Section: Miscellaneous

Original Research Article

ELTROMBOPAG AS A THERAPEUTIC OPTION TO INCREASE THE PLATELET COUNTS IN DF AND DHF IN PATIENTS OF THROMBOCYTOPENIA

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ABSTRACT

Background: Dengue is the most widespread Aedes mosquito borne viral disease which infects more than 50 million people every year. The clinical symptoms of dengue may vary from mild fever to life- threatening incidents. Eltrombopag, a non-peptide, oral TPO-R agonist, small molecular weight is quandaries with the transmembrane domain of a TPO receptor and persuades the Janus Kinase/Signal transducer and activator of transcription pathway, with a significant rise in platelet production.

Material & Methods: The present study was a cross-sectional observational study which was conducted at private hospital in central India. The study was conducted in between July 2021- December 2023. The sample size for this study was 50.

Results: The mean age in group 1 was 25±7, and in group 2 29±8. The mean Baseline PLT * $30X10^9$ /L for group 1 was 57±23, and for group 2, 51±28. Mean of systolic baseline BP (mmHg) for group 1 was 103.55±5.04 and for group 2 was 105.38±18.34 followed by the mean of diastolic baseline BP (mmHg) was 72.83±6.56 and 72.84±12.93. AEs was found in 4(12.1%) cases of group 1 where in group 2 it was 2(5.9%).

Conclusion: Dengue is a vector-borne viral disease which needs medical assistance because it may lead to life-threatening outcome. Eltrombopag can be considered as a therapeutic option to increase the PLT counts in DF and DHF patients in the management of thrombocytopenia.

Keywords: Eltrombopag, Platelets (PLT), Dengue Fever (DF) and Dengue Haemoregic Fever (DHF).

INTRODUCTION

The prevalence of dengue fever (DF), a common infectious disease transmitted by mosquitoes, has experienced a significant and rapid increase of 400% in the past thirteen years.[1] The rise of DF as a rapidly spreading infectious disease on a global scale, causing significant illness and death, is primarily attributed to the increasing urbanization and climate change.[2] The causative agents of DF are a cluster of genetically similar but serotypically distinct dengue viruses (DENV 1-4) that are primarily transmitted by the Aedes aegypti mosquito.[3] DF is highly prevalent in tropical and sub-tropical regions, such as South-East Asian, Western Pacific, Eastern Mediterranean, American, and African regions.[2] Dengue fever is characterized by three distinct phases: the acute or febrile phase, the critical phase, and the recovery or convalescent phase.[2] The acute phase is characterized by elevated viral loads, resulting in a period of high fever that typically persists for 3 to 7 days after the infection begins. Following the acute phase, there is a critical phase characterized by specific pathological symptoms, including thrombocytopenia, the leakage of plasma into the peritoneal/pleural cavities, and clinically detectable bleeding occurring between days 4 to 6 of the illness. The convalescent phase is marked by the cessation of plasma leakage and the reabsorption of

leaked fluids.[2,3] Based on the WHO classification, individuals with dengue infection can be categorized into two main groups: dengue (with symptoms or without symptoms) and severe dengue.[4]

Patients who are infected with a specific serotype of the dengue virus and have previously been exposed to a different serotype are at the highest risk of developing severe dengue.[5] Severe cases of dengue fever present with a combination of symptoms including plasma leakage, coagulopathy, and a platelet count below 100 109/L. Additionally, there is a significant increase in hematocrit levels followed by bleeding, which can lead to the development of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[2] Dengue Hemorrhagic Fever (DHF) is categorized into four grades based on its severity: Grade-I (characterized by fever and a positive tourniquet test), Grade-II (includes spontaneous bleeding in addition to Grade-I symptoms), Grade-III (indicated by a weak and rapid pulse), and Grade-IV (marked by profound shock with an undetectable pulse. The present clinical approach for treating symptomatic DF involves intravenous hydration therapy, careful monitoring of platelet count, and hematocrit levels in patients experiencing substantial vascular leakage.[6]

