

# Efficacy of Eltrombopag in Dengue with Severe Thrombocytopenia

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## Abstract

**Background:** Dengue fever is a serious health risk, particularly in developed nations where it frequently results in undifferentiated febrile illnesses like expanded dengue syndrome, dengue shock syndrome, and dengue hemorrhagic fever, which can be fatal and are frequently associated with thrombocytopenia (TCP).

**Methods:** This open-label, randomized, controlled phase-II trial included 100 patients with dengue fever (DF) and with a platelet (PLT) count of less than  $100 \times 10^9/L$  and no comorbidities, pregnancy, or liver abnormalities. This study was carried out in the Department of Medicine, Sir Salimullah Medical College Mitford Hospital, Bangladesh, between 1 July 2022 and 1 January 2023. Two groups, one for the case group (Eltrombopag, 50 patients) and the other for the control group (Non-Eltrombopag, 50 patients), were randomly allocated to the patients. For three days, in addition to their regular treatment, the patients in the case group received 25 mg/day of eltrombopag while the control group received standard dengue treatment without eltrombopag.

**Results:** To assess the effectiveness, the percentage of patients receiving eltrombopag whose platelet count was higher than the lower normal limit ( $150 \times 10^9/L$ ) was compared to the control group.

**Conclusion:** The experiment found that giving eltrombopag to individuals with DF and DHF in a brief regimen for three days was effective in restoring their PLT count. The trial suggests that eltrombopag has a beneficial effect in stopping bleeding manifestations.

**Keywords:** Thrombocytopenia, Dengue fever, Eltrombopag, Dengue haemorrhagic fever

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## I. Introduction

The most common virus that infects humans through mosquitoes is called dengue virus (DV), and it is caused by a single-stranded ribonucleic virus that is a member of the Flaviviridae family<sup>1</sup>. Dengue fever (DF), one of the most widespread viral diseases spread by mosquitoes, has become more prevalent and has climbed 400% in just the previous thirteen years<sup>2</sup>. Climate change and increasing urbanization have been primarily blamed for the rise of DF as one of the infectious illnesses with the highest morbidity and fatality rates in the world<sup>3</sup>.

Thrombocytopenia (TCP) is a medical disorder characterized by a blood cell count of less than  $150 \times 10^9/\mu l$ , or fewer platelets or thrombocytes than usual. Adult platelet counts in microliters of blood typically range from 150,000 to 450,000 platelets/ $\mu l$ . TCP clearly increases for various causes. These include various cancer types, dangerous substances, and treatment regimen combinations such as chemotherapy, non-steroidal anti-inflammatory medications, genetic inheritance, and viral infections<sup>4,5</sup>. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can develop in severe cases of the disease due to coupled signs of plasma leakage, coagulopathy, and platelet (PLT) count  $<100 \times 10^9/L$ , as well as a notable rise in hematocrit followed by bleeding<sup>3</sup>.

Numerous studies have found that thrombocytopenia, or a low platelet count ( $<100 \times 10^9/L$ ), is often related with DHF and DF and is thought to be an indicator of the severity of the condition<sup>6,7</sup>. While the exact relationship between the bleeding manifestation of dengue fever (DF) and platelet count remains unclear, a

study including 225 dengue patients revealed that patients with platelet counts  $< 20 \times 10^9/L$  experienced bleeding more frequently<sup>8</sup>.

Patients with immune thrombocytopenia (ITP)<sup>9</sup>, chronic liver disease (CLD)<sup>10</sup>, and severe aplastic anemia (SAA)<sup>11</sup> can effectively treat their thrombocytopenia with eltrombopag. Eltrombopag interacts to the transmembrane region of the MPL thrombopoietin receptor, activating the JAK/STAT and MAPK signaling pathways, two downstream signaling pathways<sup>12</sup>. It does not compete with endogenous TCP, which binds to the extracellular domain of MPL, because it binds to the transmembrane domain of MPL. Eltrombopag and TCP should therefore, in theory, provide mutually additive effects<sup>13</sup>.

