Prophylactic Platelet Transfusion in Stable Dengue Fever Patients: Is It Really Necessary?

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Abstract Our hospital is a referral centre for Jehovah's Witnesses (JW) patients, who as a matter of religious belief refuse transfusions of blood/blood components. We have treated JW patients with dengue fever (DF) and thrombocytopenia without platelet transfusion, without any mortality or major morbidities. We retrospectively compared the duration needed for platelet recovery and duration of hospitalization of DF with thrombocytopenia in those treated with prophylactic platelet transfusion and JW patients who were managed without these. Among JW patients, platelet counts recovered to $>50,000$ in 2.57 days (Mean) as compared to those who received prophylactic platelet transfusion, who recovered in 4.43 days (P value < 0.0001). They also had significantly less number of days of hospitalization (3.68 days vs 5.13 days, P value < 0.0001). These differences persisted even when a subgroup analysis

of patients who had nadir platelet count less than 10,000 were done. Most importantly, none of the patients in either group suffered any significant morbidity or mortality. Prophylactic platelet transfusion in clinically stable DF patients was associated with significant delay in platelet recovery and increased duration of hospitalization, even though was not harmful in terms of morbidity or mortality. Though number of subjects involved in the study was small, this brief report further adds to the current evidence that prophylactic platelet transfusion in clinically stable DF patients with a platelet count more than 10,000/cmm is not indicated.

Keywords Dengue fever (DF) · Jehovah's Witnesses (JW) · Platelet transfusion (PT)

Introduction

DF is endemic and is the cause of significant morbidities and mortality in India. In recent years DF cases are increasing alarmingly in various parts of the country including rural areas. The disease is now endemic in 21 states/Union territories [1]. As the disease is spreading to newer areas, not only are the number of cases and deaths increasing, but explosive outbreaks are occurring. In the absence of any specific treatment or vaccine, proper management of cases is crucial in DF. Even though the Directorate of National Vector Borne Diseases Control Programme under Government of India, in consultation with WHO SEARO has brought out broad guidelines [1], on management of dengue fever, the majority of the cases are treated according to the expert opinions of individual physicians. Most importantly there are vast differences in the management of thrombocytopenia in DF even though the guidelines clearly state that platelet transfusions are not

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needed until the platelet count is less than $10,000/\text{mm}^3$ in a patient without clinical bleeding. It is not uncommon among physicians to give platelet transfusions for stable Dengue patients who rapidly drop their platelet counts to $<50,000/\text{mm}^3$ prophylactically. Whether this prophylactic platelet transfusion is of any benefit to the patient is debatable. Hence this brief report to draw the attention of the physicians who treat the stable Dengue patients with prophylactic platelet transfusions as per expert opinions.

Rationale for the Study

Lye et al. [2] in a retrospective study analysed the prophylactic platelet transfusion among their DF patients and concluded that there was no benefit from prophylactic platelet transfusion in adult DF patients. It is increasingly realized that one of the factors causing thrombocytopenia in DF is immunological destruction of platelets and megakaryocytes [3, 4], in which case prophylactic platelet transfusion may have a deleterious impact on disease course. Also by giving prophylactic platelet support, the patient will be subjected to increased risk of transfusion related complications. Increasing utilization of platelet concentrates for prophylactic use has resulted in severe shortage of platelet rich plasma for treatment of other conditions like Aplastic Anaemia and Leukaemia [5], along with significant economic burden to the society. Hence, we need full justification before giving prophylactic platelet transfusion for stable Dengue fever patients without clinical bleed.

The Department of Haematology at Narayana Hrudayalaya, Bangalore is a referral centre for treatment of patients who belong to the JW group. We had treated JW patients with DF conservatively in spite of platelet counts being less than $10,000/\text{mm}^3$ and had good success. There is not much literature on JW patients with DF and no one till date has done a comparison of DF in JW and non-Jehovah's Witness (NJW) patients.

Objectives

To compare the patients with dengue fever with thrombocytopenia who belonged to the JW group, with age and severity matched NJW DF patients who were treated with prophylactic platelet transfusions.

Materials and Methods

This retrospective comparative study was conducted in Narayana Hrudayalaya Hospital, Bangalore, in the Department of Internal Medicine and Department of Haematology.

