RESEARCH ARTICLE

Clinical outcomes of prophylactic platelet transfusion in patients with dengue: A retrospective study of patients at a tertiary care hospital in Karachi

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Abstract

Objective: To determine the benefit of prophylactic platelet transfusion on clinical outcomes in patients with dengue fever.

Methods: The retrospective cohort study was conducted at Patel Hospital, Karachi, and comprised record of patients fulfilling World Health Organisation's diagnostic criteria for dengue between 2009 and 2015. We excluded patients with known auto-immune thrombocytopenia, isolated infection with a pathogen other than dengue virus, drug-induced thrombocytopenia and patients requiring therapeutic transfusion. SPSS 21 was used for data analysis.

Results: Of the 639 dengue patients, 209(32.7%) were transfused platelets (group 1) while 430(67.3%) were not (group 2). There was a significant difference in minor bleeding episodes (65(31.1%) in the transfused group vs. 59(13.7%) in the non-transfused group; p=0.000). Similarly, 4(1.9%) patients died in group 1vs. 1(0.2%) in group 2 (p=0.024). The mean cost of hospital stay was Rs26,733±5,780 in group 1 vs. Rs5,266±3,627 in group 2 (p=0.000).

Conclusion: Prophylactic transfusion in dengue patients provided little or no clinical benefit in preventing bleeding complications, and substantially increased medical costs.

Keywords: Dengue; Platelet transfusion; Haemorrhage; Thrombocytopenia. (JPMA 67: 1374; 2017)

Introduction

Dengue infection has emerged as a major public health problem in Pakistan over the past two decades,[1] with the first epidemic reported in 1994.[2,3] Clinical manifestations of dengue vary from asymptomatic infection to self-limiting febrile illness to severe shock.[4] Despite the increasing prevalence and burden of disease, knowledge regarding recognition and management of dengue remains below par.[5]

Thrombocytopaenia is a common feature of dengue infection.[6] It occurs due to immune-mediated response against platelets by dengue specific antigens. This destruction is highly variable.[7]

There are many studies on clinical features and outbreak of dengue in Karachi. However, few studies have examined the role or impact of platelet transfusions; to our knowledge there are no national studies specifically addressing this issue. As a result, there are many misconceptions and irrational management approaches about platelet transfusion in dengue patients.[8] The rationale of platelet transfusion is to overcome the risk of bleeding. Platelet transfusions in the absence of overt bleeding are prophylactic; they are undertaken to prevent the possibility of severe bleeding in patients with dengue infection-related thrombocytopenia. However, bleeding manifestations in dengue are highly variable and do not always correlate with coagulation profile abnormalities.[9,10]

The current study was planned to compare the outcomes (bleeding, mortality, cost of hospital stay and increment in platelet count) of patients receiving prophylactic transfusion with those not transfused.

Patients and Methods

This retrospective cohort study was conducted at Patel Hospital, Karachi, and comprised record of dengue patients from 2009 to 2015. The hospital is a 200-bed private tertiary care hospital which provides 4-year postgraduate training programme in medicine. Patients fulfilling World Health Organisation's (WHO) diagnostic criteria for dengue[11,12] were included who were admitted to adult medicine units of the hospital. Patients with known auto-immune associated thrombocytopenia, isolated infection with a pathogen other than dengue virus (e.g. malaria, salmonella and sepsis from other source); previously known drug-induced thrombocytopenia and patients who had severe bleeding requiring therapeutic transfusion were excluded. Cases in which the patient record was coded for "dengue" but not fulfilling the WHO diagnostic criteria were also excluded.

All patients were divided into two main groups: those having received prophylactic platelet transfusion (group 1) versus non-transfused (group 2). Three sub-groups

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were made on the basis of minimum platelet level of patients: group A) platelet count <10,000/uL; group B) platelet count 10,000-20,000/uL; and group C) platelet count of >20,000.