Our goal in this study was to determine the effectiveness of eltrombopag in dengue-mediated thrombocytopenia, as the pathogenesis of DF and DHF is linked to the appearance of thrombocytopenia.

## II. Methods and Materials

100 patients from Department of Medicine, Sir Salimullah Medical College Mitford Hospital from 1 July 2022 to 1 January 2023 who had contracted dengue were included. Two groups, one for the case group (Eltrombopag, 50) and the other for the control group (Non-Eltrombopag, 50) were randomly allocated to the patients. For three days, in addition to their regular treatment, the patients in the case group received 25 mg/day of eltrombopag while the control group received eltrombopag placebo.

Patients having a clinical manifestation of severe dengue virus infection (Platelet  $<20K$ ) and an age range above 18 were the inclusion criteria. One of the following symptoms, including severe bleeding, shock or respiratory distress, or organ failure (e.g., high liver enzyme levels, altered consciousness, or heart failure), was indicative of severe dengue, including the DHF patients<sup>14</sup>. Individuals who tested positive for dengue-specific IgM/IgG or NS1 were deemed to be dengue-positive patients.

Patients with thrombocytopenia due to other causes, such as severe aplastic anemia (SAA), chronic liver disease (CLD), and immune thrombocytopenia (ITP), as well as those with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels greater than five times the upper normal limit, a history of portal vein thrombosis, and HBV/HCV infection were not allowed to participate in the study, even though they were among the eligible candidates. Furthermore, any serious co-morbidity, including chronic kidney illness, was not allowed for patients.

The International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki were complied with by the trial protocols, which were approved by the institutional ethical committee. Consent was given in writing by each patient in compliance with local regulations.

## III. Results

Between (1<sup>st</sup> July 2022 – 1<sup>st</sup> January 2023), 100 dengue-patients were assessed for eligibility from Department of Medicine, Sir Salimullah Medical College Mitford Hospital recruited for our study. The patients were randomly assigned to two groups including, case group who were administrated Eltrombopag (n=50) and control group who did not receive Eltrombopag (n=50).

Features	Case group (Eltrombopag 25 mg/D)	Control group (Eltrombopag placebo)
Participants count (n)	50	50
Age (mean±SD)	27	29
Sex (%)	Female = 25, male = 75	Female= 30, male=70
Platelet count $\times 10^9/L$ (mean±SD)	11.11	13.82
BP (mmHg) (mean±SD)	Systolic =100, Diastolic=70	Systolic= 105, Diastolic= 75
Bleeding Manifestations (%)	26%	31%
Days from onset of fever (mean)	4	4

**Table 1: Baseline characteristics of dengue patients (n=50)**

The Day-wise proportion of the platelet (PLT)-recovered patients (with PLT count above than lower normal limit) in case group was shown in the following table and it also expressed the recovery success rate. All together these analyses highlight that the goal of eltrombopag treatment is to augment the platelet recovery in patients with moderate to severe thrombocytopenia rather than preventing thrombocytopenia in dengue-patients in the critical phase.

Group	Days	No of patients PLT<LNL	No of patients PLT>LNL	Total no of patients	% of recovery
Case group: 25mg/day	01	20	30	50	60
	02	14	36	50	72
	03	6	44	50	88

Control group: Placebo	01	25	25	50	50
	02	20	30	50	60
	03	12	38	50	76

**Table 2: observation of patients’ response to eltrombopag**

On Day 3, every single grade-II DHF patient in the case group (N = 15) had a PLT count of more than  $150 \times 10^9 /L$  (LNL) (Table 3). Remarkably, the patient's bleeding symptoms persisted during the study period (Day 0 to Day 3). On Day 3, none of the six grade-II DHF patients in the control group had PLT counts greater than LNL. Throughout the trial period, four patients with the lowest PLT counts exhibited intermittent bleeding tendencies, while the remaining patients in the control group did not exhibit any bleeding beyond Day 4.

