Effect of Platelet Transfusion on Clot Strength in Dengue Fever with Thrombocytopenia Related Bleeding: A Thromboelastography-Based Study

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Keywords

Dengue fever · Platelet transfusion · Thromboelastography · Clot strength

Abstract

Platelet transfusions are often administered in dengue illness complicated by thrombocytopenia-related bleeding. However, whether this practice results in an improvement of clot strength is not clear. This study assessed the impact of platelet transfusion on the control of bleeding and improvement in clot strength as assessed by thromboelastography among 74 patients with dengue. The effect of either weight-based random donor platelets or 1 unit of single donor aphaeresis units was studied. Transfusion of weight-based random donor platelets resulted in a mean platelet count increase of 10,210 cells per mm³ at 24 h from pretransfusion values, which reached marginal statistical significance ($p = 0.031$). Patients who received single donor platelets achieved a mean platelet increment of 22,874 cells per mm³ at 24 h, and the difference observed had a high statistical significance ($p < 0.001$). However, no significant improvement in clot strength was observed in thromboelastography. The mean increment in maximum amplitude value at 24 h was only 2 mm in the random donor platelet group and 5 mm in the single donor group, both of which did not reach statistical significance. Furthermore, the majority of patients had ongoing bleeding despite the administration of platelets.

This study observed that platelet transfusion in dengue patients with bleeding complication improved the absolute platelet count with no improvement in clot strength.

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Dengue fever is a mosquito-borne viral illness associated with severe thrombocytopenia leading to increased utilization of platelet transfusions [1]. While thrombocytopenia is the major hematological abnormality resulting from the illness, additional factors contribute to bleeding in dengue [2]. Though platelet transfusion is administered to improve platelet counts among dengue patients with bleeding, there is lack of evidence on the impact of such transfusions on bleeding and laboratory assessment of clot strength. Increments in platelet count ranging from 7,000 to 18,000 cells per mm³ occurs as a result of single donor or pooled random donor platelet transfusion [3]. However, whether this practice results in an improvement of platelet function and hence clot strength is not clear. Thromboelastography (TEG) is a laboratory method to assess the viscoelastic property of whole blood during the process of clotting [4]. It is used for hemostatic monitoring in the setting of trauma and major surgery [5, 6]. The method incorporates assessment of the tensile force which occurs between the clotting blood and a pin as a result of interaction between glycoprotein IIb/IIIa receptors and fibrin [4]. Important

parameters in TEG are the R time (period for a 2-mm amplitude in the clot) which depends on clotting factors, K time (period for 2- to 20-mm amplitude) which depends on clotting factors and fibrinogen, α angle (slope between R and K) which gives the relation between R and K time, MA (maximum amplitude of clot strength) which is contributed by platelet function and fibrinogen, and LT (clot lysis time after 30 and 60 min) which depends on the function of fibrinolysis [4]. Of these parameters, MA reflects the contribution of platelet function to final clot strength when clotting factors and fibrinogen are normal [4]. This study was initiated to assess the impact of platelet transfusion on the resolution of bleeding and its effect on clot strength as assessed by TEG among dengue patients with isolated thrombocytopenia and bleeding complications.

Participants were aged ≥ 18 years and were diagnosed with dengue as per the WHO 2009 definition, were seropositive, and had bleeding complications requiring transfusion of either random donor platelets (1 unit for every 10 kg of patient body weight) or 1 unit of single donor platelets [7]. We excluded participants: (a) with a prior hematological disorder, (b) with splenomegaly due to any cause, (c) with chronic liver disease, (d) on anti-platelet or anticoagulant medications, (e) on hemodialysis, (f) with high R and K values in the baseline TEG, (g) with serum fibrinogen <200 mg/dL, (h) with baseline hemoglobin less than 11 g/dL for women and 12 g/dL for men, and (i) with lack of bleeding at presentation. Platelet products were received from a blood bank accredited with national quality boards.

Kaolin-activated TEG as per instrument recommendation was performed using a TEG 5000 Hemostasis analyzer system (Haemonetics Corporation, Braintree, MA, USA) for all participants just before the initiation of platelet transfusion and repeated again at 1, 4, 12, and 24 h after the completion of platelet transfusion. Maximum amplitude (MA), a TEG indicator of clot strength (when fibrinogen and early TEG indicators like R and K are normal) was the primary TEG parameter compared between pre- and posttransfusion TEG. Platelet counts prior to transfusion and at intervals of 1, 4, 12, and 24 h were assessed by an automated method which was confirmed with manual counting. Written informed consent was obtained from patients for two additional blood samples (4- and 12-h platelet counts and TEG) apart from the usual monitoring samples. Ethics committee approval was not required since the observation was a case series study design where evaluation and treatment followed the usual standard of care.

