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Fresh frozen plasma in dengue patients with altered coagulation parameters: A randomized trial

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ABSTRACT

Objective: To evaluate the effects of fresh frozen plasma transfusion in dengue patients.

Methods: In this randomised, double blind, parallel, controlled trial, we included 200 patients with activated partial thromboplastin time (APTT) ≥40 seconds and platelet count ≤50×10^9/L, randomly assigning them to experimental (10-15 mL/kg fresh frozen plasma transfusion) or control (standard management) groups. The principal aim was to assess the alteration in APTT at 24 hours among such patients. Between-group comparisons were restricted to the initial 24 hours post-intervention. Owing to ethical concerns regarding bleeding necessitating rescue therapy, the control group was removed, and subsequent follow-up (48 hours and 7 days post-transfusion) continued only for the experimental group.

Results: Baseline characteristics in both groups were comparable. Mean age was (34.1±8.1) years and (36.1±7.8) years in the experimental and control groups, respectively. Within 24 hours, the experimental group had a significant drop in APTT compared to controls [median 38 (IQR 36-40) seconds *vs*. 44 (IQR 40-46) seconds; $P<0.001$)]. Platelet count, mean haemoglobin, and haematocrit levels rose significantly in the experimental group ($P<0.001$). Thirty (30%) control patients developed active bleeding, while none in the experimental group. Follow-up of the experimental arm showed significant sustained APTT reduction and platelet count increase.

Conclusions: Fresh frozen plasma transfusion improves coagulation markers (reducing APTT and thrombocytopenia) at short-term (24 hours). Assessing use of fresh frozen plasma to prophylactically prevent active bleeding in severe dengue needs more studies with long-term follow-up. (ClinicalTrials.gov number, NCT06642493.)

KEYWORDS: Dengue; Severe dengue; Fresh frozen plasma; Dengue haemorrhagic fever; Dengue shock syndrome; Activated partial thromboplastin time (APTT); Thrombocytopenia; Platelet

Summary

Question: What is the use of fresh frozen plasma in dengue patients with altered coagulation parameters?

Findings: This clinical trial showed the brief delivery of fresh frozen plasma transfusion improved thrombocytopenia and decreased APTT at 24 hours in non-bleeding dengue patients who already had elevated thrombocytopenia and APTT, significantly. In the experimental group, fresh frozen plasma also prophylactically improved coagulation markers.

Meaning: Our findings indicate that fresh frozen plasma transfusion could serve as an effective option for management of coagulopathy in cases of severe dengue.

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1. Introduction

Dengue fever, a prevalent arboviral disease, poses a significant public health concern throughout the tropical and subtropical regions globally[1,2]. Caused by the Dengue Flavivirus (DENV), a species within the Flaviviridae family, dengue is the most widespread arthropod-borne viral disease affecting humans. The virus comprises four established serotypes (DENV 1-4), with a fifth serotype (DENV-5) identified in 2013[3]. The primary vector for these serotypes, responsible for widespread outbreaks, is the *Aedes aegypti* mosquito; however, other *Aedes* species, such as *Aedes albopictus*, can also play a secondary role. Beyond mosquito transmission, alternative routes including maternal transfer, organ donation, and blood product transfusions have also been documented[1,2].

Dengue is endemic in over 100 countries, with approximately 3.9 billion individuals, or more than 40% of the global population, residing in areas at risk of infection[2-4]. Predictive models estimate that 390 million dengue infections occur annually, with 96 million manifesting clinically[5]. The year 2023 witnessed the most severe dengue outbreak in recorded history, culminating in over 7 300 fatalities and a global total of 6.5 million diagnosed cases. Asia bore the highest case fatality ratio (0.22), with Bangladesh reporting the highest number of fatalities globally (1 705), during this 2023 outbreak[6]. Bangladesh has recently experienced a succession of major outbreaks within a brief period, elevating dengue to a critical public health concern. Alongside the unprecedented epidemic of approximately 321 000 cases in 2023, the country has been a hotspot for dengue, with notable outbreaks in 2019 (101 354 cases and 164 deaths) and 2022 (approximately 62 500 cases and 281 deaths). The co-circulation of all four DENV 1-4 serotypes further exacerbates the vulnerability of the local population[7,8].

Typically, dengue presents as an acute, self-limiting, and often debilitating illness, or can even be asymptomatic. However, severe DENV infection can lead to a spectrum of critical clinical conditions, including dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are potentially fatal haemorrhagic and capillary leak syndromes[1,2]. Severe dengue often culminates in complications, such as plasma leakage due to heightened vascular permeability, thrombocytopenia (a reduced platelet count), and coagulopathy, which is frequently indicated by a prolonged activated partial thromboplastin time (APTT)[1,9].