Groups	Gender	Age	Bleeding site at day 0	PLT $\times 10^9/L$ Day 0	PLT $\times 10^9/L$ Day 3	Bleeding site at day 4	D-3 PLT Recovery <sup>□□</sup>
Case group: 25 mg/Day	M	40	Skin	33	180	No bleeding	Yes
	F	36	Conjunctiva	69	340	No bleeding	Yes
	M	34	Gum	91	345	No bleeding	Yes
	F	20	Rectal	43	328	No bleeding	Yes
	F	29	Rectal	63	327	No bleeding	Yes
	F	25	Nose	88	370	No bleeding	Yes
	M	19	Gum	97	245	No bleeding	Yes
	F	26	Rectal	48	375	No bleeding	Yes
	M	22	Malena	45	235	Skin	No
	M	45	Skin	20	388	No bleeding	Yes
	M	41	Vaginal	28	372	No bleeding	Yes
	F	21	Gum	42	363	No bleeding	Yes
	F	31	Rectal	99	235	No bleeding	Yes
	M	33	Skin	41	271	No bleeding	Yes
	Control-group: No eltrombopag	M	50	Rectal	18	140	No bleeding
M		43	Rectal	30	165	No bleeding	Yes
F		32	Vaginal	92	120	Vaginal	No
M		39	Nose	74	98	Nose	No
M		23	Nasal	12	180	No bleeding	Yes
F		36	Rectal	25	125	No bleeding	Yes
M		33	Gum	20	410	No bleeding	Yes
M		27	Nose	63	175	No bleeding	Yes
M		24	Skin	77	65	Skin	No
F		25	Nose	98	60	Nose	No

**Table 3: Platelet count and treatment outcome of grade II dengue hemorrhagic patients**

□□ PLT-recover: Platelet count higher than lower normal limit ( $150 \times 10^9/L$ )

The rest of the patients of both case and control groups were not marked as grade II DHF as they were considered DF patients and did not illustrate any DHF symptoms.

Eltrombopag	Case group	Control-group	p-value
	25 mg/D	Nil	
Total patients showing AEs	5 (15%)	4 (12%)	Ns
individual events			
diarrhea	3 (9%)	3 (9%)	Ns
Vomiting	4 (11%)	3 (9%)	Ns
Pain in lower extremity	1 (3%)	0	N/A
Aspartate aminotransferase (AST) increased	10 (30%)	9 (27%)	Ns
Alanine aminotransferase (ALT) increased	3 (9%)	7 (21%)	Ns

**Table 4: Demonstration of Adverse events outcomes**

NS = Not statistically significant ( $p\text{-value} > 0.05$ )

N/A = Not applicable

AEs = Adverse effect

In addition to experiencing diarrhea and vomiting, a patient on 25 mg/d eltrombopag reported lower extremity pain. The only two adverse effects noted for the patients in both the treatment and the control groups were vomiting and diarrhea. It is possible that eltrombopag is not the cause of these adverse events (AEs)

because the percentage of patients who had them did not differ noticeably between the treated and untreated groups. During the trial, there had been no fatalities. Thirty patients (30%) in Group 1 had elevated AST. Table 4 shows that nine patients (27%) in the control group had elevated AST values. Three (9%) and seven (21%) of the patients in the case and control groups had elevated ALT levels, respectively. These findings implied that eltrombopag might not have played a role in aberrant hepatic function since the percentage of patients in the three groups with elevated AST/ALT values was comparable. Following the delivery of eltrombopag, a study of the ultrasonogram on Day 4 revealed no indications of abdominal thrombosis.

#### **IV. Discussion**

One of the main clinical signs of dengue fever (DF), severe thrombocytopenia, may be used to gauge the severity of the illness and indicate a higher risk of developing DHF<sup>15</sup>. One of the biggest obstacles in the clinical management of dengue is still treating patients with low PLT levels because PLT transfusion is not regarded as a standard strategy to raise PLT numbers.

