Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Paediatric Haematology

Is Eltrombopag Useful in the Treatment of Children with Chronic Immune Thrombocytopenic Purpura

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DOI: 10.36347/sjams.2021.v09i04.004 | **Received:** 05.03.2021 | **Accepted:** 26.03.2021 | **Published:** 02.04.2021

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Abstract **Original Research Article**

Background*:** Chronic immune thrombocytopenic purpura is an autoimmune disease. Platelet count is decreased due to antibody-mediated platelet destruction as well as suppression of platelet production. So enhancement of platelet production could be a targeted goal of treatment. ***Methods: This is a placebo controlled prospective study conducted in the Department of Pediatric Hematology & Oncology, Dhaka Shishu (Children) Hospital from July 2018 to June 2020. Eltrombopag was given to chronic immune thrombocytopenic children at the dose of 25-50 mg/day according to age group and monitored clinically as well as laboratorial parameters including platelet count. ***Results*:** In thirteen (65%) of 20 study children, platelet count began to rise at day 10 and reached peak level at 5th week and all the responded children clinically improved by reduce or disappearance of bleeding manifestations. Eight (40%) responded patients maintaining platelet count for variable period while taking eltrombopag. The incidences of adverse events like headache, upper respiratory tract infections and raised transaminase (SGPT) are 10%, 10% and 15% respectively. ***Conclusion*:** It is revealed that eltrombopag increase platelet count and reduces bleeding manifestations in statistically significant proportion of chronic ITP children. No serious adverse event is seen. So eltrombopag could be use for treatment of children with chronic immune thrombocytopenic purpura.

Keywords: Chronic Immune Thrombocytopenic Purpura, Autoimmune Disease, Platelet Count, Headache.

INTRODUCTION

Immune thrombocytopenic purpura is the most common autoimmune cytopenia in children and defined as isolated low platelet count in the absence of an underlying cause in an otherwise well child [1] due to a variable combination of immune- mediated destruction of platelet by various mechanisms [2, 3] impaired platelet production [4] and inappropriate thrombopoietin response [5]. ITP occurs in 1.9 to 6.4 in1, 00,000 children [6]. The majority of children with ITP resolve spontaneously within a few weeks and do not require treatment [7], and about 20-30% children develop chronic ITP when they have persisted thrombocytopenia >12 months [8]. In the chronic form, therapeutic choices are complex and focused on improving health-related quality of life (HRQoL) [9] and controlling bleeding symptoms [10]. A few patients with significant hemorrhage require continuing therapy directed at raising the platelet count. Corticosteroid and intravenous immunoglobulin (IVIG) are recommended as first-line treatment. If first-line therapy fails-therapeutic option for managing chronic ITP in children include immunosuppressive therapy (such as rituximab, azathioprine, mycophenolate mofetil and sirolimus) [11, 12], splenectomy and more recently TPO receptor agonists (RAs) [13, 14]. Immunosuppressive agents increase platelet count in ITP primarily by reducing the extent of platelet destruction. But reduced platelet production has led to the use of treatments that enhance thrombopoietins. This approach has focused on TPO, the growth factor underlying megakayopoiesis. TPO is

the ligand for the TPO receptor on megakaryocytes & platelets [15-18]. The oral TPO-RA elthrombopag was approved by the US Food & Drug Administration (FDA) for the use in adult with chronic ITP in 2008 and in pediatric patients > 1 year of age with chronic ITP who had insufficient response to immunoglobulin, corticosteroid or splenectomy, in August 2015 [19, 20].

METHODS & MATERIALS

This placebo-controlled prospective study was conducted in the Department of Pediatric Hematology & Oncology, Dhaka Shishu (Children) Hospital from July 2018 to June 2020. The number of study case was 20 and control case was o6 children with chronic ITP. Control cases were not agreed to take eltrombopag due to financial constraint.

Inclusion criteria: Age-1-18 years, thrombocytopenia >12 months, received at least one previous treatment for ITP with no response and platelet count $<30\times10^9$ / L at enrollment. Eltrombopag was orally administered at the dose of 25 mg/day in children aged >1-5 years and 50 mg/day in children 6-18 years old 2 hours before or 2 hours after meal for better absorption, continued up to 24 weeks. The control cases were given Vitamin B complex as placebo. Rescue therapy given if needed. All the children were monitored clinically and by doing platelet count, SGPT, & S. Creatinine every month.

