SHORT RESEARCH ARTICLE

PLATELET TRANSFUSION AND TRANEXAMIC ACID IN THE TREATMENT OF BLEEDING IN DENGUE FEVER

ABSTRACT

OBJECTIVE

We conducted this study to investigate the effectiveness of platelet transfusion and/or intravenous tranexamic acid in the treatment of clinical bleeding in patients with dengue fever at a tertiary care hospital during a large outbreak (August and November, 2011) of dengue fever in Lahore, Pakistan.

METHODS

We reviewed data of patients with clinical bleeding and confirmed dengue fever at Jinnah Hospital Lahore, Pakistan. Based on the treatment, patients were classified into four groups: Baseline characteristics of patients and site and grade of bleeding were documented. A comparison of time to cessation of bleeding across four groups was made.

RESULTS

Out of 100 selected patients with clinical bleeding, 65 were male and median age was 28 years (range 13-80). There were 47 patients in group A, 12 in group B, 9 in group C, and 32 in group D. 75 patients had bleeding from a single site while 24 patients had bleeding from 2 different sites and 1 patient had bleeding from 3 sites. Median time from the initiation of treatment till the

cessation of bleeding was not significantly difference across four groups (p value = 0.724, Kruskal-Wallis test). Adverse effects included abdominal pain in group A and pruritus in group A and C.

CONCLUSION

Platelet transfusion and/or tranexamic acid do not provide significant benefit over standard of care treatment in patients with clinical bleeding in dengue fever and may be associated with adverse outcome.

KEY WORDS

Dengue fever

Dengue hemorrhagic fever

Platelet transfusion

Tranexamic acid

Bleeding

Pakistan

INTRODUCTION

Dengue is the most rapidly spreading mosquito borne viral disease in the world [1,2]. While most infections are asymptomatic, the spectrum of symptomatic disease varies from dengue fever to dengue haemorrhagic fever and dengue shock syndrome [3,4]. Bleeding is one of the common manifestations of dengue fever [5]. The pathophysiology of bleeding in dengue fever is multifactorial and yet to be fully understood [4,6,7]. Thrombocytopenia is common in dengue fever, however a linear correlation between the degree of thrombocytopenia and risk of clinical bleeding has not been documented. Similarly a number of observational studies [8,9] and two randomized clinical trials [10,11] have failed to show the benefit of prophylactic platelet transfusion in preventing clinical bleeding in dengue fever. However the effectiveness of therapeutic platelet transfusion in stopping clinical bleeding has not been fully explored.

Tranexamic acid is used in the treatment of postpartum hemorrhage, menorrhagia, trauma-associated hemorrhage, and surgical bleeding [12-14]. It works by inhibiting the conversion of plasminogen to plasmin thus leading to decreased degradation of fibrin and fibrinogen. It is also not clear if use of tranexamic acid can help in stopping the clinical bleeding in dengue fever. In order to explore the effectiveness of platelet transfusion and tranexamic acid either alone or in combination in the treatment of dengue related bleeding, we analysed the data of patients admitted to a large tertiary care hospital in Lahore Pakistan during a huge dengue outbreak.

METHODS

We reviewed the hospital record of patients admitted to Jinnah Hospital Lahore with confirmed dengue fever between August 2011 and November 2011. This time period encompasses the period of most hospital admissions during dengue epidemic. Patients were selected on the basis

of evidence of clinical bleeding. One hundred patients for whom good quality clinical data was available were selected. Based on the treatment received, patients were divided into 4 groups. Group A included patients who received intravenous tranexamic acid at a dose of 500 mg twice a day for at least 3 days. Patient in group B received at least 1 single donor platelet-pharesis unit containing a dose of $\geq 5 \times 10^{11}$ platelets. Patients in group C had received both tranexamic acid and platelet transfusion in doses as reported for group A and B. Group D comprised of patients receiving standard of care treatment as in other groups but neither received tranexamic acid nor platelet transfusion.

The demographic, clinical and laboratory data were abstracted on a standardized performa. For each patient, bleeding was graded according to WHO grading system. The site and grade of bleeding was documented at baseline and at 12, 24, 48 and 72 hours post treatment. Time from the initiation of treatment to the cessation of bleeding was documented. Any adverse effects reported by patients in each group were also analysed. The final outcome (discharge from hospital and deaths) were also documented.