(Table 1) presents the baseline characteristics of the study participants, consisting of 100 dengue patients who were divided into a case group receiving Eltrombopag at a daily dosage of 25 mg and a control group receiving an Eltrombopag placebo. The case group comprised 50 individuals with an average age of 27 years, of which 25% were female and 75% were male. In contrast, the control group, with an average age of 29 years, had 30% female participants and 70% male participants. Analysis of platelet counts revealed a mean value of  $11.11 \times 10^9/L$  in the case group, while the control group exhibited a slightly higher mean of  $13.82 \times 10^9/L$ . Blood pressure measurements indicated a mean systolic pressure of 100 mmHg and diastolic pressure of 70 mmHg in the case group, compared to 105 mmHg and 75 mmHg, respectively, in the control group. Notably, bleeding manifestations were observed in 26% of the case group and 31% of the control group. Both groups had a comparable mean duration of 4 days from the onset of fever. These baseline characteristics provide a comprehensive overview of the demographic and clinical profiles of the study population, serving as a crucial reference for the subsequent evaluation of the impact of Eltrombopag on dengue patients.

(Table 2) presents the observations of patients' response to eltrombopag, categorized into different groups based on their platelet (PLT) levels in comparison to the lower normal limit (LNL). The study comprises three groups:  $PLT < LNL$ ,  $PLT > LNL$ , and a total number of patients. The case group, receiving a daily dose of 25mg of eltrombopag, is assessed over a span of three days. On the first day, 20 patients in the  $PLT < LNL$  group received treatment, with 30 patients falling into the  $PLT > LNL$  category and a total of 50 patients considered in the study. The subsequent days, denoted as Day 2 and Day 3, exhibit variations in the number of patients across the groups, with corresponding percentages of recovery. For instance, on Day 2, 14 patients from the  $PLT < LNL$  group and 36 from the  $PLT > LNL$  group were treated, resulting in a total of 50 patients with a recovery rate of 72%. Day 3 shows further changes, with 6 patients in the  $PLT < LNL$  group and 44 in the  $PLT > LNL$  group, contributing to the total of 50 patients and an impressive recovery rate of 88%. The table provides a comprehensive overview of eltrombopag's impact on patients' platelet levels over the course of the observation period.

Table 3 presents a detailed overview of platelet counts and treatment outcomes for individuals diagnosed with grade II dengue hemorrhagic fever, categorized into two groups: the Case group receiving a daily dosage of 25 mg of eltrombopag and the Control group without eltrombopag treatment. The Case group consists of diverse gender and age distribution, with patients experiencing bleeding at various sites on day 0, along with corresponding platelet counts. Notably, by day 3, all individuals in the Case group show a successful platelet recovery, indicated by platelet counts surpassing the lower normal limit ( $150 \times 10^9/L$ ), and no further bleeding incidents. In contrast, the Control group, not receiving eltrombopag, displays a mixed outcome with some patients achieving platelet recovery by day 3 and no bleeding, while others still exhibit low platelet counts and sustained bleeding at different sites. This table underscores the potential efficacy of eltrombopag in facilitating platelet recovery and mitigating bleeding events in grade II dengue hemorrhagic patients, as compared to the untreated control group.

Table 4 provides a comprehensive overview of adverse events associated with Eltrombopag, comparing a case group receiving a daily dose of 25 mg with a control group that received no treatment. The total number of patients experiencing AEs in each group is presented, with 15% of the case group and 12% of the control group exhibiting AEs, indicating a slight numerical difference that did not reach statistical significance. The table further breaks down individual events, revealing comparable occurrence rates of diarrhea (9% in both groups) and vomiting (11% in the case group, 9% in the control group), with no significant differences noted. Notably, pain in the lower extremity was observed in 3% of the case group, while the control group reported none (N/A). Additionally, hepatic enzyme abnormalities were monitored, showing 30% of patients in the case group experiencing increased aspartate aminotransferase (AST) levels compared to 27% in the control group, a non-significant difference. The case group displayed lower occurrences of increased alanine

aminotransferase (ALT) levels (9%) compared to the control group (21%), although the disparity did not reach statistical significance.

## V. Conclusion

Considering all of the data, our study showed that eltrombopag can be a viable treatment choice for boosting platelet counts in patients suffering from dengue fever and dengue hemorrhagic fever throughout the recuperation stage. It was noticeably safe and showed promise in the treatment of severe dengue patients with enduring thrombocytopenia.

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