Current management of dengue primarily focuses on supportive care and symptom alleviation, as no specific antiviral treatment is available. Close monitoring for warning signs is crucial. Essential therapeutic strategies encompass hydration, rest, and acetaminophen for pain relief; non-steroidal anti-inflammatory drugs should be avoided due to the increased risk of bleeding. In cases of DHF/DSS with haemorrhagic shock, fluid management (generally crystalloids, with colloids as a second choice) combined with packed red blood cells (PRBC) or whole blood has historically been the mainstay of treatment[10-12]. While the prophylactic use of platelets and fresh frozen plasma in dengue patients with haemorrhagic manifestations is common in practice[13], transfusion of these blood products is generally not recommended in guidelines. Platelet transfusions, specifically, are advised only for managing life-threatening haemorrhage, in pregnant patients, or during surgical interventions in thrombocytopenic dengue patients[10-12]. These recommendations for blood product use are largely derived from studies that often included platelet transfusion as an intervention[10]. Consequently, the potential benefits of plasma transfusion in non-bleeding thrombocytopenic dengue patients with elevated APTT remain largely underexplored in the existing literature.

Coagulation abnormalities are notably prevalent in dengue patients experiencing haemorrhage[9,14]. Haemostatic defects during DENV infection can arise from a confluence of factors, including autoantibodies and cytokines elicited by the viral infection, haemostatic molecules produced on infected cells, and the viral proteins of DENV itself. The interplay of these host and viral characteristics can perturb the delicate balance of coagulation and fibrinolysis, thereby predisposing patients to bleeding[15]. Given that plasma contains essential coagulation factors capable of normalising APTT and stabilising the haemostatic system, it holds potential for preventing progression to overt bleeding episodes[13,16]. Therefore, we hypothesised that plasma transfusion in non-bleeding thrombocytopenic dengue patients with elevated APTT would improve coagulation parameters and mitigate the risk of bleeding complications. This study aimed to assess the effect of fresh frozen plasma transfusion on APTT in non-bleeding thrombocytopenic dengue patients. Concurrently, we evaluated clinical outcomes, including the incidence of bleeding complications, in patients receiving plasma transfusions to determine the safety and feasibility of plasma transfusion in this specific patient population. Furthermore, we measured changes in other coagulation parameters, such as International Normalised Ratio (INR) and platelet levels, following transfusion.

2. Methods

2.1. Design and settings

This investigation was designed as a parallel, double-blinded, randomized controlled trial (RCT), with an observational follow-up of the experimental arm after the predetermined laboratory main endpoints were evaluated at 24 hours. The trial was registered under the clinical trial identifier NCT06642493 (https://clinicaltrials.gov/study/NCT06642493). The study was conducted at a tertiary care hospital in Bangladesh, with data collection extending from June 2024 to April 2025.

2.2. Inclusion and exclusion

We enrolled non-bleeding adult patients (age >18 years) who had a confirmed diagnosis of dengue fever, either through serological testing or PCR. Eligible patients also presented with thrombocytopenia (platelet count ≤50×10^9/L) and elevated APTT (≥40 seconds), specifically in the absence of active bleeding. Patients were systematically excluded if they exhibited active bleeding, possessed known coagulopathies unrelated to dengue, or had any contraindications to plasma transfusion. The calculated sample size for this RCT was 30 per group, using the equation for two independent intervention groups with a continuous outcome [$n= 2\sigma^2 (Z_{\omega/2} + Z_{\beta})^2/d^2$], and data were used from the work of Raturi *et al.*[17]. However, we recruited a total of 200 patients for the study.

2.3. Randomisation, groups, interventions and blinding

Participants were randomly allocated to two distinct groups using computer-generated random numbers, ensuring simple random sampling. Allocation concealment was meticulously maintained through the use of 'sequentially numbered, opaque sealed envelopes' (SNOSE). Of the recruited participants, 100 patients were assigned to the experiment group, which received fresh frozen plasma transfusions, while the remaining 100 patients constituted the control group, receiving standard supportive care.

Fresh frozen plasma was administered intravenously at a dose of 10-15 mL/kg body weight. Participants in the control arm received standard supportive care without plasma transfusion, strictly adhering to the national guidelines[12].

