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Efficacy and Safety of Low Dose, Short Course Eltrombopag in Management of DF and DHF

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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:** This study was a cross-sectional observational study which was conducted at Tairunnesa Memorial Medical College and Hospital (TMMCH), Gazipur and Shin Shin Japan Hospital, Uttara, Dhaka. The study was conducted in between July 2021- December 2021. The sample size for this study was 100. **Results:** The mean age in group 1 was 25±7, in group 2 29±8 and in control group 29±7. The mean Baseline PLT * 109 /L for group 1 was 57±23, for group 2, 51±28 and for control group 54±29. Mean of systolic baseline BP (mmHg) for group 1 was 103.55± 5.04 for group 2 was 105.38±18.34 and for control group was 101.97±8.28 and followed by the mean of diastolic baseline BP (mmHg) was 72.83±6.56, 72.84±12.93 and 71.97±4.75. AEs was found in 4(12.1%) cases of group 1 where in group 2 it was 2(5.9%) and in control group was 3(9.1%). In day 7, the recovery rate of group 1 was 93.9% and in group 2 the recovery rate was 94.1%. **Conclusions:** 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:- Dengue fever, Dengue Haemorrhagic Fever, Eltrombopag.

INTRODUCTION

Dengue is the most widespread mosquito caused viral disease which infects more than 50 million people every year.[1] The clinical symptoms of dengue may vary from mild fever to life-threatening incidents.[2] The World Health Organization (WHO) reported around 23 million dengue cases and 82,000 deaths due to dengue from 1955 to 2012.[3] It is predicted that the incidence of dengue was increased up

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to 40% in 2019 compared to the incidence in 2018.[4] Another report found above 2.5 billion people were in high-risk dengue-transmission areas where 400 million infections occurs every year with a 5%-20% mortality rate.[5] Also, more than 125 countries, together with Europe and the United States (US), were found to be dengue-endemic with approximately 75% of the dengue-infected population living in the Asia-Pacific region.[5,6,7] Dengue fever or DF is a non-definite febrile state, which is caused by the transmission of the virus through mosquito bite from an infected person to another person and can cause a mild to severe fever, general body pain, weakness, arthralgia, myalgia and rashes on the skin.[8,9,10] On the contrary, DHF or Dengue Haemorrhagic Fever is such a condition which is found among 1% - 5% of cases where some critically serious issues such as plasma leakage, haemorrhage, ascites and reduction in leukocytes and platelets can be seen.[8,] However, 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.[11] Eltrombopag had been proved as equally effective but less costly than romiplostim.[12] Multiple clinical studies were conducted to identify the safety and efficacy of the drug where mostly perceived mild to moderate side effects of eltrombopag, including headache, dizziness, muscle ache, nausea in most patients, and, very rarely, serious effects, such as vascular occlusions, myocardial infarction, stroke, cataract, and rebound thrombocytopenia (upon eltrombopag withdrawal).[13,14,15,16,17] But literature directly related to the objective of this study was not sufficient. Hence, the aim of this study was to investigate the efficacy and safety of low dose, short course eltrombopag in the management of DF and DHF to fulfil the study gap in this field.

Objective of the Study

The objective of this study was to investigate the efficacy and safety of low dose, short course Eltrombopag in the management of DF and DHF.

MATERIALS AND METHODS

This study was a cross-sectional observational study which was conducted at Tairunnesa Memorial Medical College and Hospital (TMMCH), Gazipur and Shin Shin Japan Hospital, Uttara, Dhaka. The study was conducted in between July 2021- December 2021. The sample size for this study was 100.

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.

Exclusion criteria:

Patients with pregnancy, receiving immunosuppressive therapy.

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Thrombocytopenia caused by other factors such as severe aplastic anemia (SAA), chronic liver disease (CLD) and Immune thrombocytopenia (ITP), aspartate aminotransferase (AST)/alanine aminotransferase (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. 25 mg and 50 mg Eltrombopag tablets were directed orally daily for three consecutive days to the patients of Group-1 and 2. 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 100×109/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. For statistical analysis, the SPSS version 21 was used as a statistical tool.