The data was analysed using SPSS Statistics software Version 20 (SPSS Inc., Chicago, IL, USA). For nominal variables comparison was made across these groups by cross tabulation of the data. Fisher exact test was used to calculate p value. Due to the lack of normality of the data across groups, continuous variables were analysed by applying non parametric test (Kruskal-Wallis test). The difference was considered to be statistically significant with a confidence interval of 95 % and a p value equal to or below 0.05.

RESULTS

The data of 100 patients was analysed, the median age was 28 years (range 13-80) and 65 (65%) were male. The diagnosis was dengue fever in 48 patients while 52 had dengue haemorrhagic fever (DHF1 n=0, DHF2 n=37, DHF3 n=14, DHF4 n=1).There were 47 patients in tranexamic acid only (group A), 12 in platelet transfusions only (group B), 9 in combined tranexamic acid and platelet transfusions (group C) and 32 in the control group that did not receive tranexamic acid or platelet transfusions (group D). Baseline characteristics of patients in all four groups are given in table I.

Table I: Baseline characteristics of patients in four groups

	Group			
Parameter*	**A**	**B**	**C**	**D**
Gender				
Male	29 (62)	10 (83)	6 (67)	19 (61)
Female	18 (38)	2 (17)	3 (33)	12 (39)
Age (years)	30 (13-80)	25.5 (14-65)	29 (18-60)	28 (15-47)
Diagnosis				
DF	30 (64)	2 (17)	1 (11)	15 (48)
DHF 1	0	0	0	0

DHF 2	12 (25)	7 (58)	4 (44)	13 (42)
DHF 3	5 (11)	3 (25)	4 (44)	2 (6)
DHF 4	0	0	0	1(3)
Skin rash	9 (19)	1 (8)	1 (11)	4 (13)
Vomiting	32 (68)	7 (58)	6 (67)	23 (74)
Myalgias	40 (85)	8 (67)	9 (100)	26 (84)
Arthralgias	21 (45)	4 (33)	4 (44)	8 (26)
Headache	38 (81)	7 (58)	6 (67)	18 (58)
Retro-orbital pain	14 (30)	2 (17)	6 (67)	6 (19)
Sore throat	10 (21)	3 (25)	3 (33)	9 (29)
Loose motions	16 (34)	5 (42)	6 (67)	9 (29)
Constipation	6 (13)	0	0	1 (3)
Petechiae	0	1 (8)	0	3 (10)
Ecchymosis	0	0	0	1 (3)
Gum bleeding	14 (30)	4 (33)	4 (44)	5 (16)
Epistaxsis	9 (19)	6 (50)	1 (11)	7 (23)

Pruritus	3 (6)	0	0	2 (6)
Hematemesis	17 (36)	3 (25)	2 (22)	9 (29)
Malena	6 (13)	3 (25)	2 (22)	9 (29)
Abdominal pain	16 (34)	2 (17)	6 (67)	5 (16)
Vaginal bleeding	6 (13)	1 (8)	1 (11)	6 (19)
Rigors/Chills	25 (53)	4 (33)	5 (56)	13 (42)
Hematuria	3 (6.4)	1 (8.3)	2 (22)	7 (23)
Pleural effusion	6 (13)	6 (50)	3 (33)	7 (23)
Ascities	7 (15)	7 (58)	6 (67)	10 (32)
Rectal bleed	6 (13)	0	1 (11)	0
Hemoptysis	8 (17)	0	0	3 (10)
Positive Tourniquet test	1 (2)	0	2 (22)	2 (6)
Duration of fever in days median (range)	6 (2-15)	6.5 (2-16)	7 (5-10)	6 (3_15)
HCT (%)	41.2 (23.5-49.2)	40.5 (33.1-45.2)	36.3 (24.7-49.6)	40.2 (22.1-53.0
Hemoglobin (g/dl)	13.3 (8.0-17.8)	13.6 (9.4-	11.3 (8.1-	12.7 (5.8-

		15.8)	16.5)	17.0)
Total Leukocyte Count/mm^3	3800 (1400-11000)	3150 (1600-7700)	3200 (1900-7200)	3100 (1500-9400)
Platelet Count/µl	43 (8-210)	31 (3-125)	31 (5-55)	42 (3-395)

*Data for nominal variables is presented as numbers (percentages) and for continuous variables as median (range).