For the preparation of fresh frozen plasma, whole blood was meticulously drawn from the antecubital vein using a standard sterile triple blood bag system under rigorous aseptic procedures. The interval between blood collection and initial processing did not exceed 30 minutes. To optimize component separation, the whole blood underwent two centrifugation steps at an ambient temperature of 22 ℃. In the initial separation phase, red blood cells were isolated from plasma and the buffy coat *via* a gentle spin at 2 200 revolutions per minute (rpm) for ten minutes. To enhance red cell preservation during storage, red blood cells were carefully expressed into a satellite bag using a manual plasma expressor, intentionally retaining approximately ten percent (10%) of the original plasma volume. The plasma-containing bag then underwent a more vigorous second spin for eight minutes at 3 400 rpm under identical temperature conditions (22 ℃). This second centrifugation ensured the complete elimination of any remaining cellular components. The resultant supernatant plasma, now virtually cell-free, was then separated using the plasma expressor. To safeguard the integrity of coagulation factors, particularly labile factors such as Factor Ⅷ, the separated plasma was immediately transferred to a specialized plasma storage bag and rapidly chilled to −30 ℃. The frozen plasma was subsequently stored in accordance with standard transfusion medicine practices[18].

Because plasma transfusion is visible, it was not possible to completely blind the treating professionals. But the lab workers who did the coagulation and haematological tests didn't know which group they were in. The evaluation of laboratory outcomes was performed without awareness of treatment allocation. The clinicians in charge of giving transfusions did not do the laboratory tests or interpret the findings.

2.4. Methodology and data collection

This study primarily aimed to assess the change in APTT values from baseline to 24 hours post-transfusion. Secondary outcomes assessed at 24 hours included changes in platelet count, haemoglobin, haematocrit, and INR. The occurrence of bleeding within the first 24 hours was recorded as an exploratory clinical outcome. Bleeding was defined as any new commencement of clinically evident haemorrhage, encompassing mucosal bleeding (oral, nasal, or gingival), gastrointestinal bleeding (melena or hematemesis), haematuria, or clinically significant soft-tissue bleeding. Isolated petechiae, absent further bleeding signs, were not categorized as bleeding occurrences. During regular clinical evaluations in the first 24 hours, bleeding assessments were done using a standardized checklist. Bleeding severity was classified as mild or clinically significant according to the necessity for therapeutic intervention. Bleeding outcomes were deemed experimental owing to the absence of blinded adjudication. When required World Health Organization's (WHO) criteria for classifying the severity of dengue was followed.

Following withdrawal of the control group after 24 hours, additional laboratory parameters (platelet count, APTT, INR, and complete blood count indices) were monitored in the experimental group at 48 hours and 7 days as part of observational follow-up.

Data were systematically collected using a pre-tested, semi-structured questionnaire. Prior to the finalization of the data collection instrument, the investigative team reached a comprehensive consensus. Medical records of registered patients were meticulously examined, and observations regarding age, sex, and pre-existing comorbidities were meticulously documented. Baseline laboratory investigations were conducted for all participating patients within 24 hours of admission. These included a complete blood count (CBC), APTT, and INR, with all results carefully recorded.

All interventions in both treatment arms were meticulously executed under controlled clinical conditions. In the experimental group, fresh frozen plasma was transfused intravenously under the direct supervision of an expert clinician. Follow-up laboratory values were reassessed in both arms at 24 hours post-intervention. However, to uphold ethical considerations and prevent confounding effects, the

complete control group was withdrawn from further follow-up after 24 hours, as several of these patients required rescue measures, such as platelet transfusions, due to the onset of active bleeding. Following withdrawal of the control group after 24 hours, additional laboratory parameters (platelet count, APTT, INR, and complete blood count indices) were monitored in the experimental group at 48 hours and 7 days as part of observational follow-up. Clinical data, encompassing bleeding episodes and other adverse events, were systematically recorded throughout the entirety of the hospital stay. Outcome assessments and laboratory analyses were performed by personnel blinded to treatment allocation. The clinicians who were in charge of giving the transfusion did not take part in the outcome assessment. A detailed illustration of the allocation procedure is provided in the Consolidated Standards of Reporting Trials (CONSORT) flow chart (Figure 1).

2.5. Ethics

The study and the procedures were conducted in strict adherence to the principles outlined in the Declaration of Helsinki. Prior to the commencement of data collection, ethical approval was obtained from the ethical review committee (ERC) of the then Sheikh Hasina National Institute of Burn & Plastic Surgery (Registration no: SHNIBPS: June2024/03, dated 11/06/2024). Informed consent was meticulously secured from participants or their legally authorised guardians.