Categorical variables are expressed as number (%) and continuous variables are expressed as the mean $\pm$ SD. Differences between pretransfusion and posttransfusion platelet count and MA values were analyzed with

Table 1. Baseline characteristics and coagulation parameters of study participants ($n = 74$)

Variable	Number (%) or mean $\pm$ SD
Gender	
Male	41 (55)
Female	31 (45)
Age in years	
Male	28 $\pm$ 9.4
Female	26 $\pm$ 6.6
Day of illness	6 $\pm$ 1.5
Nature of bleeding	
Oral mucosal	20 (27)
Epistaxis	6 (8)
Hematuria	20 (27)
Hematemesis	12 (16)
Melena	8 (11)
Menorrhagia	8 (11)
Coagulation profile	
INR	0.86 $\pm$ 0.12
aPTT, s	28 $\pm$ 3.25
Fibrinogen level, mg/dL	296 $\pm$ 42.5

INR, international normalized ratio; aPTT, activated partial thromboplastin time.

one-way analysis of variance (ANOVA) followed post hoc comparison between groups using the Tukey HSD test. A p value <0.05 was considered statistically significant. The analysis was conducted with SPSS version 19.1.

Fifty-two (70%) patients received random donor platelets and 22 (30%) received single donor platelets. Table 1 describes the baseline characteristics and coagulation profile of the study participants. All 6 patients with epistaxis received nasal packing which controlled the bleeding before the initiation of platelet transfusion. Six out of 20 participants who had oral mucosal bleeding improved with oral rinse with diluted adrenaline, while the remaining 14 had persistent bleeding for a mean duration of 18.5 h after the infusion of platelets. Ten out of 12 participants who had hematemesis had persistent hemorrhagic nasogastric tube aspirate until endoscopic adrenaline lavage was given. Melena persisted in 6 out of 8 patients for a mean period of 36.8 h after platelet transfusion. Hematuria persisted for the 20 patients for a mean period of 22.2 h. All the 8 patients who had menorrhagia had persistent bleeding for a mean period of 26.4 h and improved a day after oral hormonal therapy. Immediate control of bleeding after platelet transfusion occurred only in 2 patients who had hematemesis (as evidenced by clear nasogastric tube aspirate).

Table 2 describes the baseline platelet and TEG parameters, increments in platelet count, and MA values

Table 2. Platelet count and TEG parameters before and after transfusion

Platelet count and TEG parameters	Random donor platelets (n = 52)	<i>p</i> value ¹	Single donor platelets (n = 22)	<i>p</i> value ¹
Platelet Count, cells/mm ³				
Pretransfusion	22,820±12,218		16,760±7,220	
Increment at 1 h	9,000±3,560	0.027	24,200±2,660	<0.001
Increment at 4 h	12,360±4,680	0.018	26,210±3,582	<0.001
Increment at 12 h	11,220±2,218	0.021	25,310±3,640	<0.001
Increment at 24 h	10,210±3,560	0.028	22,874±2,684	<0.001
Baseline R value in TEG (normal 4–8 min), min	5.4±0.8		5.2±0.6	
Baseline K value in TEG (normal 0–4 min), min	2.1±0.6		1.9±0.5	
Baseline angle in TEG (normal 47–74°), °	54±12		48±10	
Maximum amplitude value in TEG (normal 54–72 mm), mm				
Pretransfusion	26±8		22±4	
Value at 1 h	28±6	0.47	26±3	0.33
Value at 4 h	30±4	0.42	28±4	0.21
Value at 12 h	29±3	0.39	26±4	0.39
Value at 24 h	28±4	0.44	27±4	0.44

¹ Comparison with pretransfusion value.

in each group. Participants who received random donor platelets had a mean platelet count increment of 10,210 cells per mm³ at 24 h from the pretransfusion value, which reached marginal statistical significance ($p = 0.031$). The group which received single donor platelets achieved a mean platelet increment of 22,874 cells per mm³ at 24 h, with the difference observed from the pretransfusion value having a high statistical significance ($p < 0.001$). However, improvement in clot strength as indicated by an improvement in the MA value in TEG was not observed. The mean increment in MA value at 24 h was only 2 mm in the random donor platelet group and 5 mm in the single donor group, both of which did not reach statistical significance. Of the 2 patients (with hematemesis) who appeared to have benefitted from platelet transfusion the MA value increment was only 4 mm (from baseline MA of 24 mm) and 6 mm (from baseline MA of 28 mm), respectively. Follow-up R, K, and angle values remained normal after transfusion for all participants.

The inference from this preliminary study with a small sample of dengue patients who had thrombocytopenia-related bleeding (since we excluded patients with a multifactorial cause for bleeding) is that platelet transfusion, despite producing a 50–100% increment in platelet count, has no significant impact in clinical bleeding and clot strength as assessed by TEG. The majority of patients continued to have persistent bleeding despite platelet transfusion. The study raises a larger question of the status of platelet function in both random and single apheresis platelets prior to transfusion. It appears that the transfused platelets do not have adequate function

to improve clot strength or possible in vivo factors, which do not allow the proper function of transfused platelets. Future studies can incorporate assessment of platelet function in platelet preparations prior to transfusion to determine whether there is a pretransfusion functional defect in platelets. Our study has the significant limitation of not comparing TEG observations with better laboratory studies for platelet function like platelet aggregometry, secretory studies, and flow cytometry [8]. With literature evidence emerging on the delay in platelet recovery in patients receiving platelet transfusions, further studies which analyze platelet function prior to and following transfusion will provide more information on our study observation and clarify the uncertainty on clinical benefits of platelet transfusion in dengue [9].

Statement of Ethics

Written informed consent was obtained from participants as required for a case series observation. Patient confidentiality was maintained as per national guidelines for research involving human participants.

Disclosure Statement

The authors have no conflicts of interest to declare.

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