RESULTS

The [Table 1] shows the demographic characteristics of the respondents. The age range of group 1 was in between 21-35 years and followed by group 2 was 22-35 and control group was 23-33. The mean age in group 1 was 25±7, in group 2 29±8 and in control group 29±7. In group 1 male was 26(78.8%) and female was 7(21.2%) and followed by in group 2, 22(64.7%) and 12(35.3%) and control group 26(78.8%) and 7(21.2%).

[Table 2] shows the baseline characteristics of the respondents. The mean Baseline PLT * 109 /L for group 1 was 57±23, for group 2, 51±28 and for control group 54±29 and followed by the mean Baseline IPF (%) in those group was 10.62±4.15, 11.92±4.41 and 12.9±4.38, mean Baseline A-IPN was 5.54±2.32, 5.9±3.48 and 6.54±3.55, mean Baseline Hct (%) was 39±3, 40±4 and 41±5. Mean of systolic baseline BP (mmHg) for group 1 was 103.55± 5.04 for group 2 was 105.38±18.34 and for control group was 101.97±8.28 and followed by the mean of diastolic baseline BP (mmHg) was 72.83±6.56, 72.84±12.93 and 71.97±4.75. Bleeding Manifestations (%) was found in 8(24.2%) cases of group 1, 5(14.7%) for group 2 and 6(18.2%) for control group. Days from onset of fever was ranged from (2-7) in group 1, (2-8) in group 2 and (2-7) in control group and the mean days from onset of fever was 4.05±1.40, 4.18±1.45 and 4.2±1.21 respectively.

[Table 3] shows the adverse events (AEs) of the respondents. AEs was found in 4(12.1%) cases of group 1 where in group 2 it was 2(5.9%) and in control group was 3(9.1%) and followed by diarrhea was found in 3(9.1%), 2(5.9%) and

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3(9.1%), vomiting was in 4(12.1%), 3(8.8%) and 3(9.1%), Pain in lower extremity was found only in 1(3%) cases of group 1, Aspartate aminotransferase (AST) increased was in 9(27.3%), 13(38.2%) and 8(24.2%) and Alanine aminotransferase (ALT) increased was found in 3(9.1%), 8(23.5%) and 6(18.2%) patients.

[Table 4] represents the odds ratio (OR) of the response to Eltrombopag. In day 1, the PLT<LNL (150*109 /L) of group 1 was in all 33 cases hence there were no recovery of group 1 in day 1 and the OR ratio was 1 which implies that, in day 1 there was no statistically significant recovery in patients (P-value <0.05). In day 7, PLT<LNL (150*109 /L) was only in 2 cases where PLT>LNL (150*109 /L) was found in 31 cases and the recovery rate was 93.9% and the OR ratio was 8.23 which denotes a statistically significant recovery in patients receiving eltrombopag (P-value <0.05). Similarly, in day 1, the PLT<LNL (150*109 /L) of group 2 was found in 32 cases where PLT>LNL (150*109 /L) was found in 2 and the recovery of group 2 in day 1 was 5.9 and the OR ratio was 4 and also not much statistically significant recovery was found (P-value <0.05). In day 7, PLT<LNL (150*109 /L) was only in 2 cases where PLT>LNL (150*109 /L) was found in 32 cases and the recovery rate was 94.1% and the OR ratio was 8.79 which denotes a statistically significant recovery (P-value <0.05).

Table 1: Demographic Characteristics of the Respondents.

Demographic Characteristics		**Group 1 (25 mg/D)**	**Group 2 (5 0mg/D)**	**Control Group (Nill)**
Age	Range	21-35	22-35	23-33
	(Mean± SD)	25±7	29±8	29±7
Gender	Male	26(78.8%)	22(64.7%)	26(78.8%)
	Female	7(21.2%)	12(35.3%)	7(21.2%)

Table 2: Baseline Characteristics of the Respondents.

Baseline Characteristics		**Group 1 (25 mg/D), N=33**	**Group 2 (5 0mg/D), N=34**	**Control Group (Nill), N=33**
Baseline PLT * 10^9 /L	(Mean± SD)	57±23	51±28	54±29
Baseline IPF (%)	(Mean± SD)	10.62±4.15	11.92±4.41	12.9±4.38
Baseline A-IPN	(Mean± SD)	5.54±2.32	5.9±3.48	6.54±3.55
Baseline Hct (%)	(Mean± SD)	39±3	40±4	41±5
Mean of Baseline BP (mmHg)	Systolic	103.55± 5.04	105.38±18.34	101.97±8.28
	Diastolic	72.83±6.56	72.84±12.93	71.97±4.75
Bleeding Manifestations (%)		8(24.2%)	5(14.7%)	6(18.2%)
Days from onset of fever	Range	(2-7)	(2-8)	(2-7)
	(Mean± SD)	4.05±1.40)	4.18±1.45	4.2±1.21

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Table 3: Adverse events (AEs) of the Respondents.