All the case records of serologically confirmed DF patients who were treated between June 2009 and Dec 2010 were reviewed. The diagnosis was established by positivity of Anti Dengue IgM antibodies and/or positive NS1 antigen assay. Only stable patients between 18 to 45 years of age without any active clinical bleeding, who fulfilled the criteria for DF by WHO with admission Platelet count less than $50,000/\text{mm}^3$ were selected. All those stable patients who had clinical bleeding or those with DHF/DSS (Dengue Hemorrhagic fever/Dengue Shock Syndrome) as per WHO definition were excluded. Moreover, the patients with Acute/Chronic Renal Failure, Endocrinopathy, Obstructive airway disease, Sepsis and Co-infection with Malaria/Leptospirosis/Hepatitis were excluded to avoid the bias as they themselves may cause thrombocytopenia. The patients were then categorized into two groups, one Jehovah's Witnesses (JW) and the other non-Jehovah's Witnesses (NJW).

From the case records, the following parameters were assessed and compared between the groups: Age, Sex, Peak Haemoglobin, Peak Hematocrit, Nadir Platelet Count (before Platelet Transfusion in NJW group), Nadir Total Leukocyte Count, Number of Units of Platelet Transfused, Platelet count drop after PT (in NJW group), Days needed for Platelet recovery $>50,000/\text{mm}^3$ from nadir, Days needed for Total Leukocyte Count recovery $>4,000/\text{mm}^3$, and Total Duration of Hospitalization.

Statistical Analysis

The statistical analysis was done using the SPSS for Windows Evaluation Version 15. The difference between the two groups was analyzed using the Independent Samples test, Levene's Test for equality of variances and *t* test for Equality of Means.

A *P* value <0.05 along with 95 % confidence intervals were considered statistically significant.

Results

A total of 202 patients were treated for DF from June 2009 to December 2010 at our centre. 30 patients belonged to JW of whom 28 were eligible for comparison. In the rest of the 172 patients, 23 were eligible for analysis. The baseline characteristics of the patients who were eligible for comparison is given in Table 1. The severity of the disease was determined using parameters, (a) absence of clinical bleeding, (b) severity of hemo-concentration and (c) absence of end organ damage. The patients in both the groups were comparable with regards to age and severity of disease.

The duration of hospitalization, number of days needed for the platelets to recover above $50,000/\text{mm}^3$ and number

Table 1 Baseline Characteristics

	JW	NJW	<i>P</i> value
No. of patients	28	23	–
Mean age (years)	28.5 (18–44)	29 (18–38)	0.781
Males	17 (60.7 %)	19 (82.6 %)	–
Females	11 (39.3 %)	4 (17.4 %)	–
Mean peak Hb (gm %)	15.41 (12.2–19.1)	15.95 (11.6–18.6)	0.301
Mean peak Hct (%)	45.13 (35.8–55.8)	47.22 (35.5–54.8)	0.164
Mean nadir PLT count (/mm ³)	19,178 (6,000–38,000)	17,608 (4,000–37,000)	0.552
Mean nadir WBC count (/mm ³)	4,862.5 (2,000–10,000)	5,747.2 (1,100–13,900)	0.263
PLT transfusion	Nil	100 %	
Subgroup analysis			
% Pts <30 years of age	60	52.2	
% Pts with Hb >16 gm%	46.5	47.8	
% Pts with Hct >45 %	57.4	78.3	
% Pts with nadir PLT <20,000	71.4	73	
% Pts with nadir PLT <10,000	21.4	26.1	
% Pts with TLC <4,000/cmm	46.6	43.5	

Range is given in parenthesis

JW Jehovah's Witnesses, *NJW*

Non-Jehova's Witnesses, *Hb*

haemoglobin, *Hct* hematocrit,

PLT platelet, *TLC* total

leukocyte count, *Pts* patients

of days needed for Total leukocyte count to recover above 4,000/mm³ were assessed and compared between the two groups. The results are shown in Table 2. Among JW patients, who received no PT, platelet counts recovered to >50,000 in significantly less time (2.57 vs 4.43 days, $P < 0.0001$) as compared to NJW patients who received prophylactic PT. They also had significantly less number of days of hospitalization (3.68 vs 5.13 days, $P < 0.0001$). The days needed for the recovery of total leukocyte count was not significantly different. Most importantly, none of the patients in either group suffered any significant morbidity or mortality. A subgroup analysis of the patients who had a nadir platelet count less than 10,000/cmm in either group was done and the results are given in Table 3. There were six patients each in both arms with a nadir platelet count of less than 10,000/cmm. The significant differences noted between the two groups in terms of mean duration needed for platelet recovery and mean duration hospitalization persisted even in the subgroup analysis, confirming the possible benefits of not transfusing platelets on a routine basis.