Thrombocytopenia, characterized by a decreased platelet count (<100 £ 109/L), is commonly observed in cases of Dengue Hemorrhagic Fever (DHF) and Dengue Fever (DF). This condition is regarded as an indicator of the severity of DF, as indicated by multiple studies.[7,8] While the exact correlation between bleeding in dengue fever and platelet count has not been fully determined, a study involving 225 dengue patients found that bleeding occurred more frequently in patients with platelet counts below 20 £ 109/L.[9] Despite an incomplete understanding of the precise mechanisms responsible for the development of thrombocytopenia and bleeding in cases of DF, various hypotheses have been proposed. One hypothesis suggests that DENV may directly or indirectly hinder the activity of bone marrow progenitor cells, leading to bone marrow suppression during the acute febrile phase of DF.[10] The precise mechanisms by which DENV causes bone marrow suppression during the acute phase are not yet fully understood. However, several factors have been suggested, including direct harm to progenitor cells, infection of stromal cells, and alterations in bone marrow regulation caused by DENV.[11]

In the late febrile or critical phase, platelet consumption occurs due to disseminated intravascular coagulation (DIC). This leads to platelet destruction through apoptotic mechanisms, destruction by the complement system, and/or anti-platelet antibodies.[11,12] A previous study, which included 372 patients with DF and a platelet count of 20 x 109/L, found that prophylactic platelet transfusion did not provide better results than supportive care in preventing bleeding. In fact, it may even be associated with negative effects.[13] Considering the idea that platelet transfusion may not provide any benefits to patients with dengue, multiple studies have put forth the argument that platelet transfusion should not be done as a standard practice in the treatment of dengue. In fact, the World Health Organization (WHO) does not recommend platelet transfusion for dengue patients.[14]

Thrombopoietin (TPO) is the primary natural controller of platelet production, which functions by binding to the TPO receptor (MPL). In order to address the issue of low platelet count, two different types of human thrombopoietin (TPO) were tested in clinical trials: a full-length glycosylated form of recombinant human TPO (rhTPO) and pegylated megakaryocyte growth and development factor (PEG-rHuMGDF).[15,16] These forms of TPO were investigated as potential therapeutic agents due to their ability to manipulate the physiological activity of human TPO. Nevertheless, a study conducted on healthy volunteers revealed the emergence of auto-antibodies in thirteen individuals after the administration of PEG-rHuMGDF. These auto-antibodies exhibited cross-reactivity with endogenous TPO, leading to the termination of all clinical studies involving rhTPO and PEG-rHuMDGF.[17] In order to address this initial obstacle, two commercially accessible thrombopoietin-receptor agonists, romiplostim and eltrombopag, were created. These agonists have proven to be advantageous in rectifying the deficiency of platelets.[18] Eltrombopag has been demonstrated to possess equivalent efficacy but a lower cost compared to romiplostim .[19]

Eltrombopag effectively corrects thrombocytopenia in patients with different pathological conditions, such as Immune thrombocytopenia (ITP),[20] chronic liver disease (CLD).[21] and severe aplastic anemia (SAA).[22] Eltrombopag interacts with the transmembrane domain of the thrombopoietin receptor, known as MPL. This interaction triggers the activation of two signaling pathways, namely JAK/STAT and MAPK pathways.[23] Eltrombopag binds to the transmembrane domain of MPL without competing with endogenous TPO, which binds to the extracellular domain. Therefore, it is expected that eltrombopag and TPO would have combined effects that enhance each other.

Given that the development of DF and DHF is linked to the occurrence of thrombocytopenia, we postulated that eltrombopag may have the potential to effectively address dengue-induced thrombocytopenia. In this study, we will investigate the impact of eltrombopag on patients diagnosed with dengue fever and a platelet count of 30 £ 109/L.

MATERIALS AND METHODS

The present study was a cross-sectional observational study which was conducted at private hospital in central India. The study was conducted in between July 2021- December 2023. The sample size for this study was 50.

