Research Article

Dengue: platelet and immature platelet dynamics a study done at a tertiary care centre from South India

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Abstract

Background: Thrombocytopenia is a common haematologic abnormality in dengue which demands platelet transfusion. Platelet transfusion though life saving has its own hazards so that unnecessary usage is to be avoided. There is a need to find out a laboratory parameter which can predict platelet recovery. **Aims and objectives:** We aim to study the platelet and immature platelet dynamics and the immature platelet fraction **Methods:** This is a observational descriptive study done in 2012 on all the dengue patients who were positive for NS1 antigen or IgM antibody or both and treated at Sri Ramachandra Medical Center. The values of platelet and IPF were retrieved for day 1st, 3rd, 5th and 7th day of admission Association between values of IPF and significant clinical change in platelet values during the subsequent 48 hrs is done. A sensitivity analysis was carried out to ascertain the cut-off of IPF on the corresponding days which yielded increase in platelet values of over 20,000 in the subsequent 48 hours. **Results:** There is statistically significant ($P < 0.01$) improvement in platelet values within 48 hours when the IPF is more than 6.1% If the IPF value is more than 6.25% and10.6% there is 67% and100% chance of platelet recovery within 48 hours respectively. **Conclusion:** IPF is an additional parameter to predict platelet recovery, so that prophylactic platelet transfusion can be deferred and also the hazards associated with it.

Keywords: Dengue, platelets, immature platelet fraction, platelet transfusion.

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INTRODUCTION

Dengue is a mosquito borne viral infection with potential fatal complications. According to the ministry of health, India there were 50,000 dengue cases including 227 deaths in the year 2012. Among them 5376 cases were reported from Tamilnadu as per the national vector borne diseases control program of which Chennai reported 988 cases. The main hematological abnormalities in dengue are thrombocytopenia and leucopenia[1]. Thrombocytopenia is often symptomatic demanding platelet transfusion. As there is inherent risk associated with platelet transfusion, it is imperative to define precise criteria and transfusion trigger for platelets in dengue patients[2]. Immature platelets are recently released platelets with high RNA content[3]. The immature platelet fraction (IPF%) is raised in diseases where there is increased platelet destruction and consumption. It is decreased in marrow failure[4]. The IPF% can predict the timing of platelet recovery. The platelet recovery time is 1-2 days of IPF increase[5,6]. The cut off value above which platelet recovery is expected is yet to be validated. The IPF is identified by Sysmex XE2100 hematology analyzer in the reticulocyte channel using a fluorescent dye and a carefully designed gating system and counted by a special software termed IPF master[7].

AIM AND OBJECTIVES

With the burden of dengue fever in India, demanding platelet transfusion, we aim to study the platelet and immature platelet dynamics and the immature platelet

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fraction cut off to predict platelet recovery so that platelet transfusion can be deferred.

MATERIALS AND METHODS

This is a observational descriptive study done at the department of pathology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University, Porur, Chennai, South India where information were collected from records for the period from January to December 2012. This study is approved by the Institutional Ethics Committee. The study population includes all the dengue patients who were positive for NS1 antigen or IgM antibody or both and treated at Sri Ramachandra Medical Center and Sri Ramachandra Medical College Hospital. The patients details were retrieved from the hospital in patient management system. The platelet count and IPF were retrieved from System XE2100 hematology analyzer (Sysmex, Koba, Japan). The values of platelet and IPF were available for day 1st, 3rd, 5th and 7th day of admission for each patient.

The patients were grouped into 5 categories according to their platelet counton the day of the admission[2].