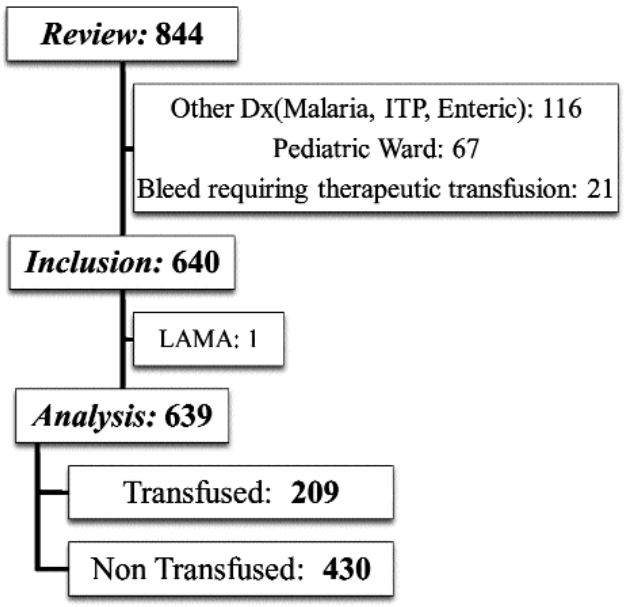
The outcomes were to observe the prevention of bleeding, in-hospital mortality, cost of hospital stay and increment in platelet count after 48 hours or at discharge. Severity of bleeding was categorised on the basis of clinical site and haemodynamic status (Table-1). Besides, we also observed adverse reaction/s of transfusion.

Data was collected through proforma and was filled in by two of the authors from February to April 2016. Dengue diagnosis and management were reviewed in detail prior to collection of data. Data was analysed using SPSS 21. Categorical variable proportions were compared between groups using chi-square with level of significance of 95%. Mean and standard deviation of continuous variables were compared between groups using Student's t-test with confidence interval of 95%. Approval for the study was obtained from the institutional ethics review committee.

Results

Of the 844 patients reviewed, 639(75.7%) were selected. Of them, 209(32.7%) patients were transfused platelets (group 1) while 430(67.3%) patients were not transfused (group 2).

Moreover, 95(14.9%) patients fulfilled clinical criteria, and 544(85.1%) had positive dengue immunoglobulin M (IgM) or non-structural protein 1(NS1).



ITP: Idiopathic thrombocytopenic purpura.
LAMA: Leaving against medical advice.

Table-1: Modified WHO Scale.[12]

Grade 1	Epistaxis/oral bleeding <1 hour duration, occult blood in stool, vaginal spotting, petechiae, microscopic haematuria
Grade 2	Epistaxis/oral bleeding ≥1 hour duration, melena, haemoptysis, purpura > 1inch diameter
Grade 3	Requires RBC transfusion, grossly bloody bodily fluids, asymptomatic CNS bleeding evident on imaging only
Grade 4	Bleeding resulting in joint damage, retinal bleeding with visual impairment, symptomatic CNS bleeding, and/or haemodynamic instability

WHO: World Health Organisation
RBC: Red blood cells
CNS: Central nervous system.

Table-2: Platelet counts of the patients in the transfused and non-transfused group.

	Transfusion (n= 209)	Non Transfusion (n= 430)	P Value
Gender			0.008
Male	155 (74.2%)	274 (63.7%)	
Female	54 (25.8%)	156 (36.3%)	
Age			0.001
<20 years	30 (14.4%)	96 (22.3%)	
21-30 years	74 (35.4%)	186 (43.3%)	
31-40 years	64 (30.6%)	84 (19.5%)	
>40 years	41 (19.6%)	64 (14.9%)	
Clinical Features			
Petechiae	48 (23%)	49 (11.4%)	0.0
Ecchymosis	4 (1.9%)	2 (0.5%)	0.075
Epistaxis	15 (7.2%)	13 (3%)	0.016
Gum Bleed	30 (14.4%)	18 (4.2%)	0
Haematuria	8 (3.8%)	10 (2.3%)	0.282
Retro Orbital Pain	9 (4.3%)	16 (3.7%)	0.72
Rash	37 (17.7%)	84 (19.5%)	0.579
Headache	47 (22.5%)	110 (25.6%)	0.394
Back Pain	13 (6.2%)	34 (7.9%)	0.443
Joint Pain	10 (4.8%)	11 (2.6%)	0.139
Minimum Platelet Counts			
<10,000/uL	33 (15.8%)	0	0
10,000-20,000/uL	116 (55.5%)	19 (4.4%)	
>20,000/uL	60 (28.7%)	411 (95.6%)	

Furthermore, 116(55.5%) of patients in the transfused group had counts between 10,000-20,000/uL. In non-transfused group, 411(95.5%) had counts >20,000/uL (Table-2).

Our primary outcome was to note the efficacy of platelet transfusion in preventing bleeding in patients with dengue. A total of 124(19.4%) patients had minor bleeding equivalent of modified WHO scale grade 1. These included 65(31.1%) from group 1 and 59(13.7%) from group 2 (p=0.000). Among the secondary outcomes,

Table-3: Cost of hospital stay in transfused and the non-transfused group.