Inclusion Criteria

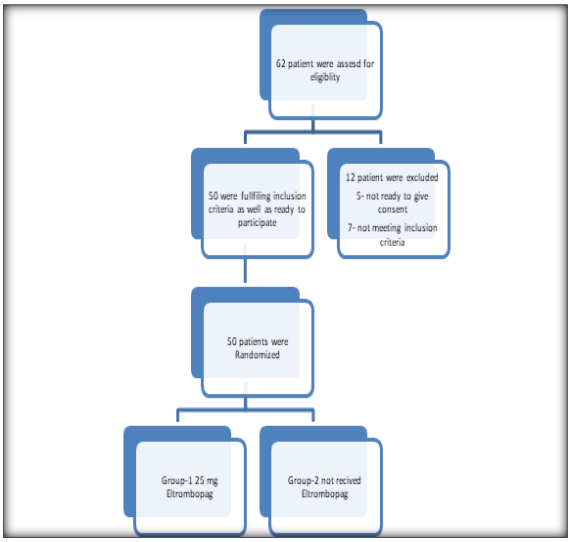
- Adult patients both male and female.
- Patients diagnosed with dengue virus infection were screened for eligibility to enter the trial.
- The patients who were willing to give their consent after knowing the study purpose were also included in this study.
- Diagnosed cases of DF by NS-1 antigen or ICT for Dengue (IgM/IgG) positive hospital admitted cases were included in this study.
- Eltrombopag started when platelets went to 30×10^9/L.

Exclusion Criteria

- Patients with pregnancy, receiving immunosuppressive therapy.
- Thrombocytopenia caused by other factors such as severe aplastic anemia (SAA), chronic liver disease (CLD) and Immune thrombocytopenia (ITP), aspartate amino transferase (AST)/ alanine amino transferase (ALT) levels higher than 5 times of upper normal limit were excluded.
- History of portal vein thrombosis and HBV/HCV infection were excluded.
- Patients with any severe comorbidity such as chronic kidney disease were excluded.

The suspected patients were undergone to dengue specific nonstructural antigen (NS1) and antibody (IgM/IgG) tests. Patients NS1 antigen showing positive results for NS1 or dengue specific IgM/IgG were considered as dengue positive patients. a total 50 patients were selected for the study and after randomization in Group-1 50 mg Eltrombopag tablets were directed orally daily for three consecutive days to the patients while control group i.e. Group -2 patient who are not received Eltrombopag. The days from onset of fever for each patient were recorded. The enrollment phase included the day of enrollment of the patients to the trial (Day-0) when their PLT count falls below 30×10^9/L.

Patients were monitored routinely. The course of their ailment during the trial period and any adverse effect was recorded. A wide range of tests including complete blood count (CBC) and immature platelet fraction (IPF) during the intervention (Day-0 to Day-2) and follow-up (Day-3 to Day-7) was recommended to all enrolled patients. Serum AST/ALT levels were measured on Day-0 and Day-7. In Day-4 and Day-7, patients underwent USG of the abdomen. Besides, the centralized laboratory testing system was introduced to reduce laboratory-specific variability in the measurements.



RESULTS

Table 1 displays the demographic characteristics of the participants. The age range of group 1 was 21-35 years, followed by group 2 with an age range of 22-35 years. The average age in group 1 was 25±7, in group 2 it was 29±8. The male population in group 1 accounted for 78.8% (20 individuals), while the female population accounted for 21.2% (5 individuals). In group 2, the male population accounted for 64.7% (16 individuals), and the female population accounted for 35.3% (9 individuals). [Table 1]

[Table 2] displays the fundamental attributes of the participants. The average baseline platelet count (PLT) in group 1 was 57±23 * 10^9 /L, in group 2 it was 51±28 * 10^9 /L. The mean baseline immature platelet fraction (IPF) percentage in these groups was 10.62±4.15, 11.92±4.41, respectively. The average baseline absolute immature platelet count (A-IPN) was 5.54±2.32, 5.9±3.48, in the respective groups. The mean baseline hematocrit (Hct) percentage was 39±3, 40±4, in the respective groups. The average systolic baseline blood pressure (BP) for group 1 was 103.55±5.04 mmHg, for group 2 was 105.38±18.34 mmHg. The average diastolic baseline BP was 72.83±6.56 mmHg, 72.84±12.93 mmHg, respectively. [Table 2]