High risk	< 20,000/c.mm
Moderate	> 20,000 – 40,000 / c.mm
Low risk	> 40,000 – 1,00,000 / c.mm
No risk	> 1,00,000 – 1,50,000 / c.mm
Normal	> 1.5 lakhs / c.mm

A platelet value of < 1,50,000 was considered as thrombocytopenia. For this study a change in platelet value of more than 20,000 count in 48 hrs was considered as a clinically significant change. For the IPF a value>6.1% was considered as a high IPF value. Data were entered in Microsoft Excel 2010 and analysed in GNU PSPP 0.82. Descriptive analysis was initially performed. This was followed by associating between high values of IPF and significant clinical change in platelet values during the subsequent 48 hrs. This analysis was carried only in the thrombocytopenics. Further a sensitivity analysis was carried out for observations of platelet below 1.5 lakh for all patients (n=386) for Day 1, 3 and 5 and ascertained the cut-off of IPF on the corresponding days which yielded increase in platelet values of over 20,000 in the subsequent 48 hours.

RESULTS

286 dengue patients positive for IgM antibody or NS1 antigen or both are treated. Dengue was more common below 5 years (55%) and among males (61%). The patients who had thrombocytopenia on day1 were 174 (60.8%). Among them 54 (31%) were of no risk category and 120 (69%) were in the risk group. This 120 patients are grouped into risk categories (Figure 1). 78.3% were in the low risk, 11.7% in the moderate risk and 10% in the high risk groups. On day 3,5 and 7 the risk categories improved with 78.3% (69.5% low, 8.3% moderate, 0.5% high) 49.2% (46.7% low 2.5% moderate 0.5% high), 49.2% (46.7% low 2.5% moderate) and 16.7% (16.7%, low) patients on day 3,5 and 7 respectively.

Among the non-thrombocytopenic patients on day 1 of admission, 94% remained non thrombocytopenic till 7th day; 6% had low platelets on day 3 (5.2%in low risk, 0.8% in moderate risk). 2% had thrombocytopenia on day 5 (2%in low risk). The IPF was higher than normal range (>6.1%) for 56.7% of the patients on day 1. The IPF was increased for 69.2% and 72.5% of patients on day 3 and 5. (Figure 2) Table 1 shows 55.9% of patients with high IPF showed a change in risk category, but 9.6% of patients with < 6.1% showed change. 41.2% of patients with high IPF showed no change and 2.9% showed change to high risk with fall in platelets.60% of the patients with high IPF who did not show platelet increment on day 3, (i.e. 24.75% of day 1 high IPF) showed increment on day 5. There is statistically significant (P < 0.01) improvement in platelet values within 48 hours when the IPF is more than 6.1% It was observed that in thrombocytopenia a cut off value of IPF more than 6.25% yield maximum positive likelihood ratio. The sensitivity, specificity and positive predictive value (PPV) for the cut off was 77%, 63% and 67%. A PPV of 67% indicates that if the IPF value is more than 6.25%, there is 67% chance of platelet recovery within 48 hours. If the IPF is more than 10.6% there is 100% chance of platelet recovery within 48 hours.

Figure 1: Platelet level categories on various days in risk group (n=120)

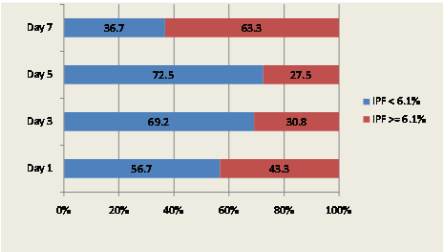

Figure 2: Immature platelet fraction level categories on various days in risk group (n=120)

Table 1: Association between change in platelet category from day 1 to 3 and day 1 IPF value > 6.1%(n=120)

	Day 1 to 3 Change in platelet category			
Day 1 IPF >=6.1	>=20000	-20000-<20000	<=20000	Total
>=6.1%	38.0	28.0	2.0	68.0
	55.9%	41.2%	2.9%	100.0%
<=6.1%	5.0	44.0	3.0	52.0
	9.6%	84.6%	5.8%	100.0%
Total	**43.0**	**72.0**	**5.0**	**120.0**
	35.8%	**60.0%**	**4.2%**	**100.0%**