	Transfusion (n= 209)	Non Transfusion (n= 430)	P Value
Bleeding	65 (31.1%)	59 (13.7%)	0.000[a]
Mortality	4 (1.9%)	1 (0.2%)	0.024[a]
Increment in Platelet Count at 48 hours or D/C (x10^9uL)*	62.8 ± 39.9	101.7 ± 49.0	0.000[b]
Cost of Hospital Stay (Rupees)*	26733 ± 5780	5266 ± 3627	0.000[b]

[a]Chi-square test. [b]Student's t-test *: mean ± standard deviation
D/C: Discharge.

Table-4: Bleeding and mortality compared between two groups at different platelet counts.

Platelet Count: <10,000/uL

	Transfusion (n= 33)	Non Transfusion (n= 0)	P Value
Bleeding	13 (39.4%)	0	-
Mortality	0	0	-

Platelet Count: 10,000-20,000/uL

	Transfusion (n= 116)	Non Transfusion (n= 19)	P Value
Bleeding	26(22.4%)	4(21.1%)	0.895
Mortality	3(2.6%)	0	0.478

Platelet Count: >20,000/uL

	Transfusion (n= 60)	Non Transfusion (n= 411)	P Value
Bleeding	26(43.3%)	55(13.4%)	0.000
Mortality	1(1.7%)	1(0.2%)	0.113

5(0.8%) patients expired: 4(1.9%) in transfused group and 1(0.2%) in the non-transfused group (p=0.024). Increment in platelet levels noted after two days or at discharge showed mean increase of platelet count 62.8 x 109 ± 39.9 in the transfused group while in non-transfused group mean increase was 101.7 x 109 ± 49.0 (p=0.000). The mean cost of stay was Rs26,733±5,780 in transfused patients and Rs5,266±3,627 in the non-transfused group (p=0.000) (Table-3).

In further subgroup analysis, bleeding and mortality were compared between group 1 and group 2 at different platelet counts i.e. <10,000/uL, 10-20,000/uL and >20,000/ul (Table-4).

Increment of platelets after 48 hours or at discharge and mean cost of hospital stay were compared between these subgroups (Figures-1 and 2).

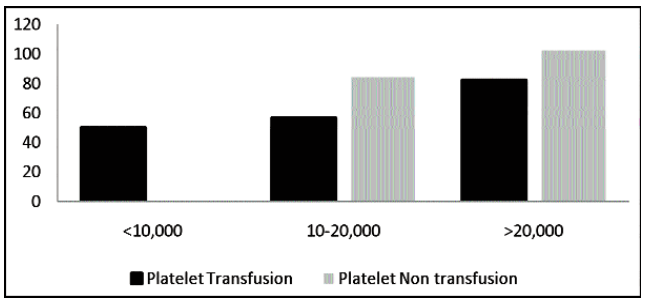


Figure-1: Increment in Platelet Counts (after 48 hours or at discharge).

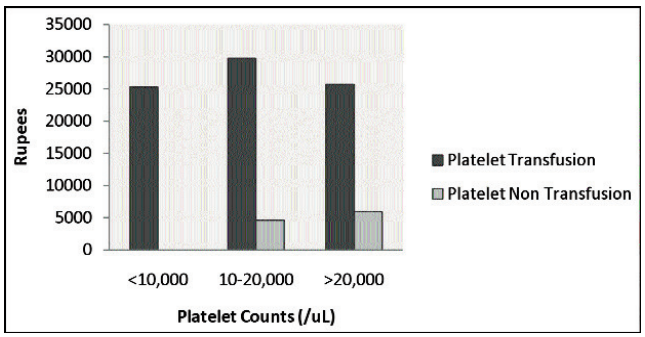


Figure-2: Cost of hospital stay.

Adverse reactions of transfusion like fever, itching and transfusion reactions were noted. Moreover, 11(5.3%) of transfused patients experienced adverse reactions.

Discussion

First reported in Pakistan in 1985, dengue infection has continued to plague the country as a major infection over the past two decades.[12] Despite this, adherence to evidence-based management remains below par.[5] Thrombocytopenia is common and significant fear and panic is associated with this feature both among the general public as well as health professionals caring for them. Evidence regarding management of thrombocytopaenia specific to dengue is lacking and inappropriate transfusions are common.