The occurrence of bleeding manifestations was observed in 24.2% of cases in group 1, 14.7% in group 2. In group 1, the number of days from the onset of fever ranged from 2 to 7. In group 2, it ranged from 2 to 8. The average number of days from the onset of fever was 4.05±1.40, 4.18±1.45 respectively. [Table 3] displays the negative occurrences (AEs) experienced by the participants. Adverse events (AEs) were observed in 12.1% of cases in group 1, 5.9% in group 2, Diarrhoea was reported in 9.1% of cases in group 1, 5.9% in group 2. Vomiting was reported in 12.1% of cases in group 1, 8.8% in group 2. Lower extremity pain was observed in only 1 (3%) of the cases in group 1. Elevated levels of aspartate aminotransferase (AST)

were observed in 7 (27.3%), 10 (38.2%), patients, while increased levels of alanine aminotransferase (ALT) were found in 2 (9.1%), 6 (23.5%) patients. [Table 4] displays the odds ratio (OR) for the response to Eltrombopag. On day 1, the peripheral lymphocyte count (PLT<LNL) of group 1 was present in all 25 cases, indicating no recovery in group 1 on day 1. The odds ratio (OR) was 1, suggesting that there was no statistically significant recovery in patients on day 1 (P-value <0.05). [Table 3]

On the seventh day, the PLT<LNL (150*109 /L) was observed in only two instances, while PLT>LNL (150*109 /L) was detected.

There were 23 cases in which patients received eltrombopag. The recovery rate in these cases was 93.9%, and the odds ratio (OR) was 8.23. This indicates a statistically significant recovery, as the P-value was less than 0.05. On day 1, group 2 had a PLT<LNL (platelet count less than lower normal limit) in 24 cases, while PLT>LNL (platelet count greater than lower normal limit) was found in 1 cases. The recovery rate of group 2 on day 1 was 5.9, with an odds ratio of 4. However, there was not a statistically significant recovery observed (P-value <0.05). On the seventh day, the PLT<LNL (platelet count less than lower normal limit) was observed in only 2 cases, while PLT>LNL (platelet count greater than lower normal limit) was found in 23 cases. The recovery rate was 94.1% and the odds ratio (OR) was 8.79, indicating a statistically significant recovery (P-value < 0.05). [Table 4]

Table 1: Demographic Characteristics of the Respondents

Demographic Characteristics		**Group 1 (50 mg/D)**	**Group 2**
Age	**Range**	**21-35**	22-35
	(Mean± SD)	**25±7**	29±8
Gender	**Male**	**20(78.8%)**	16(64.7%)
	Female	5(21.2%)	9(35.3%)

Table 2: Baseline Characteristics of the Respondents

Baseline Characteristics		**Group 1 (50 mg/D), N=25**	**Group 2, N=25**
Baseline PLT * 10^9 /L	(Mean± SD)	57±23	51±28
Baseline IPF (%)	(Mean± SD)	10.62±4.15	11.92±4.41
Baseline A-IPN	(Mean± SD)	5.54±2.32	5.9±3.48
Baseline Hct (%)	(Mean± SD)	39±3	40±4
Mean of Baseline BP (mmHg)	Systolic	103.55± 5.04	105.38±18.34
	Diastolic	72.83±6.56	72.84±12.93
Bleeding Manifestations (%)		6(24.2%)	4(14.7%)
Days from onset of fever	Range	(2-7)	(2-8)
	(Mean± SD)	4.05±1.40)	4.18±1.45

Table 3: Adverse events (AEs) of the Respondents

Eltrombopag	**Group 1 (50 mg/D), N=25**	Group 2, N=25
Total patients showing AEs	**3(12.1%)**	1(5.9%)
Diarrhea	**2(9.1%)**	1(5.9%)
Vomiting	**3(12.1%)**	2(8.8%)
Pain in lower extremity	**1(3%)**	0
Aspartate amino transferase (AST) increased	**7(27.3%)**	10(38.2%)
Alanine amino transferase (ALT) increased	2(9.1%)	6(23.5%)