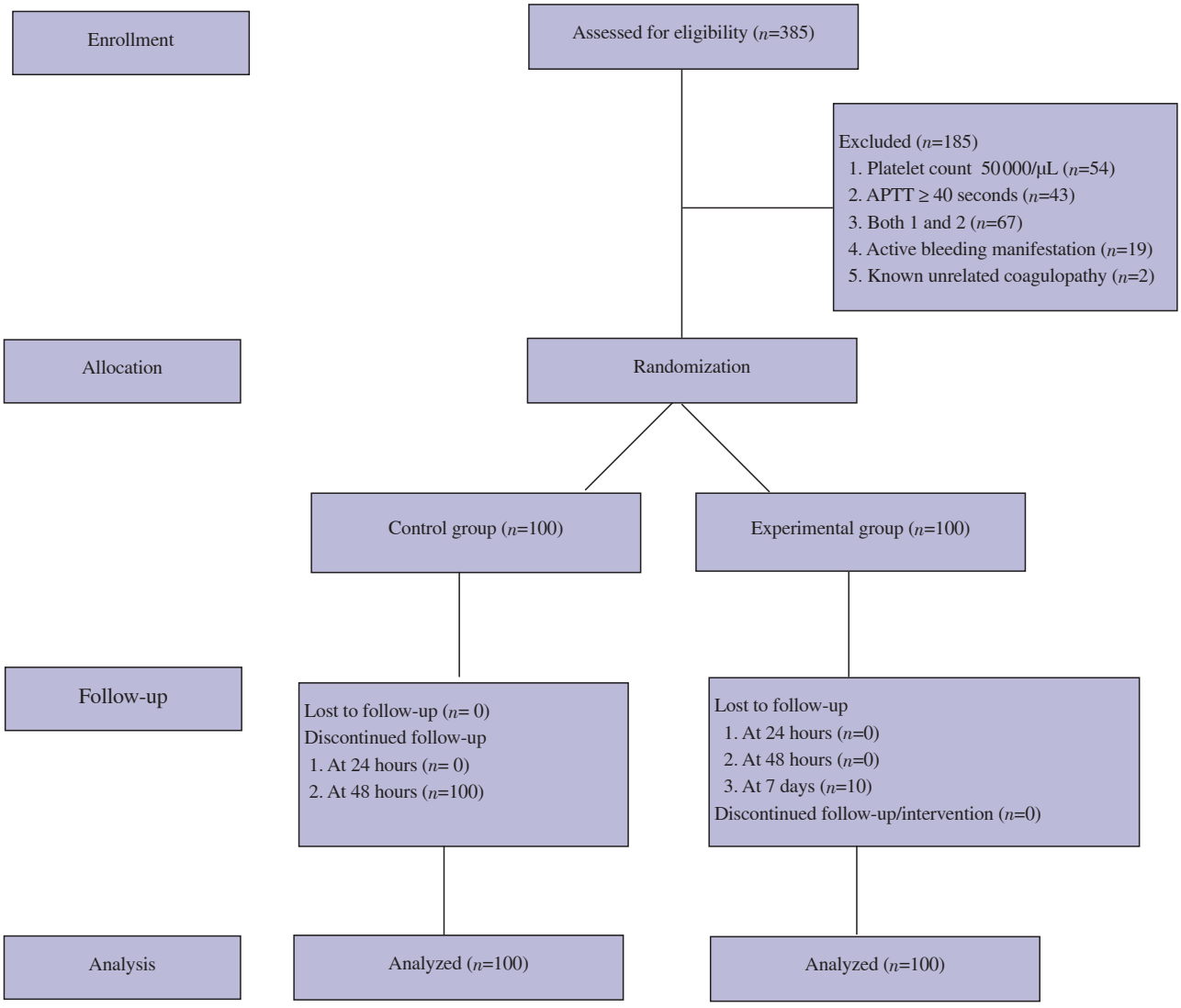

Figure 1. Flow diagram of this study.

Table 1. Baseline characteristics of the study patients (n=200).

Characteristics	Experimental group (n=100)	Control group (n=100)
Median age (IQR), years	34 (30-42)	34 (29-39)
Age group, years		
20 to 39	77 (77)	66 (66)
40 to 49	18 (18)	29 (29)
50 and above	5 (5)	5 (5)
Sex	-	-
Male	74 (74)	77 (77)
Female	26 (26)	23 (23)
Comorbidity	-	-
Hypertension	33 (33)	32 (32)
DM	14 (14)	22 (22)
Laboratory findings*		
Haemoglobin, g/dL	12.60 (11.8-13.5)	12.55 (11.8-13.3)
Hct, %	36 (31-40)	36 (31-40)
WBC, $\times10^9$/L	5 (4-6)	5 (4-6)
Neutrophil, %	41 (40-56)	40 (40-55)
Lymphocyte, %	54 (50-62)	54 (50-62)
Platelet, $\times10^9$/L	20.0 (14.3-22.0)	20.0 (14.0-22.0)
APTT, seconds	42 (40-46)	42 (40-46)
INR	1.35 (1.2-1.5)	1.4 (1.2-1.5)

Data were expressed as n (%) unless otherwise indicated; DM=Diabetes mellitus; WBC=Whole blood count; APTT=Activated partial thromboplastin time; INR=International Normalized Ratio; *data were expressed as median (IQR).

