm [Table 3]. None of the adverse effects,

observed in the study, was severe for discontinuation of therapy. The difference between the two arms in terms of adverse effects was insignificant. This proved that the adverse effect profile of HD-DXM was similar to prednisolone, which is an established therapy in frontline management of pediatric ITP. When analyzed in terms of individual adverse effects, there was also no significant difference between the two cohorts [Table 4].

DISCUSSION

Primary ITP is a major cause of bleeding in children. Management of it includes corticosteroids, IVIg, or anti-D Ig. Among corticosteroids, prednisolone is an established first-line therapy for children with newly diagnosed ITP. Few researchers had used HD-DXM as frontline therapy for similar purposes but data comparing these two corticosteroids are very little. This present study was done to compare the efficacy and safety of HD-DXM and to compare it with prednisolone in children with newly diagnosed ITP.

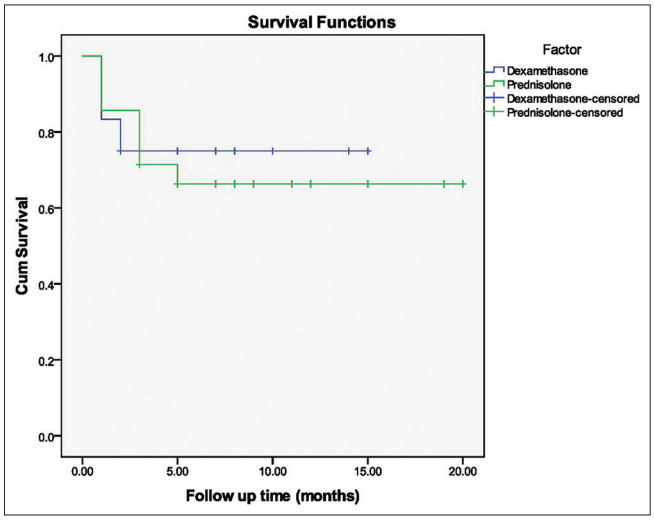

Figure 2: Relapse-free survival in the two cohorts – Kaplan–Meir survival analysis.

A total of 42 patients were enrolled in the study and randomized into two cohorts. Before the intervention, these two cohorts were comparable in terms of age, sex, prior duration of disease, and baseline platelet count. In the HD-DXM cohort, the initial rate of response was 67%. OR, that is, the response sustained over some time was 42.9% with a CR of 33.3%. The relapse rate was 30%.

In the prednisolone cohort, the initial response was 90.4%, much higher than that observed in the HD-DXM arm. The OR was 57.1% with a CR of 66.7%. The relapse rate was 33.3%.

On a statistical comparison between the two cohorts, there was no significant difference in terms of OR, CR, and relapse rate. There was no difference in RFS between the two cohorts. The median time to response was also similar between the two cohorts.

The safety profile of the two groups was also similar. There were no serious adverse effects that lead to the disruption of the study. The adverse effect in the HD-DXM arm was 28% and the prednisolone arm is 24%, which were statistically similar. On analysis of a specific adverse effect profile, there was no significant difference between the two groups.

Few previous studies compared the efficacy of high HD-DXM to prednisolone in newly diagnosed ITP [Table 5]. All of those were done on adults. All except one concluded that the efficacy of HD-DXM is similar to prednisolone.

Table 3: The final comparison between high-dose dexamethasone and prednisolone cohort.

Characteristics	High-dose dexamethasone (*n*=21) (%)	Prednisolone (*n*=21) (%)	Significance test	*P*-value
OR	9 (42.9)	14 (66.7)	Chi-square$_{df1}$=2.403	0.121
CR	7 (33.33)	14 (66.6)	Z test of proportion Z=1.86	0.063
Median time (days) to response (range)	14 days (7–63)	14 days (7–90)	No difference	
Relapse	(*n*=13,74 months follow-up) Four patients (30.1%)	(*n*=21, 194 months follow-up) Seven patients (33.3%)	Fisher's exact test	0.7098
Relapse episodes	Four episodes (5.40/100 person months)	Seven episodes (3.60/100 person months)	Z=0.28 SE=6.3915	0.779
Relapse-free survival	11.58 (95% CI=8.23–14.93)	14.09 (95% CI=10.5–17.67)	Chi-square$_{df1}$=0.026	*P*=0.872
Adverse effects (%)	28%	24%	Z=0.00	*P*=1.0

OR: Overall response, CR: Complete response

Table 4: Adverse effects observed in two cohorts.

Adverse events	Dexamethasone arm (*n*=21) No. (%)	Number of patients (CTC grade)	Prednisolone Arm (*n*=21) No. (%)	Number of patients (CTC grade)	Significance (*P*-value)
Arthralgia	1 (4.7)	1 (I)	2 (9.5)	2 (I)	0.996
Cushingoid appearance	3 (14.2)	3 (I)	5 (23.8)	5 (I)	0.689
Diarrhea	0		1 (4.7)	1 (I)	-
Edema	4 (19.0)	4 (I)	0		-
Fever	2 (9.5)	2 (I)	2 (9.5)	2 (I)	-
Hyperglycemia	0		0		-
Hypertension	1 (4.7)	1 (I)	2 (9.5)	2 (I)	0.996
Infection	4 (19.0)	3 (I) 1 (II)	3 (14.2)	3 (I)	0.997
Nausea	5 (23.8)	2 (I) 3 (II)	4 (19.0)	3 (I) 1 (II)	0.998
Gastritis	4 (19.0)	1 (I) 3 (II)	5 (23.8)	6 (I)	0.718
Weight gain	6 (28.0)	3 (I) 3 (II)	5 (24)	4 (I) 1 (II)	0.745
Proximal myopathy	1 (4.7)	NA	1 (4.7)	NA	-

Table 5: Comparison of the previous studies with the present study.

Study	High-dose dexamethasone regimen	Prednisolone regimen	Results (dexamethasone vs. prednisone)
Bae *et al.*[9]	40 mg/day×4 days for 1–2 cycles	1 mg/kg/day for 28 days	33.3% versus 45.0% (*P*=0.33)
Mashhadi *et al.*[16]	40 mg/day×4 days for 1 cycle	1 mg/kg/day for 28 days	90% versus 53.3% (*P*≤0.0001)
Wei *et al.*[17]	40 mg/day×4 days for 1–2 cycles	1 mg/kg/day for 28 days	40.0% versus 41.2% (*P*=0.884)
Present study	40 mg/m^2/day (Max 40 mg) for 4 days/28 days cycle×3 cycles	2 mg/kg/day for 2 weeks followed by tapering over next 2 weeks	42.9% versus 66.7% (*P*=0.121)

The limitation of the study is that the sample size in this study is small to draw any definite conclusion. Further study with a large sample size may overcome the limitation.

CONCLUSION

HD-DXM is a safe and effective therapy compared to prednisolone in frontline management of children with newly diagnosed ITP. It is non-inferior to prednisolone in terms of OR and CR. Both the drugs had an almost similar median time to response and adverse effect profile. Thus, HD-DXM can be used as safely and effectively in pediatric patients with newly diagnosed ITP, as prednisolone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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