Table 4: Odds Ratio (OR) of Response to Eltrombopag

Odds Ratio (OR) of Response to Eltrombopag						
Groups	**Days**	**Number of patients PLT<LNL (150*109 /L)**	**Number of patients PLT>LNL (150*109 /L)**	**% of Recovery**	**OR Ratio**	**P-value (<0.05)**
Group 1 (25 mg/D), N=25	Day 1	25	0	0	1	1
	Day 7	5	23	93.9	8.23	0.0023
Group 2 , N=25	Day 1	24	1	5.9	4	0.3027
	Day 7	1	24	94.1	8.79	0.0015

DISCUSSION

The age range of group 1 was 21-35 years, followed by group 2 with an age range of 22-35 years. The average age in group 1 was 25±7, in group 2 it was 29±8.The proportion of males in group 1 was 78.8%, while the proportion of females was 21.2%. In group 2, the proportions were 64.7% for males and 35.3% for females. The following is Table 1: In a related study, it was found that the age range of group 1 was between 20 and 35 years, followed by group 2 which had an age range of 23 to 35 years. The average age in group 1 was 26±8, in group 2 it was 30±10.The male proportion in group 1 was 79%, while the female proportion was 21%. In

group 2, the proportions were 63% for males and 37% for females.[24]

A study comparing a treatment group and a control group found that the median age in the treatment group ranged from 33 (with a range of 15-65) to 36 (with a range of 16-78). In the treatment group, males accounted for 65% and females accounted for 35%, while in the control group, males accounted for 66% and females accounted for 34%.[19]

The average initial platelet count (PLT) for group 1 was 57±23 * 109 /L, for group 2 it was 51±28 * 109 /L,. The average initial immature platelet fraction (IPF) for these groups was 10.62±4.15%, 11.92±4.41%, respectively. The average initial absolute immature platelet number (A-IPN) was 5.54±2.32, 5.9±3.48. The average initial hematocrit (Hct) was 39±3%, 40±4%, for these groups. The average systolic baseline blood pressure (measured in mmHg) for group 1 was 103.55±5.04, for group 2 was 105.38±18.34. The average diastolic baseline blood pressure (measured in mmHg) was 72.83±6.56, 72.84±12.93 respectively. The incidence of bleeding manifestations was 24.2% in group 1, 14.7% in group 2. In group 1, the number of days from the onset of fever ranged from 2 to 7. In group 2, it ranged from 2 to 8. The average number of days from the onset of fever was 4.05±1.40, 4.18±1.45, respectively. The following is Table 2 The research conducted by S. Chakraborty et al discovered. The average baseline platelet count (PLT) in group 1 was 58±24 * 10^9 /L, in group 2 it was 52±29 * 10^9 /L. Additionally, the average baseline immature platelet fraction (IPF) percentage in these groups was 10.71±4.25, 12.82±5.31.

The average Baseline A-IPN values were 5.74±2.62, 6.10±3.68. The average Baseline Hct (%) values were 40±4, 41±5.The average systolic baseline blood pressure (measured in mmHg) for group 1 was 104.54±5.05, for group 2 was 106.28±19.14. The average diastolic baseline blood pressure was 73.63±6.76, 73.14±13.93 respectively. The occurrence of bleeding manifestations was observed in 27% of cases in group 1, 14% in group 2. The duration of fever ranged from 2 to 8 days in group 1, 2 to 9 days in group 2. The average duration of fever was 4.15±1.50 days in group 1, 4.28±1.50 days in group 2.[18]

Adverse events (AEs) were observed in 12.1% of cases in group 1, 5.9% in group 2. Diarrhoea was found in 9.1%, 5.9%, of the respective groups, while vomiting was reported in 12.1%, 8.8%. Lower limb pain was observed in only 3% of cases in group 1. The prevalence of increased Aspartate aminotransferase (AST) was 27.3%, 38.2%, while increased Alanine aminotransferase (ALT) was found in 9.1%, 23.5%, of patients. The text refers to Table 3. In their study, S. Chakraborty et al discovered adverse events (AEs) in 15% of cases in group 1, 9% in group 2. Additionally, they observed that diarrhoea occurred in 9% of cases in group 1, 6% in group 2. The prevalence of vomiting was 11%, 9%. Lower limb pain was present in only 3% of cases in group 1.AST levels were elevated in 30%, 40%, of patients, while ALT levels were elevated in 9%, 26%, of patients. In their study, Muhammad et al. discovered that 7% of the participants experienced adverse events (AEs), and among those, there were two fatalities.[25]