2.6. Statistical analysis

Data were analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, US). For intergroup comparisons, continuous variables were assessed using independent sample t-tests or Mann-Whitney U tests, as appropriate. The data analysis followed the Intention-to-Treat (ITT) principle to the 24-hour comparisons. The analysis for the primary outcome and all other 24-hour comparisons (haemoglobin, haematocrit, platelet count) has used the full randomized cohort ITT principle. The denominators were 100 in each group for these comparisons. The longer-term outcomes are within the experimental arm follow-up only. Since the control group was withdrawn/lost, no comparative analysis could be performed after 24 hours. For intra-group comparisons in longer-term follow-ups, repeated-measures ANOVA test, and pairwise comparisons were performed with Bonferroni adjustment for continuous variables in multiple comparisons. Results were confirmed by non-parametric testing to ensure robustness against data skewness. A P-value of < 0.05 was considered statistically significant for all analyses.

3. Results

3.1. Patients

A total of 200 non-bleeding thrombocytopenic dengue patients were enrolled in this randomized controlled trial, with 100 patients allocated to the experimental group (receiving plasma transfusion) and 100 to the control group (receiving standard supportive care). Baseline characteristics, including age, sex, and comorbidities, were comparable between the groups (P>0.05). The mean age was (34.1±8.1) years in the experimental group and (36.1±7.8) years in the control group. Most patients were male, 74 (74/100, 74%) in the experimental group and 77 (77/100, 77%) in the control group, and common comorbidities included hypertension and diabetes mellitus. Baseline laboratory parameters such as haemoglobin, haematocrit, Total white blood cell (WBC) count, differential counts, platelet count, APTT, and INR were mostly similar (Table 1) and showed no significant differences between groups (P>0.05).

3.2. Primary outcome

After 24 hours, APTT was significantly lower in the experimental group than that in the control group [median 38 (IQR 36–40) *vs.* 44 (IQR 40–46) seconds; P<0.001] (Table 2).

Table 2. Laboratory findings after 24 hours (n=200).

Findings	Reference range	Experimental group (n=100)	Control group (n=100)	Effect size	95% *CI*	*P*-value
Haemoglobin, g/dL	Total	12.60 (11.80-13.50)	11.80 (10.20-12.50)	0.76	0.68 to 1.46	<0.001†
	Male: 13-17	12.60 (11.80-13.50)	11.80 (10.40-12.50)			-
	Female: 12-16	12.50 (11.38-13.20)	11.20 (10.20-12.50)			-
Hct, %	Total	35.80±5.45	31.63±5.02	0.80	2.71 to 5.63	<0.001‡
	Male: 40-50	36.23±5.30	31.77±5.00			-
	Female: 36-44	34.57±5.70	31.17±5.10			-
WBC, $\times10^9$/L	4-11	5 (4-6)	5 (4-6)	-0.01	-0.87 to 0.71	0.988†
Neutrophil, %	40-75	41 (40-56)	40 (40-55)	0.02	-2.88 to 3.32	0.889†
Lymphocyte, %	20-45	54 (50-62)	54 (50-62)	0.04	-2.50 to 1.90	0.876†
Platelet, $\times10^9$/L	150-450	25 (19-32)	18 (12-28)	-0.03	-1.31 to 2.06	<0.001†
APTT, seconds	30-40	38 (36-40)	44 (40-46)	0.85	-7.20 to -3.63	<0.001†
INR	0.9-1.2	1.35 (1.20-1.50)	1.40 (1.20-1.50)	0.49	-0.05 to 0.03	0.789†

Data were expressed as median (IQR) or mean±SD. †: Mann-Whitney test for skewed data, ‡= Independent sample t-test for normally distributed data.

3.3. Secondary outcomes

The experimental group demonstrated significantly higher haemoglobin [12.60 (11.80-13.50) *vs.* 11.80 (10.20-12.50) g/dL; $P<0.001$], haematocrit [(35.80±5.45)% *vs.* (31.63±5.02)%; $P<0.001$], and platelet count [25 (19-32) $\times10^9$/L *vs.*18 (12-28) $\times10^9$/L; $P<0.001$] compared to the control group after 24 hours, while WBC count, neutrophil and lymphocyte percentages, and INR remained similar between groups (Table 2). Notably, 30 (30%) of patients in the control group developed bleeding within 24 hours, while none in the experimental group did. Bleeding outcomes were deemed exploratory. Among the bleeding type, 13 (13%) had melena, whereas 12 (12%) had mucosal bleeding and 5 (5%) had hematemesis

3.4. Observational follow-ups of the experimental group

Follow-up laboratory evaluation among patients in the experimental group revealed significant haematological changes from baseline to day 7 of plasma transfusion therapy (Table 3). Ten (10%) of the 100 individuals who were first placed in the experimental group couldn't be included in the laboratory follow-up by day 7. The main causes of loss to follow-up were consent withdrawal, transfer of care, and hospital discharge. The observational analysis incorporated all accessible data.

