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RECOVERY TIME OF PLATELET COUNT AND IMPACT OF PLATELET TRANSFUSION IN PEDIATRIC DENGUE PATIENTS WITH THROMBOCYTOPENIA

Paediatric Medicine

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ABSTRACT

Objective: Thrombocytopenia is common and self-limited in dengue. However, the time taken to recover from thrombocytopenia isn't clearly known. The present study was conducted to determine platelet recovery time and effect of platelet transfusion in pediatric dengue.

Methods: It was an observational descriptive study on admitted pediatric dengue cases (≤12 years), conducted at a tertiary care center (July, 2019 – June, 2020). One hundred and thirty-two patients were followed up regarding their serial platelet counts, time taken to recover from thrombocytopenia and signs of fluid leak/bleeding manifestations. The entire cohort was then classified into 4 groups namely, uncomplicated dengue (UD), platelet transfused uncomplicated dengue (PTUD), complicated dengue (CD) and platelet transfused complicated dengue (PTCD). The platelet recovery time, effect of platelet transfusion and degree of thrombocytopenia in dengue cases was then analyzed.

Results: Thrombocytopenia was observed in 86 (65.2%) patients and was mild/moderate (93%) in majority. The lowest platelet count recorded was 65,731(± 18,238)/cmm, 27,083 (±13,162)/cmm, 46,409 (± 18,528)/cmm, and 26,666 (± 1,211)/cmm in UD, PTUD, CD and PTCD group respectively. All (100%) CD and PTCD had fluid leak. Systemic bleeding was noticed in all PTCD even with moderate thrombocytopenia. Platelet transfusion resulted in longer platelet recovery time in uncomplicated dengue [2(0.9) vs 3(0.9) days, p=0.01] and complicated dengue [2.4(0.8) vs 4.7 (01.9), p value= 0.001].

Conclusions: The complications in dengue are mostly due to fluid leak. Absolute platelet counts alone, may not serve as predictor of systemic bleeding and injudicious platelet transfusion resulted in delayed recovery.

KEYWORDS

INTRODUCTION:

Dengue is a vector borne disease, described first in India in 1956. Following rapid urbanization, dengue outbreaks have progressively increased. Presently, pan India is facing a surge of dengue fever and the strain is also changing with time, [1,2,3,4]. Although most dengue fevers are benign, few may develop severe dengue, [5]. Dengue fever associated with low platelet counts often creates panic amongst doctors aggravated by anxiety of parents, [6]. Although there are national guidelines, occasionally platelet transfusions tend to given inappropriately due to lack of literature on normalization of platelet counts in dengue with thrombocytopenia and complications associated with degree of thrombocytopenia. Hence, we attempted to find out the platelet count recovery time, the degree of thrombocytopenia and the effect of platelet transfusion in pediatric dengue fever.

Aim of the Study:

1. To determine platelet recovery time in pediatric dengue patients
2. To determine the effect of platelet transfusion in pediatric dengue patients

MATERIAL AND METHODS:

This observational descriptive study was conducted (July, 2019 – June, 2020) at our hospital after clearance from the institutional ethics committee. The inclusion criterion was inpatient NS1 positive Dengue fever. NS1 tests were done by *DENV Detect ™ NS1 ELISA – INBIOS International*. Viral RNA was extracted by *QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany)*. Serotyping of Dengue virus (DENV1, DENV2, DENV3 and DENV4) was done by Nested RT-PCR according to the method of Lanciotti et al. 1992. Those who received platelet transfusion prior to admission and those with co-infections were excluded from the study.

Each child was treated by the treating physician of the respective unit. Thrombocytopenia was defined as having platelet counts < 1 Lakh/cmm [Mild (≥ 50000/cmm), Moderate (20,001-49999/cmm) and Severe (≤20000/cmm)] for the present study. Platelet counts were done daily in patients with thrombocytopenia till count >1 lakh/cmm via an automated hematology analyzer (*Horiba Pentra ES60*) along with manual confirmation via the same pathologist. Platelet recovery time (PRT) was the time (days) taken by the immunological system of the patients to return to a platelet count ≥ 1 lakh/cmm from < 1 lakh/cmm.

The Indian national guidelines for clinical management of dengue fever 2015 were referred upon to decide on the appropriateness of platelet transfusion [7]. The whole cohort was then divided for the purpose of study into four groups. Henceforth they will be called as Uncomplicated Dengue (UD) i.e., Dengue Fever with thrombo cytopenia only/minor bleeding manifestations like petechiae/ gum bleed, Complicated Dengue (CD) i.e., Dengue Fever with thrombocy topenia and signs of fluid leak or systemic bleeding, Platelet transfused Uncomplicated Dengue (PTUD) i.e., Uncomplicated dengue cases received platelets, and Platelet Transfused Complicated Dengue (PTCD) i.e., Complicated Dengue cases received platelets. The data was managed and analyzed using IBM Statistical Package for Social Sciences (SPSS version 25.0, SPSS, Inc., Chicago, IL, USA) for Macintosh. Frequency and percentage for categorical variables were calculated. Student T test was used to compare degree of thrombocytopenia and platelet recovery time amongst various groups.