Eltrombopag	**Group 1 (25 mg/D), N=33**	**Group 2 (5 0mg/D), N=34**	**Control Group (Nill), N=33**
Total patients showing AEs	4(12.1%)	2(5.9%)	3(9.1%)
Diarrhea	3(9.1%)	2(5.9%)	3(9.1%)
Vomiting	4(12.1%)	3(8.8%)	3(9.1%)
Pain in lower extremity	1(3%)	0	0
Aspartate aminotransferase (AST) increased	9(27.3%)	13(38.2%)	8(24.2%)
Alanine aminotransferase (ALT) increased	3(9.1%)	8(23.5%)	6(18.2%)

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=33	Day 1	33	0	0	1	1
	Day 7	2	31	93.9	8.23	0.0023
Group 2 (50 mg/D), N=34	Day 1	32	2	5.9	4	0.3027
	Day 7	2	32	94.1	8.79	0.0015

DISCUSSION

The age range of group 1 was in between 21-35 years and followed by group 2 was 22-35 and control group was 23-33. The mean age in group 1 was 25±7, in group 2 29±8 and in control group 29±7. In group 1 male was 78.8% and female was 21.2% and followed by in group 2, 64.7% and 35.3% and control group 78.8% and 21.2%. [Table 1] A similar study in this field showed the age range of group 1 was in between 20-35 years and followed by group 2 was 23-35 and control group was 23-33. The mean age in group 1 was 26±8, in group 2 30±10 and in control group 30±9. In group 1 male was 79% and female was 21% and followed by in group 2, 63% and 37% and control group 79% and 21%.[18] Another related study conducted in between the treatment group and control group showed the median age ranged between 33(15-65) and 36(16-78) where in treatment group the male was 65% and female was 35% and in control group was 66% and 34%.[19]

The mean Baseline PLT * 10^9 /L for group 1 was 57±23, for group 2, 51±28 and for control group 54±29 and followed by the mean Baseline IPF (%) in those group was 10.62±4.15, 11.92±4.41 and 12.9±4.38, mean Baseline A-IPN was 5.54±2.32, 5.9±3.48 and 6.54±3.55, mean Baseline Hct (%) was 39±3, 40±4 and 41±5. Mean of systolic baseline BP (mmHg) for group 1 was 103.55± 5.04 for group 2 was 105.38±18.34 and for control group was 101.97±8.28 and followed by the mean of

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diastolic baseline BP (mmHg) was 72.83±6.56, 72.84±12.93 and 71.97±4.75. Bleeding Manifestations (%) was found in 24.2% cases of group 1, 14.7% for group 2 and 18.2% for control group. Days from onset of fever was ranged from (2-7) in group 1, (2-8) in group 2 and (2-7) in control group and the mean days from onset of fever was 4.05±1.40, 4.18±1.45 and 4.2±1.21 respectively. [Table 2] The study of S. Chakraborty et al found The mean Baseline PLT * 10^9 /L for group 1 was 58±24, for group 2, 52±29 and for control group 55±30 and followed by the mean Baseline IPF (%) in those group was 10.71±4.25, 12.82±5.31 and 13.8±4.58, mean Baseline A-IPN was 5.74±2.62, 6.10±3.68 and 6.64±3.65, mean Baseline Hct (%) was 40±4, 41±5 and 42±6. Mean of systolic baseline BP (mmHg) for group 1 was 104.54±5.05 for group 2 was 106.28±19.14 and for control group was 102.87±8.38 and followed by the mean of diastolic baseline BP (mmHg) was 73.63±6.76, 73.14±13.93 and 72.27±4.85. Bleeding Manifestations (%) was found in 27% cases of group 1, 14% for group 2 and 30% for control group. Days from onset of fever was ranged from (2-8) in group 1, (2-9) in group 2 and (2-8) in control group and the mean days from onset of fever was 4.15±1.50, 4.28±1.50 and 4.303±1.23 respectively.[18]