The mean haemoglobin level increased slightly from baseline (12.58±1.29) g/dL to day 7 (12.62±1.20) g/dL, though this change was not statistically significant ($P=0.067$). Haematocrit decreased significantly from baseline [(36.00±5.80)%] to day 7 [(33.52±2.65)%] ($P<0.001$), with significant differences noted between baseline, 24-hour, and 48-hour values compared to day 7. WBC count from baseline and 24-hour follow-up rose initially at 48 hours (8.29±2.15)$\times10^9$/L but significantly declined by day 7 (5.74±1.27)$\times10^9$/L, showing a significant difference compared to 48-hour levels ($P<0.001$). Neutrophil percentage increased until 48 hours [(49.57±9.01)%] but significantly decreased by day 7 [(41.55±2.54)%] ($P<0.001$), while lymphocyte percentage declined steadily from baseline [(54.98±7.94)%] to day 7 [(39.39±3.38)%] with statistically significant differences at each time point ($P<0.001$).

Platelet count showed a marked and statistically significant rise from baseline (19.42±6.22)$\times10^9$/L to day 7 (194.87±45.64)$\times10^9$/L, with each follow-up showing significant improvement ($P<0.001$). APTT levels progressively declined from (44.10±5.72) seconds at baseline to (28.22±0.97) seconds at day 7 ($P<0.001$), indicating improved coagulation status. INR values remained stable throughout the follow-up period ($P=0.055$).

3.5. Safety

Although none of the patients developed bleeding, among the experimental group, 30 (30%) experienced transfusion-related reactions, including 6 (6%) with febrile non-haemolytic transfusion reactions and 24 (24%) with itching. There was no reported serious transfusion-related problems.

Table 3. Laboratory findings in the experimental group (n=100).

Findings		Reference range	Baseline (n=100)		After 24 hours (n=100)		After 48 hours (n=100)		After 7 days (n=90)		P
			Level	95% *CI*	Level	95% *CI*	Level	95% *CI*	Level	95% *CI*	
Hemoglobin, g/dL	Total		12.58±1.29	12.33-12.83	12.58±1.29	12.33-12.83	12.59±1.25	12.35-12.84	12.62±1.20	12.38-12.85	0.067
	Male: 13-17		12.67±1.20	12.45-12.89	12.67±1.20	12.45-12.89	12.66±1.16	12.43-12.49	12.71±1.09	12.50-12.92	-
	Female: 12-16		12.32±1.50	12.09-12.55	12.32±1.50	12.09-12.55	12.35±1.47	12.06-12.64	12.32±1.43	12.04-12.60	-
Hct, %	Total		36.00±5.80	34.86-37.14	35.80±5.45	34.73-36.87	35.51±5.42	34.45-36.57	33.52±2.65	32.97-34.07‡§	<0.001
	Male: 40-50		36.50±5.70	35.38-37.62	36.23±5.30	35.16-37.30	36.08±5.38	35.03-37.13	33.42±2.40	32.94-33.90	-
	Female: 36-44		34.57±6.00	33.42-35.72	34.57±5.70	33.46-35.68	34.27±5.50	33.19-35.35	33.82±3.50	32.94-34.70	-
WBC, $\times10^9$/L		4-11	5.69±2.84	5.14-6.28	5.73±2.82	5.18-6.25	8.29±2.15	7.87-8.71 ‡§	5.74±1.27	5.48-6.01§	<0.001
Neutrophil, %		40-75	47.83±11.28	45.62-50.04	47.65±11.05	45.48-49.82	49.57±9.01	47.80-51.34	41.55±2.54	41.03-42.07†‡§	<0.001
Lymphocyte, %		20-45	54.98±7.94	53.42-56.54	54.61±8.07	53.03-56.19	53.72±7.98	52.16-55.28†	39.39±3.38	38.69-40.09†‡§	<0.001
Platelet, $\times10^9$/L		150-450	19.42±6.22	18.20-20.64	27.34±9.98	25.38-29.40†	98.68±8.17	82.68-114.69†‡	194.87±45.64	185.44-204.29‡§	<0.001
APTT, seconds		30-40	44.10±5.72	42.98-45.22	39.43 ± 5.87	38.28-40.58†	30.10±2.32	29.65-30.55‡§	28.22±0.97	28.02-28.42‡§	<0.001
INR		0.9-1.2	1.34±0.15	1.31-1.37	1.34 ± 0.15	1.31-1.37	1.34±0.15	1.31-1.37	1.34±0.13	1.31-1.37	0.055