The primary outcome was the proportion of patients achieving a platelet count of 50×10^9 / L or more at least once from within 1-24 weeks in the absence of rescue therapy. We assessed safety in all patients receiving eltrombopag throughout the study period. Data were analyzed by SPSS and considered significant at p value <0.0001

RESULTS

From July, 2018 we began to enroll Chronic ITP children according to inclusion criteria and up to December, 2019 total 20 patients were enrolled as study case and 6 as control case. Among the study 20 children 6 were >1-5 years, 14 were 6-18 years old, 7 were girl and 13 were boy (Table-1).

Table-1: Age and sex distribution of study & control cases

Variables	Study cases	Control cases
Age		
>1-5 years	06 (30%)	02 (33%)
6-18 years	14 (70%)	04 (67%)
Sex		
Girl	07 (35%)	03 (50%)
Boy	13 (65%)	03 (50%)

In the study group getting Eltrombopag, 13 (65%) patients began to increase platelet count from day 10 and reached peak level at 5th week and in the placebo group platelet count minimally increased (up to 30×10^9 / L) in 02 ((33%) patients (Table-2). Comparison between eltrombopag vs placebo patients was 65% vs 33% which is statistically significant (P value <0.0001).

All the 65% responded patients with increased platelet count showed reduce or disappearance of bleeding manifestations and became hemodynamically stable without concomitant or rescue therapy. Clinically significant bleeding was found in only 2 (10%) non responded study patients vs in 3 (50%) placebo patients which is also statistically significant. These patients required rescue therapy (Table-2). Regarding sustained response, 8 (40%) responded patients in study group were maintaining raised platelet count for variable period which is statistically significant in comparison to placebo patient (Table-2).

Table-2: Distribution of treatment response.

Variables	Eltrombopag in %	Placebo in %	P value	
Platelet response	13 (65%)	02 (33%) *	<0.0001	Significant
Sustained response	08 (40%)	00 (0%)	< 0.0001	Significant
Required rescue therapy	02 (10%)	03 (50%)	< 0.0001	Significant
Clinically significant bleeding	02 (10%)	03 (50%)	< 0.0001	Significant

*The platelet count raised minimally (up to 30×10^9 / L).

Platelet count began to rise in eltrombopag group at 10th day and continue to rise at 35th day. Mean platelet count of study and control cases are summarized in Table-3. The highest count was 210×10^9 / L.

Table-3: Mean platelet count ($\times10^9$ / L) at treatment

Treatment	Day 0	Day 10	Day 15	Day 25	Day 35
Eltrombopag	12	25	50	105	160
Placebos	15	15	20	30	20

Regarding adverse events with eltrombopag 2 (10%) patients developed headache vs 3 (50%) patients in placebo group, 2 (10%) with eltrombopag vs 1 (17%) with placebo developed upper respiratory tract infection

and 3 (15%) with eltrombopag vs no patient with placebo having raised SGPT (Table-4). The patients with transaminitis required discontinuation of drug temporarily.

Table-4: Adverse events in Eltrombopag and Placebo group

Adverse events	Eltrombopag group	Placebo group
Headache	2 (10%)	3 (50%)
Upper respiratory tract inflection	2 (10%)	1 (17%)
Raised SGPT	3 (15%)	0 (0%)

DISCUSSION

The age of study children was divided in two categories: >1-5 years and 6-18 years for dosing concern of eltrombopag- 25 vs 50 mg/day which have been followed by other studies [19-23]. Regarding primary outcome, platelet count raised to 50×10^9 / L or more in 13 (65%) of study cases vs slightly increased in 2 (33%) placebo cases which was statistically significant and close to the other studies [21, 23] but lowers than few studies [22, 24]. In our study platelet count began to rise at day 10 and reached peak level at day 35 with highest 210×10^9 / L and similar to the other studies [21, 22]. Regarding clinical improvement, all the 65% responded patients with increased platelet count showed reduce or disappearance of bleeding manifestations and became hemodynamically stable without concomitant or rescue therapy which are the finding of other studies also [21-23]. Clinically significant bleedings were found in only 14% non-responded study patients vs in 50% placebo patients which is also statistically significant, these patients required rescue therapy. These findings are also similar to few other studies [21, 22]. The sustainability of raised platelet count was maintaining in various levels in 40% responded children for variable period. These findings are similar or close to the few other studies [21-23]. There was no clinically significant adverse event in our study. Only 2 (10%) patients developed headache, 2 (10%) developed upper respiratory tract infection and 3 (15%) having raised SGPT which are a little beat higher than study abroad [21-25].

CONCLUSION

Eltrombopag, a recent FDA approved, oral TPO-RA for pediatric chronic ITP with insufficient response to first-line therapy appeared effective and well-tolerated but further studies are needed to evaluate new doses strategies and real long- term efficacy as well as toxicity of Eltrombopag.

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