AEs was found in 12.1% cases of group 1 where in group 2 it was 5.9% and in control group was 9.1% and followed by diarrhea was found in 9.1%, 5.9% and 9.1%, vomiting was in 12.1%, 8.8% and 9.1%, Pain in lower extremity was found only in 3% cases of group 1, Aspartate aminotransferase (AST) increased was in 27.3%, 38.2% and 24.2% and Alanine aminotransferase (ALT) increased was found in 9.1%, 23.5% and 18.2% patients. [Table 3] S. Chakraborty et al in their study found AEs in 15% cases of group 1 where in group 2 it was 9% and in control group was 12% and followed by diarrhea was found in 9%, 6% and 9%, vomiting was in 11%, 9% and 9%, Pain in lower extremity was found only in 3% cases of group 1, Aspartate aminotransferase (AST) increased was in 30%, 40% and 27% and Alanine aminotransferase (ALT) increased was found in 9%, 26% and 21% patients.[18] Muhammad et al., found 7% AEs where there were 2 deaths.[19]

In day 1, the PLT<LNL (150*10^9 /L) of group 1 was in all 33 cases hence there were no recovery of group 1 in day 1 and the OR ratio was 1 which implies that, in day 1 there was no statistically significant recovery in patients (P-value <0.05). In day 7, PLT<LNL (150*10^9 /L) was only in 2 cases where PLT>LNL (150*10^9 /L) was found in 31 cases and the recovery rate was 93.9% and the OR ratio was 8.23 which denotes a statistically significant recovery in patients receiving eltrombopag (P-value <0.05). Similarly, in day 1, the PLT<LNL (150*10^9 /L) of group 2 was found in 32 cases where PLT>LNL (150*10^9 /L) was found in 2 and the recovery of group 2 in day 1 was 5.9 and the OR ratio was 4 and also not much statistically significant recovery was found (P-value <0.05). In day 7, PLT<LNL (150*10^9 /L) was only in 2 cases where PLT>LNL (150*10^9 /L) was found in 32 cases and the recovery rate was 94.1% and the OR ratio was 8.79 which denotes a statistically significant recovery (P-value <0.05). [Table IV] A similar study also observed the eltrombopag response in patients in duration of 7 days where in day 1, the PLT<LNL (150*10^9 /L) of group 1 was also in 33 cases hence there were no recovery

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of group 1 in day 1 and the OR ratio was 1 which implies that, in day 1 there was no statistically significant recovery in patients (P-value <0.05). In day 7, PLT<LNL (150*10^9 /L) was only in 3 cases where PLT>LNL (150*10^9 /L) was found in 33 cases and the recovery rate was 90.90% which was less than the recovery rate of this present study and the OR ratio was 8.33 which denotes a statistically significant recovery in patients receiving eltrombopag (P-value <0.05). Similarly, in day 1, the PLT<LNL (150*10^9 /L) of group 2 was found in 33 cases where PLT>LNL (150*10^9 /L) was found in 2 and the recovery of group 2 in day 1 was 5.7 and the OR ratio was 5 and also not much statistically significant recovery was found (P-value <0.05). In day 7, PLT<LNL (150*10^9 /L) was only in 3 cases where PLT>LNL (150*10^9 /L) was found in 32 cases and the recovery rate was 91.42% which also showed less recovery than the present study and the OR ratio was 8.89 which denotes a statistically significant recovery (P-value <0.05).[18]

CONCLUSIONS

Dengue is an insect-borne viral disease which needs careful medical attention because it may lead to life-threatening conditions. In Asia pacific region dengue fever has become a wide spread distribution. The scenario has become worse day by day. In 2019, the incidence of dengue had increased almost doubled considering the incidence in 2018. However, the Eltrombopag can be considered as a therapeutic option to increase the PLT counts in DF and DHF patients in the management of thrombocytopenia. Eltrombopag may potentially be beneficial in treating severe dengue patients with persisting thrombocytopenia. Hence, the use of Eltrombopag in treating dengue patients should be more frequent and accessible. Proper medical assistance is also needed in this regard. Futher studies are also needed to fulfil the literature gap in this field.

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