On the first day, the PLTLNL (150*109 /L) was detected in 23 instances, with a recovery rate of 93.9% and an OR ratio of 8.23. This indicates a statistically significant improvement in patients who received eltrombopag (P-value <0.05). On day 1, the PLTLNL count was 150*109 /L in group 2, with a recovery rate of 5.9 and an OR ratio of 4. However, the statistical analysis showed that the recovery was not significantly different from baseline (P-value <0.05). On the seventh day, a concentration of PLTLNL (150*109 /L) was detected in 24 cases. The recovery rate was 94.1%, and the OR ratio was 8.79, indicating a statistically significant recovery (P-value <0.05). The text refers to Table IV. In a comparable study, the response to eltrombopag was examined in patients over a period of 7 days. On day 1, the platelet count (PLT) of group 1 and the odds ratio (OR) were both 1, indicating that there was no statistically significant improvement in patients on day 1 (P-value <0.05). On the seventh day, the value of PLT<LNL (150*109 /L) occurred only in three instances where PLT>LNL (150*109

Eltrombopag in dose of 50 mg per day in two divided doses was given to randomly assigned 25 patients who had platelet count of 30 X 109 / L (irrespective of bleeding manifestations) .

Purpose of prescribing eltrombopag was to minimize transfusion of RDP or single donor platlets and platelets counts were monitored 12 hourly x 3 days after starting therapy and then daily x 2 days. Out of 25 patients who received Eltrombopag one patient showed no rise in platelet counts while remaining 24 showed failure to decline or rise in platelet count above basal level (30 x 10 raise to 9/L).In 6 / 12 patients platelet count stared rising within 12 hr of starting therapy. In 12 / 24 responders, platlet counts started rising only after 36 hour of starting therapy while in 6/ 24, it took 60 hours has for platelet to rise after starting therapy . It is important to mention that in none of these 24 responders platelet went down to less than 18 x 10 @ 9 ,and developed bleeding complications hence needed platelet transfusion. The odds ratio (OR) was calculated to be 8.33, indicating a statistically significant recovery in patients who received Eltrombopag (P-value <0.05). In day 1, group 2 had a PLT<LNL (150*109 /L) in 25 cases, while PLT>LNL (150*109 /L) was found in 5 cases. The recovery rate of group 2 on day 1 was 5.7, with an OR ratio of 5. However, the statistical significance of the recovery was not substantial (P-value <0.05). On the seventh day, the PLT<LNL (150*109 /L) was observed in only 1 cases, while PLT>LNL (150*109 /L) was found in 24 cases. The recovery rate was 91.42%, which was lower than the recovery rate observed in the current study. The OR ratio was

8.89, indicating a statistically significant recovery (P-value <0.05).[24]

CONCLUSION

Dengue is a vector - borne viral illness that has the potential to cause life - threatening complications. Dengue fever has got extensive distribution in the Asia - Pacific region, and the situation is detoriating as in recent years, the incidence of dengue is increasing exponentially. Major cause of fatality in dengue fever is hemorrhagic complications and multiorgan failure. Transfusion of platelets in needy cases is the cornerstone of therapy in dengue hemorrhagic fever. Thrombocytopenia correction using tpo receptor agonists, Eltrombopag, can also be a viable treatment choice for elevating platelet levels in patients with Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) as part of thrombocytopenia management but there is paucity of literature using Eltrombopag or other tpo receptor agonists. Eltrombopag has the potential to be advantageous in the treatment of severe dengue patients who have thrombocytopenia. Therefore, there should be an increase in the frequency and accessibility of Eltrombopag for the treatment of dengue patients. Additional research, larger RCT's and multicentric studies are required to address the existing knowledge gap in this area and appropriate guidelines must be drafted to address this challenging issue.

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