RESULTS:

Of the 148 dengue NS1 positive patients admitted during the study period, seven were excluded [Coinfections (Scrub typhus four, Chikungunya two), Platelet transfusion prior to admission one], five left against medical advice and four died. The study was then performed on 132 subjects [50% females, 7.7 (3.1) years, 0.3-12 years]. Serotyping of the subjects revealed majority infections caused by subtype 2 [DENV2 (78.3%), DENV3 (11.2%), DENV1 and DENV4 (5.3%) each].

Out of the study cohort, 86 (65.2%) had thrombocytopenia [6 (7%) Severe, 28 (32.5%) Moderate and 52 (60.5%) Mild. The groups UD, PTUD, CD and PTCD had 54, 6, 20 and 6 patients respectively (Table 1).

Table 1: Degree Of Thrombocytopenia Amongst Various Groups

Thrombocytopenia	UD	CD	PTUD	PTCD
Mild (52)	42	10	-	-
Moderate (28)	10	10	2	6
Severe (6)	2	-	4	-

The lowest platelet count observed was 65,731(± 18,238)/cmm, 27,083 (±13,162)/cmm, 46,409 (± 18,528)/cmm, and 26,666 (± 1,211)/cmm in UD, PTUD, CD and PTCD group respectively (Figure 1).

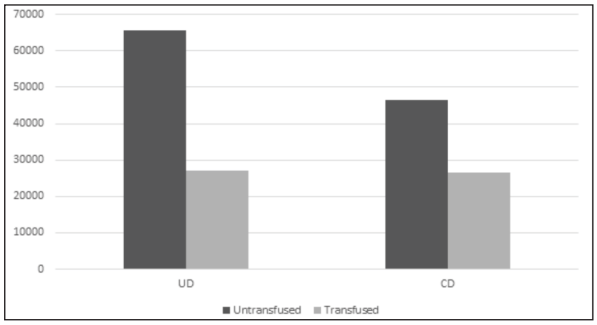

Figure 1: Comparison of platelet counts among uncomplicated and complicated Dengue

The severity of thrombocytopenia was significantly more in CD group when compared to UD group (p = 0.000). The groups transfused platelets also had significantly more thrombocytopenia [PTUD vs UD (p=0.000) and PTCD vs CD (p=0.002)]. The lowest platelet count was reached on day 5.5 (± 1.4), 6.7 (± 0.5), 7.5 (± 2.8) ,4.7 (± 0.5) in UD, PTUD, CD and PTCD respectively. Platelet transfusion resulted in longer platelet recovery time in uncomplicated dengue [2(0.9) vs 3(0.9) days, p=0.01] and complicated dengue [2.4(0.8) vs 4.7 (01.9), p value= 0.00]. Amongst the four cases who died, two cases had severe thrombocytopenia and moderate thrombocytopenia each.

There were 28 (21.2%) and 104 (78.8%) patients in the age groups of 0-5 and 6-12 years respectively. The incidence of CD in the age groups of 0-5 and 6-12 years was 7.1 % and 19.2 % respectively but this association was not statistically significant (p=0.11). All (100%) PTCD were in the age group of 6-12 years.

Only four (20%) CD had systemic bleeding as against all (100%) in PTCD while fluid leak was found to be common to all CD and PTCD cases. The clinical cause of death in each of the four cases was intractable shock from fluid leak. None of the subjects had clinical evidence of intracranial bleed even with platelet count of < 20,000/cmm.

DISCUSSION:

Our study shows that thrombocytopenia in dengue is transient, mild to moderate (93%) in severity and uncomplicated in most (62.8%). Platelet transfusions in hemodynamically stable children with low platelet counts (>10,000/cmm) is common although inappropriate as per national guidelines, [3]. Studies have shown that avoiding platelet transfusions in a hemodynamically stable child even with platelet count of <20,000/cmm is not associated with increased complications, [7, 8]. Our study found 50% inappropriate and inadequately dosed platelet transfusions (Table 2) with all (100%) PTUD cases being transfused platelets due to

Table 2: Indication Of Platelet Transfusion And Dosing Of Platelets (n = 12)