The site and WHO grade of bleeding at onset are given in table II. Seventy five (75) patients had bleeding from a single site while 24 patients had bleeding from 2 different sites and 1 patient had bleeding from 3 sites. We looked at whether the median time from the initiation of treatment till the cessation of bleeding was different across these groups. There was no statistically significant difference between these groups (p value= 0.724, Kruskal-Wallis test) (Figure I). However there was significant difference in the duration of hospital stay across the groups being longest in group C [median 5 days (range 3-6 days)] followed by group B [median 2.5 (range 2-5)], group A [median 2 (range 1-5)] and group D [median 2 (range 1-5)].This shows that groups receiving platelet transfusions had longer duration of hospital stay. However it is not clear whether this prolong duration of hospital stay can be attributed to the treatment given as there was difference in the baseline disease severity across groups.

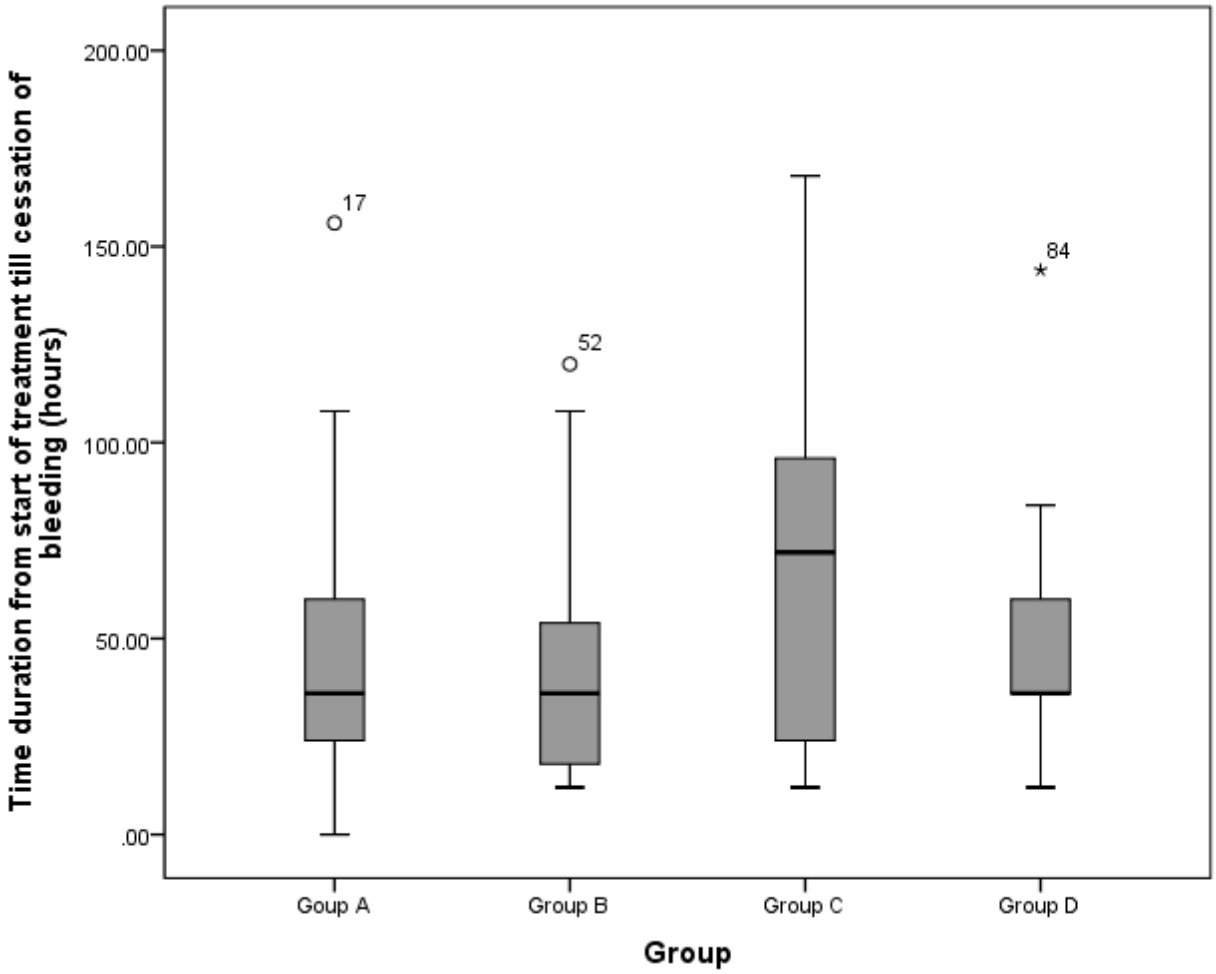

Figure I: Comparison of time duration (hours) from the initiation of treatment to the cessation of clinical bleeding across four groups