P-value was determined by repeated measures ANOVA test, and pairwise comparisons were performed with Bonferroni adjustment for multiple comparisons. † = denotes significant difference from baseline, ‡ = denotes significant difference from 24-hour follow-up, and § = denotes significant difference from 48-hour follow-up.

4. Discussion

In tropical nations, patients who suffer from feverish diseases typically have an infectious cause and may also present with thrombocytopenia in general[19]. Dengue commonly causes fever with thrombocytopenia due to cytokine-induced endothelial damage[9,20]. Bleeding in dengue due to low platelet count can present as melena, epistaxis, oral bleeding, and petechiae. Warning signs include abdominal pain, vomiting, mucosal bleeding, respiratory distress, and shock from plasma leakage[21].

This study assessed the short-term impact of fresh frozen plasma transfusion on coagulation parameters in non-bleeding dengue patients with thrombocytopenia and extended activated partial thromboplastin time. Using a randomized comparison restricted to the initial 24 hours, the current study indicated that in dengue patients with thrombocytopenia and raised APTT, infusion of fresh frozen plasma alongside conventional supportive care, may contribute to an increase in platelet count and reduction in APTT. Beyond this initial phase, follow-up data from the experimental group were gathered through observation and represent within-group trends rather than comparative treatment effects.

While baseline characteristics and laboratory profiles were comparable between the experimental and control groups, notable differences emerged after 24 hours. Patients in the experimental group showed significantly higher mean haemoglobin, haematocrit, and platelet counts, along with lower APTT values compared to controls, indicating early haematological improvement. The observed decrease in APTT within 24 hours is biologically plausible, as fresh frozen plasma provides coagulation factors that may temporarily rectify laboratory abnormalities linked to dengue-associated coagulopathy. The simultaneous increase in platelet count and stabilization of hemoglobin and hematocrit during the same period may indicate a combination of hemostatic support, disease progression, and supportive clinical management. Importantly, these findings should be understood within the framework of a laboratory-based primary endpoint rather than as conclusive proof of clinical efficacy. These findings are supported by previous studies highlighting that fresh frozen plasma may help correct coagulation abnormalities and improve platelet dynamics in dengue patients by addressing endothelial dysfunction and restoring hemostatic balance[20,22]. A study conducted in Thailand investigated the management strategies for adults with severe dengue, emphasising the role of fluid therapy and hemostatic support. The researchers highlighted that in patients with dengue-associated plasma leakage and coagulopathy, early administration of blood products such as fresh frozen plasma may be beneficial in restoring hemodynamic stability and correcting prolonged coagulation profiles. Their findings align with current observations, where early fresh frozen plasma infusion led to improvement in haematological parameters and potentially reduced bleeding complications[23]. In contrast, 30 (30%) of patients in the control group developed bleeding within the first 24 hours. Due to the onset of active bleeding, these patients required rescue interventions (including platelet transfusions) and, therefore, the entire control group was excluded from further follow-up after 24 hours to maintain ethical integrity and avoid confounding effects. However, due to the early termination of the control arm on ethical grounds and the lack of blinded adjudication, hemorrhage outcomes in this study should be considered exploratory. These findings suggest a potential indication that merits further exploration but do not establish a causal link between plasma transfusion and the prevention of hemorrhage.