DISCUSSION

Dengue was more common below 5 years (55%) in the present study. A study from Brazil reported more patients below 10 years whereas Pakistan study group reported it to be common in adults[8,9]. In this study males (61%) were more commonly affected like a report from Delhi in 2006[10]. A study from Brazil has more number of female patients[11]. In the present study thrombocytopenia was noted in 60.8% of patients on day 1 of admission. Francisca R.F. *et al* and Ahmed S. et. Al observed thrombocytopenia on the 4th day and between 3rd and 8th day of the disease[8,11]. However in our study as we collected data from the first day of admission only, prior clinical illness was not evaluated. The platelet counts were in the risk category for more patients on day 1, with 10%, 11.7% and 78.3% in the high, moderate and low risk group. Grouping of patients under the risk category is essential as high risk patients receive prophylactic platelet transfusion and moderate risk group when they are symptomatic. As per the Director of Health Services (DHS) guidelines also platelet transfusion trigger is < 20,000/ c.mm. Makroo R N *et al* concluded in his study that all hospitalized patients can be grouped into high, moderate, low and no risk[2]. The trend of platelet counts was on the increase with risk category becoming favorable reaching normal count or no risk category on 7th day. Ahmed S *et al* had found platelet increment on the 7th day while Francisia F *et al* observed only by 11th day[8,11]. The patients who had normal count on the day of admission can show platelet fall as the present study states 6% on day 3 and 2% on day 5. This indicates monitoring the platelet count for a minimum of one week from the day of admission is essential. Immature platelets are reticulated platelets, presences of which show the thrombopoietic activity of the marrow. This is similar to reticulocytes which predict erythropoietic acitivity. The immature platelets are measured as percentage of platelets or absolute counts. Sarah J B *et al* reported IPF as an indicator of thrombopoietic state whereas Briggs C *et al* concluded that recovery from thrombocytopenia in chemotherapy and transplant patients was preceded by increase IPF %[12,13]. The IPF is identified by flow cytometery technique using a nucleic acid specific dye in the reticulocyte / platelet optical channel. This application is available in the XE 2100 blood cell counter with upgraded software (Sysmex, Kobe, Japan). The reference range for IPF had been established as 1.1-6.1% with a mean of 3.4% by Briggs C *et al* (2004), 1.1 – 6.1% by Rolf Hizmann (2005), 1 – 10.3% by Abe *et al*, 0.1% - 5.9% with a mean of 3.3% by Jung H *et al* (2010),0.7-4.3% by Sehgal K K *et al* (2013) and 0.3-8.7% by Sachdev R *et al* (2014)[4,14-18]. In this study, the reference range of 1.1 – 6.1% was considered as per the manufacturer's information[14]. The IPF values were also on the rising trend from day1 to day 5. From day 5 to day 7 it is on the decreasing trend. This is because the IPF increases 1-2 days to 3 -7 days before platelet recovery[5,19]. In this study we found 55.9% of patients with high IPF showed change in risk category within 2 days and 24.75% within 4 days and 15% within 6 days. 9.6% of patients with IPF less than 6.1 % showed platelet recovery. This may be due to lower normal level of IPF in these patients or it may due to a fall of IPF immediately before platelet recovery. 2% of patients with high IPF did not show improvement. This may be due to sepsis, antibiotics and antifungal therapy or regular platelet transfusion. It was observed that in thrombocytopenic patients, a cut off value of IPF >= 6.25 indicated that there is a 67% chance that there will be a rise in platelet count by 20,000 within 48 hours. A cut off value of 10.6 or more indicated that there is 100% chance of platelet recovery by 20000 within 48 hours. As per earlier studies IPF cut off values were 12.1% and 10%[5, 6].

CONCLUSION

Dengue epidemic calls for platelet transfusion, sometimes inappropriate also. Careful clinical watch and monitoring platelet count may help to group the patients under risk category. Immature platelet fraction is an additional parameter that can be monitored to predict platelet recovery, so that prophylactic platelet transfusion can be deferred and also the hazards associated with it.

Limitations of the study

Clinical correlation, analysis of platelet count and IPF on daily basis would have thrown more light.

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