*Grp**	*Platelet count*	*Bleeding manifestations*				*Indication*	*Platelet units*		*DOP§*
		Petechiae	*Melena*	*Hematuria*	*GB†*		*Required*	*Received*	
PTUD	45000	✔				Petechiae	3	3	✔
PTUD	18000					LPC ‡	3	3	✔
PTUD	20000	✔				LPC	2	2	✔
PTUD	17000					LPC	5	5	✔
PTUD	19500	✔				LPC	3	3	✔
PTUD	43000	✔			✔	Petechiae	2	2	✔
PTCD	26000	✔	✔			GI bleed	6	4	X
PTCD	26000	✔	✔	✔		GI bleed	7	6	X
PTCD	25000		✔			GI bleed	4	3	X
PTCD	27000		✔			GI bleed	8	4	X
PTCD	28000	✔	✔			GI bleed	4	3	X
PTCD	28000	✔	✔	✔	✔	GI bleed	5	4	X

***Group**
†Gum Bleed
‡Low Platelet Count
§Dose of Platelets

severe thrombocytopenia alone similar to previous studies, [9,10]. This can therefore contribute to acute platelet shortages during dengue outbreaks in subjects actually needing platelet transfusions. The reasons of inappropriate platelet transfusions in our study were non-life-threatening bleeding manifestations like gum bleeding, petechiae and low platelet counts. Inadequate dosing of platelets to the tune of 89 % was also reported by Kumar ND, underscoring the need for regular awareness programs to reemphasize the need of protocol-based management of dengue amongst treating physicians, [10]. The present study also found that platelet transfusions were given when counts were actually recovering. Therefore, knowing the natural history of platelet recovery time in dengue will aid in clinical management and curtail treatment costs.

Our study is unique as we have found out PRT for different categories of dengue patients [UD 2(0.9); PTUD 3(0.9); CD 2.4(0.8) and PTCD 4.7 (1.9) days]. Spontaneous platelet recovery time in primary and secondary dengue cases have been found to be 3 (± 2.6) days and 3 (± 1.87) days respectively, [11]. Our study did not classify dengue cases as primary or secondary due to economical constraints.

In our experience PRT varied with disease category with CD group taking longer to recover when compared to UD group. Prophylactic platelet transfusions led to significantly longer time to recover from thrombocytopenia [UD 2(0.9) vs 3(0.9) days, p=0.01 and CD 2.4(0.8) vs 4.7 (01.9), p value= 0.00] similar to a previous finding, [8]. It is difficult to explain the reason of this observation. The severity of disease process and/or platelet transfusion may be responsible for it.

Even though all PTCD had moderate thrombocytopenia, they had systemic bleeding like melena and hematuria. This lends credence to the study findings of platelet dysfunction being the cause of bleeding in Dengue rather than absolute decrease in platelet count, [13,14]. So, although low platelet count is a prominent hemostatic defect responsible for bleeding, thrombocytopenia does not reliably predict bleeding in dengue infection, [15,16,17]. The ability of platelet transfusion to prevent development of severe bleeding or shorten the time to cessation of bleeding has also been questioned in recent times, [18]. Therefore, transfusing platelets in subjects with clinically significant bleeds causing hemodynamic compromise alone is the appropriate step till other modalities of treatment are discovered. Also, all (100%) CD and PTCD had fluid leak so clinical monitoring should be given the highest priority as deaths occur mainly due to fluid leak leading to intractable shock.

Our data shows significantly higher rates of CD in the age group of 6-12 years. This is unlike a previous study conducted in 2016 which showed higher rate of complications in the lower age group, [12]. This association may be related to the changing strain of Dengue. DENV 2 was predominant in our study unlike previous where DENV 3 was common, [4].

Ours being an observational study and due to ethical issues, platelet transfusion was not withheld in hemodynamically stable patients with melena post admission (PTCD). However, we had four patients with pre-admission melena and thrombocytopenia but asymptomatic at admission (CD) who recovered uneventfully. So, a prospective study needs to be done to ascertain whether platelet transfusion is required in all dengue with melena or if time equal to the average PRT can be allowed for observation of these patients before platelet transfusion, in cases where they maintain stable hemodynamics.

Limitations

The limitations of our study are a very small sample size with respect to the volume of dengue cases per year in the Indian setting. The generalizability our of findings also remain unclear as we had only six patients of severe thrombocytopenia. The unavailability of emergency

imaging techniques to identify intracranial bleeds also remains a drawback.

CONCLUSIONS

Dengue remains a predominantly benign disease even with its exploding numbers. Platelet counts alone may not predict bleeding and platelet transfusions may delayed PRT. Therefore, with clinical monitoring the mainstay and transfusing platelets in those having systemic bleeding with hemodynamic compromise is the best present bet to save lives.

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