Table II: Site and grade of clinical bleeding at baseline

	Group			
Bleeding	**A**	**B**	**C**	**D**
Site of bleeding				

Oral and nasal	19 (40)	8 (66)	4 (44)	8 (26)
Gastro-intestinal	26 (55)	5 (42)	4 (44)	17 (55)
Genito-urinary	9 (18)	2 (17)	3 (33)	10 (32)
Pulmonary	6 (13)	0	0	3 (10)
Grades of bleeding				
Grade 1	14 (30)	5 (42)	4 (44)	5 (16)
Grade 2	40 (85)	8 (66)	4 (44)	31 (100)
Grade 3	6 (13)	2 (17)	3 (33)	2 (6)

We also compared the adverse effects reported after the initiation of treatment and results are presented in table III. Abdominal pain was reported only in group A and pruritus was observed in group A and C. Other reported adverse effects were comparable across different groups. There were 2 deaths (1 each in group B and D) while 98 patients recovered and were discharged. Overall, our study shows that treatment with tranexamic acid or platelet transfusions (either alone or in combination) does not reduce the duration or severity of the bleeding and is associated with higher incidence of adverse reactions.

Table III: Adverse events reported across groups

	Group

Adverse event	A	B	C	D
Hypotension	2 (4.3)	2 (16.7)	1 (11.1)	1 (13.1)
Nausea	6 (12.8)	2 (16.7)	2 (22.2)	2 (6.3)
Vomiting	0	1 (8.3)	0	1 (3.1)
Diarrhea	0	0	0	0
Blurring of vision	0	0	0	0
Headache	3 (6.4)	2 (16.7)	2 (22.2)	6 (18.8)
Abdominal pain	8 (17.0)	0	0	0
Skin rash	1 (2.1)	1 (8.3)	0	1 (3.1)
Pruritus	5 (10.6)	0	2 (22.2)	0
Bronchospasm	0	0	0	0
Volume overload	0	0	0	0
TRALI	0	0	0	0

DISCUSSION

Our study shows that treatment with platelet transfusion and tranexamic acid either alone or in combination does not shorten the time to complete cessation of bleeding compared to the standard treatment group. The exact pathogenesis of bleeding in dengue fever is not yet fully understood. The proposed risk factors for bleeding in DF include low platelet count, platelet dysfunction, coagulation defect and vascular fragility [7,15]. However, it is unclear how these individual risk factors contribute towards overall risk of bleeding. Two randomized clinical trials of prophylactic platelet transfusion in dengue fever have shown that platelet transfusion in patients with dengue related thrombocytopenia does not decrease the risk of bleeding despite an increase in the platelet count [10,11]. While platelet transfusion is given to patients with ongoing clinical bleeding in patients with thrombocytopenia and dengue fever, the effectiveness of this practice has not been well studied [16]. While some clinical guidelines recommend the usage of tranexamic acid in women during menstrual cycle in dengue fever to minimize the risk of heavy menstrual blood loss [17], the role of tranexamic acid in the treatment of clinical bleeding in DF has also not been well studied. A case was reported in which injectable tranexamic acid was given to a patient of dengue hemorrhagic fever with upper GI bleed at dose of 15mg/kg/day but there was minimal improvement and hematemesis continued [18]. We have shown here that neither treatment was superior to standard treatment in stopping the clinical bleeding.

We also observed higher number of adverse events reported in study arms as compared to control group. For example, abdominal pain was reported exclusively in patients who had received tranexamic acid. Similarly, we observed higher frequency of pruritus in patients who had received tranexamic acid alone or in combination with platelet transfusion.

The limitations of our study include non-randomized study population with heterogeneous group composition and smaller sample size. A larger randomized clinical trial with prospectively collected data is needed to validate the results of our study in an unbiased manner.

CONCLUSION

Platelet transfusion and/or tranexamic acid do not provide significant benefit over standard of care treatment in patients with clinical bleeding in dengue fever and may be associated with adverse outcome.

ETHICAL APPROVAL

Ethical review committee of Allama Iqbal Medical College/ Jinnah Hospital Lahore approved the study protocol.

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