Furthermore 89.9 % of patients platelet count recovered to >50,000/cmm in 3 days in JW group as opposed to only 6 % of patients in NJW group. None of the patients had drop in platelet count after admission in JW group as opposed to 65 % patients in NJW group. All these NJW patients had received prophylactic PT before drop in platelet count. The median number of random units of platelets transfused was five with a range of 2–14 units. Surprisingly, 17.4 % of patients in NJW group dropped total leukocyte count also after PT indicating a possible immunological reaction. There were no incidence of Platelet refractoriness or transfusion associated complications. Again, the paradoxical drop in

platelet count or total leukocyte count did not lead to any complications. There was fall in Haemoglobin levels of patients in both the groups, secondary to correction of hemoconcentration. Incidentally, the two patients excluded from the study in JW group due to co-existence of Sick cell disease in one and Beta Thalassemia major in the other also recovered in 3 days on conservative management only.

Discussion

In the retrospective study by Lye et al. [2], there was no major difference between the patients who received PT as opposed to those who did not receive PT. After PT, the median platelet increment the next day was lower than the platelet increment in patients who did not receive PT. Comparison was made with the day after the platelet count dropped to <20,000/mm³ in those who did not receive platelets. The median length of hospital stay was 6 days for patients given PT, compared with 5 days for patients not given PT. One patient died in the group given PT, compared with none in group not given transfusion. However these differences were statistically not significant. This was probably because their study included DF patients who had DHF/DSS and also those with co-morbidities were not excluded. Our study also showed similar results but, with statistical significance. We could not assess the median platelet increment post transfusion. But the fact that 65 % of the patients who received platelet transfusions had a paradoxical fall in platelet count boosts the theory that one cause for thrombocytopenia in Dengue is immunological destruction of platelets. This phenomenon is very similar to what happens when PT given to ITP patients. Though there

Table 2 Final analysis results

	JW	NJW	<i>P</i> value
No. of Pts	28	23	
Mean duration of PLT recovery (days)	2.57 (1–4)	4.43 (2–6)	<0.0001
Mean duration of hospitalization (days)	3.68 (2–6)	5.13 (4–9)	<0.0001
Mean duration of WBC recovery (days)	0.89 (0–2)	1.52 (0–4)	0.121
Clinical bleeding	Nil	Nil	
End organ damage	Nil	Nil	
ICU admission	Nil	Nil	
Mortality	Nil	Nil	

Range is given in parenthesis

Table 3 Final analysis results of subgroup of patients who had nadir platelet count less than 10,000

	JW	NJW	<i>P</i> value
No. of Pts with PLT <10,000	6	6	
Mean duration of PLT recovery (days)	3 (2–4)	4.5 (4–4)	0.001
Mean duration of Hospitalization (days)	3.68 (2–5)	5.13 (4–7)	0.009

Range is given in parenthesis

was no major morbidity or mortality secondary to prophylactic PT, the prolonged platelet recovery and increased duration of hospitalization resulted in increased economic burden on the patient's family. The prospective observational study by Thomas et al. [6] showed that a restrictive strategy for PT based on clinical features and low platelet count thresholds is feasible and safe for adult DF patients. Another large scale ongoing prospective randomized trial by Lye et al., Adult Dengue Platelet Study (ADEPT) will surely throw more light on this subject.

There is wide variation in prophylactic PT among physicians. Kumar et al. [7] in a retrospective observation study of transfusion practices during DF epidemic note that only 25 % PT requests had information on platelet counts. In 65 % of cases, history of active clinical bleeding was not obtained. Up to 35 % of patients received unnecessary PT and 89 % of times inappropriate doses of platelets were given. The results of this study can be extrapolated to most parts of India and it indicates the poor knowledge regarding PT among the treating doctors and the need for increased awareness on this subject. This also explains why there's severe shortage of blood products during epidemics of DF. The "not to take any chance" approach should therefore be abandoned to give way for an evidence based practice.

Moreover, as suggested by several studies, there is no much correlation between the degree of thrombocytopenia and bleeding tendency in Dengue Haemorrhagic fever. However, the recovery of platelet count correlates with clinical improvement [8, 9]. Our study assumes greater importance in the background of above study. With more stringent policies for prophylactic PT, not only do we avoid unnecessary transfusions, but also the transfusion associated complications. On a larger perspective, this will avoid the deficits in blood products for the patients in greater need like those with DHF/DSS or aplastic anaemia.

Conclusions

Managing Stable DF patients with thrombocytopenia in absence of active clinical bleeding conservatively without PT is safe. Routine prophylaxis with platelet support whilst is reasonably safe, results in prolonged hospitalization with increased economic burden to the patient and to the society. Judicious use of PT in DF will reduce the severe shortage of blood products during Dengue epidemics.

Conflict of interest None.

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