Among the 100 patients initially enrolled in the experimental group, only 90 (90%) completed the 7-day follow-up, with 10 (10%) patients lost to follow-up due to various reasons, including hospital discharge, transfer, or withdrawal of consent. Previous studies have concluded that haematocrit elevation, thrombocytopenia, leukopenia, and reactive lymphocytes are valuable diagnostic markers for dengue fever, facilitating timely case identification and intervention[24]. In a recent study, patients who received fresh frozen plasma demonstrated significant haematological improvements over the 7-day follow-up period. Importantly, no bleeding episodes were observed in the experimental group throughout the follow-up period, highlighting a potential protective role of fresh frozen plasma in hemorrhagic complications. In the current study, platelet counts, which initially averaged $(19.42\pm6.22)\times10^9$/L at baseline, rose markedly to $(27.34\pm9.98)\times10^9$/L after 24 hours, $(98.68\pm8.17)\times10^9$/L after 48 hours, and peaked at $(194.87\pm45.64)\times10^9$/L by day 7 ($P<0.001$) in the experimental group. According to a prospective randomized study on the effectiveness of fresh frozen plasma in dengue patients concluded fresh frozen plasma increases the platelet count in the first 12 hours of treatment[21]. Similarly, APTT values improved significantly—from (44.10±5.72) seconds at baseline to (28.22±0.97) seconds at day 7 ($P<0.001$)—reflecting enhanced coagulation stability. A transient neutrophilia was noted at 48 hours, followed by normalization by day 7, while lymphocyte percentages showed a gradual decline, possibly reflecting the waning immune activation. Haemoglobin and INR values remained stable, indicating no adverse haematological compromise. Interestingly, haematocrit showed a statistically significant decline over time, which may reflect hemodilution or vascular leak reversal. WBC levels showed a biphasic trend. The mean WBC count remained relatively stable from baseline to 24 hours, followed by a significant rise at 48 hours, indicating a possible reactive leukocytosis, likely in response to resolving inflammation or infusion-related immune stimulation. By day 7, WBC values returned closer to baseline levels, suggesting resolution of the acute-phase response. This progressive improvement suggests a strong therapeutic impact of fresh frozen plasma on thrombocytopenia resolution[22]. Similarly, another study

also revealed that a rise in platelets with a significant *P* value was found in patients given fresh frozen plasma and suggested that the demand for platelets and fresh frozen plasma is increasing due to the increasing number of cases with severe dengue[25]. In dengue patients with thrombocytopenia, infusion of fresh frozen plasma may contribute to early haematological improvement, including a significant rise in platelet counts and normalization of coagulation parameters, while also potentially reducing bleeding complications and associated morbidity.

However, the limitation of this study was, first, even though the study used random assignment, the comparison was only based on the first 24 hours, due to the early exclusion of the control group after 24 hours due to the onset of bleeding, preventing extended comparison. So, results after this point in time are just observations within the experimental group and don't allow us to draw any conclusions about the cause of events between the groups. Second, the main outcome was a lab test called APTT, which shows that the coagulation parameters were fixed but doesn't directly show a clinical effect. Although bleeding happened during the random time, it wasn't decided by a committee that wasn't aware of the patients' identities, so it should only be seen as an exploratory outcome. Third, treating physicians couldn't be completely blinded, as plasma transfusions are obvious, which may led to performance/ detection bias. However, lab tests were done by professionals who didn't know about the treatment allocation. Moreover, 10 (10%) of patients in the experimental group were lost to follow-up, which may have affected the assessment of long-term outcomes. Another notable limitation of this work is, it was carried out in a single center, and selection bias is therefore possible. Therefore, despite the sample size was bigger than the bare minimum needed to find changes in lab parameters, these issues highlight the significance of doing larger, multicenter studies with long-term, randomized follow-up and unambiguous clinical outcomes to completely comprehend the function of plasma transfusion in dengue-associated coagulopathy.

In conclusion, the findings of our work suggest that the intervention applied to the patients exhibiting elevated APTT and reduced platelet count is clinically effective and safe in improving haematological parameters and associated with a rapid (within 24 hours) improvement compared to no infusion. As well as being effective within a short period, in the intra-group follow ups, fresh frozen plasma also improves crucial haematological parameters, such as platelet count, APTT in the intermediate period, confirming its association with coagulation stability.

The findings indicate that fresh frozen plasma may provide temporary repair of coagulation abnormalities in some dengue patients and therefore, offers a potential, biologically possible substantial benefit in preventing complications such as active bleeding and DHF/DSS. This element greatly increases its appeal in such scenarios where dengue patients present with coagulation abnormalities evident with laboratory findings. However, its efficacy in reducing clinical bleeding necessitates validation through trials with prolonged randomized follow-up and explicitly specified clinical objectives.

Conflict of interest statement

None of the contributing authors declare any conflicts of interest.

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Authors' contributions

Conceptualization: A.H. and S.K.B.; Methodology: A.H. and M.A.; Data-collection: A.H., S.K.B., M.A. and S.M.C.; Formal analysis: M.A. and S.M.C.; Investigation: A.H., S.K.B., M.U.H. and A.A.M.; Resources: A.H., S.K.B., M.U.H., M.A., S.M.C. and A.A.M.; Data curation, A.H., M.A. and S.M.C; Writing/ Drafting—original draft, M.A.; Writing—review and editing, A.H., S.K.B., M.U.H. and A.A.M.; Critical Revision/ supervision: A.H., A.A.M. and S.K.B.; Project administration: A.H. and M.A. All authors have read and agreed to the published version of the manuscript.

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