Our data shows that prophylactic platelet transfusions do not prevent or shorten bleeding in patients with thrombocytopenia secondary to dengue infection. A study in Lahore reached similar conclusion.[4] In another study, Lye et al. reported no significant difference in clinical bleeding episodes between transfused and non-transfused patients.[9] Some people have suggested empirical prophylactic platelet transfusion at counts below 20,000/ul;[10,13] however, it is well documented that there is no correlation between clinical bleeding and platelet count.[14] A recent study confirms the lack of

benefit from prophylactic platelet transfusion in dengue patients with thrombocytopaenia <20,000/ul.[15] Further, patients with lower platelet counts frequently do not respond to platelet transfusion. Guidelines issued by Sri Lanka's Ministry of Health in 2005 discourage platelet transfusions, even with counts <10,000/ul as there is no benefit of prophylactic transfusion[16] while transfusion with a mega-unit or six platelet concentrates leads to an increase in platelet count of 30-50,000/ul. Assir et al. have hypothesised that there is immune-mediated destruction of platelets in dengue; thus patients with low counts (i.e. more severe dengue) will have greater rate of immune-mediated destruction.[4]

In our study, five patients died; 4 (1.9%) from the transfused group and 1(0.2%) from the non-transfused group. This is comparable with observations by other groups where platelet transfusion did not confer any mortality benefit.[16]

In our study, among patients with counts >10,000/ul, mean increase in platelet count was significantly higher in the non-transfused group. This is similar to the results of Lye et al.[9] who found no difference in the median time to achievement of counts >50,000/ul among transfused versus non-transfused groups. However, Assir et al.[4] reported that transfused patients had significantly greater increments in platelet counts at 24 hours as compared to controls; however, this difference was not sustained at 72 hours in "non-responders". They hypothesised that, as "non-responders" had significantly lower baseline platelet counts, they may have had a greater degree of immune-mediated destruction, thus blunting the beneficial effect of platelet transfusion.

A striking difference in cost of stay between transfused and non-transfused groups was observed in our study. Increased cost was largely driven by the cost of transfusion. Thus, if non-bleeding patients are hydrated meticulously, their cost of treatment can be significantly curtailed even if they are treated in the intensive care setting. To our knowledge, no other study has examined the impact of cost of prophylactic platelet transfusion. Our result has great implications for developing countries such as ours where most patients are not covered by health insurance and astronomical medical bills have significant adverse influence on their lives. Even in other healthcare models, bringing down unnecessary hospital costs is a main concern. We hope other groups will add this to their investigations in the future to support or counter our findings.

Moreover, 5.3% of transfused patients experienced mild to moderate adverse transfusion reactions in our study. We noted that most of the patients received pre-transfusion prophylaxis with hydrocortisone and anti-histamines. A study reported 7% adverse transfusion reactions, including one due to transfusion-related acute lung injury (TRALI).[4]

Many studies have found a very high rate of inappropriate platelet transfusion in patients with dengue. In our study we found a high rate of prophylactic platelet transfusion (33.3%); almost every patient with a count of <10,000/uL was transfused (irrespective of bleeding), while a very high percentage (87%) of patients with counts of 10-20,000/uL were transfused. Makroo reported transfusion in 42.6% (32.2% were inappropriate),[10] and Kulkarni reported 78.4% platelet transfusion (51% were inappropriate).[17] Pallavi reported 36.2% inappropriate transfusion.[18] These researchers have cited social pressure, unawareness of guidelines and "dengue panic reaction" as causes for the high rate of unwarranted transfusions, at times leading to serious dearth of blood products for other patients.

To our knowledge, our study highlights two important aspects which had not been examined before: the impact of prophylactic transfusion on cost of medical care and outcomes of prophylactic platelet transfusions in patients with counts <10,000/ul. Also, most groups have reported on a much smaller number of patients; only one other study has examined a similarly large patient group.[16]

The limitations of our study include the fact that this is a retrospective review. There were no non-transfused patients in the group with platelet count <10,000/ul. There were no cases of major bleeding (modified WHO scale grade 2 to 4[12]) in either group. While increased mortality occurred in the transfused group, it can be argued that they may have been more clinically unwell to begin with, thus impacting their final outcome. In addition, the total number of mortalities was low. Cost of hospital stay was not calculated for each patient; it was done for a representative portion of each group and sub-group. We cannot provide accurate insight into adverse effects of transfusion as most patients received pre-transfusion prophylaxis with anti-allergic.

Conclusion

Prophylactic transfusions in dengue patients provided little or no clinical benefit, especially in terms of preventing bleeding complications, and substantially increased medical costs. They may also increase morbidity from adverse effects or mortality. The best approach when treating dengue fever is to hydrate well, be clinically vigilant and ensure cost-effectiveness and evidence-based management.

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Conflict of Interest: None.

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