A Study of the Clinical Profile, Diagnostic Workup and Outcome of Children with Thrombocytopenia

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ABSTRACT

Introduction: Incidence of thrombocytopenia varies from 13 to 58% in various studies. Manifestations can range widely, from minor bleeds to the life threatening hemorrhages. There is a very poor co-relation between the extent of thrombocytopenia and the severity of the bleeding manifestations. This study was thus undertaken to evaluate the occurrence of thrombocytopenia, assess the causes for it and its associated mortality in the pediatric age group. In addition to this, the association with bleeding and the requirement of blood products was also studied.

Material and Methods: The present study is a descriptive cross sectional study done on 125 children of both sexes aged 2 months to 12 years, who were admitted to the Pediatric intensive care unit, King George Hospital, Visakhapatnam with new onset thrombocytopenia of less than one lakh, during December 2018 to July 2020.

Results: The commonest age group among the study groups is 6-10 years, constituting around 47.2% of the cases. Mortality is highest among infants. Out of a total of 8 infants, 4 expired (50%). The commonest etiology for newly diagnosed thrombocytopenia in the present study is Dengue fever. Dengue shock syndrome (DSS) had the highest mortality rate of nearly 44.4%.

Conclusion: Thrombocytopenia is commonly seen in the pediatric age group. Infants and children less than 5 years with thrombocytopenia have a poor prognosis. Therefore, they need intensive monitoring and standardized management.

Keywords: Thrombocytopenia, Clinical Profile, DSS, Sepsis, Mortality

INTRODUCTION

Normal hemostasis is not only a complex process but also a resourceful system which maintains the vascular system of our body free from clots, of which the vital element is being platelets[1]. The incidence of thrombocytopenia varied from 13 to 58% in various studies[2]. Manifestations of thrombocytopenia range widely from minor bleeds to life threatening hemorrhages. There is a very poor relation between the extent of thrombocytopenia and the severity of the bleeding manifestations. Hence the treatment has to be guided by an understanding of its cause and the course. The main goal in the treatment of the patients with thrombocytopenia is to maintain a safe platelet count which prevents significant bleeding episodes. What constitutes a safe count varies, depending on the etiology as to whether it is transient or chronic, as well as the patient's expected level of disease activity[3].

There are a number of studies in the adult population about the various clinical aspects of patients with thrombocytopenia in the Intensive care units[4]. But such studies are lacking in the pediatric age group. There are very few studies to assess the relative frequency of different conditions which present as newly found thrombocytopenia in children presenting to a tertiary care centre. This study was done to assess the clinical and laboratory profile of children admitted with new onset thrombocytopenia, to evaluate the relative frequency of various causes for it and to assess the complications and outcome associated with thrombocytopenia, especially in those with bleeding manifestations.

MATERIAL AND METHODS

This is a Descriptive Cross sectional study done, from December 2018 to July 2020, in children 2 months to 12 years of age and admitted to Pediatric Intensive Care Unit, King George Hospital, Visakhapatnam with new onset thrombocytopenia of less than 1 lakh/µL. Patients already diagnosed with a known cause of thrombocytopenia, patients who received platelet transfusion prior to admission, patients with spurious thrombocytopenia or thrombocytopenia due to lab associated errors were excluded from the study. Out of a total of 790 admissions to the pediatric facility during the study period, 125 consecutive patients admitted with new onset thrombocytopenia were included in the study.

Institutional ethics committee approval was obtained for the present study. Parental consent was also obtained. History, physical examination and investigation findings were recorded on a predesigned proforma. Any evidence of bleeding manifestations in the form of rash, petechiae or purpura were examined. CBC which includes Hb, TC, DC, ESR, PCV, Platelet count were done at admission and are monitored every 12 to 24 hourly till a platelet count of 1 lakh/

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µL is reached with or without intervention. Investigations for BT, CT, PT, APTT, INR, sepsis/infection, liver function and renal function were carried out. Chest x ray, ultrasound abdomen, Bone marrow study and ANA profile were done if necessary.

Patients were treated as per standard protocol. Blood products were transfused as per the treating physician's discretion and the patients' general condition rather than platelet counts.

Statistical Package for Social Sciences (SPSS) software version 21.0 was used for the final analysis. The presentation of the Categorical variables was done in the form of number and percentage (%). The presentation of the continuous variables was done as mean ± SD. The association of the variables which were quantitative in nature was analyzed using Independent t test (for two groups) and ANOVA (for more than two groups). Repeated measure ANOVA was used to compare repeated measurements across follow up. The association of the variables which were qualitative in nature was analyzed using Chi-Square test/Fisher's exact test. For statistical significance, p value of less than 0.05 was considered as significant.

RESULTS

Of the total 790 admissions to the pediatric facility during the study period, 125 patients were admitted with new onset thrombocytopenia giving an incidence of 15.9%. In 119 patients a cause for the thrombocytopenia could be identified where as 6 patients were left undiagnosed despite full battery of investigations.

The commonest age group in the study is 6-10 years group, constituting around 47.2% of the cases. Mean age of presentation is 6.5 years (SD=3.4). 66 (52.8%) of the patients were girls. The male to female ratio in the study is 0.89:1.

The most common presenting symptom among the study group is found to be fever (96%) which is statistically significant (p value = 0.001) with the second most common symptom being identified as vomiting (64.8%). All the major diagnosed diseases in the present study including ALL had fever. Abdominal pain was most common in dengue/enteric fever co-infection while vomiting was most common among isolated cases of enteric fever (Table 1).

Most patients at admission (48.8%) had platelet counts in the range of 50,000 to 1 lakh/µL. Single lowest count reached was 6200/µL. Mean platelet count at admission was 58,720/µL. Platelet trend analysis showed a significant increase in repeat platelet counts indicating that most thrombocytopenia was transient. Rather than absolute values, it is the drop in counts which is significantly associated with poor outcome ($p < 0.05$) (Table 2).

The commonest etiology for newly diagnosed thrombocytopenia in the present study among children is Dengue infection. Total cases of dengue were 73, comprising 58.4% of the total study population. Among dengue cases, dengue fever with or without hemorrhage (DF) was most common (32%) presentation. The second most common diagnosis was enteric fever; 11.2% of the thrombocytopenia cases had enteric fever. 4 cases were due to co infection with both dengue and enteric fever. In 6 cases, a final diagnosis could not be reached (4.8%), which is within allowable limits.

Bleeding manifestations were observed in a total of 71 patients (56.8%). GI bleed in the form of hematemesis or malena was the commonest bleeding manifestation associated with thrombocytopenia, seen in a total of 47 patients (37.6%) (Figure 1).

Nine patients expired during the course of hospital stay. Mortality rate is 7.2%. In 109 (87.2%) patients the platelet count improved prior to discharge and the thrombocytopenia was transient (Figure 2). Seven patients were referred to other centers on request.

The mean age of expired children is 2.6 years which is statistically significant ($p<0.05$). Mortality is highest among infants. Out of 8 infants studied, 4 expired (50%) which is statistically significant ($p<0.05$).

Dengue shock syndrome (DSS) is the leading cause of mortality in the study population comprising a total of 4 among the total 9 deaths. DSS comprised only 8% of the total cases with thrombocytopenia, but had the highest mortality rate of nearly 44.4%. The next leading cause of mortality was sepsis. 12 cases had rarer diagnosis; there were 2 deaths among these 12 cases. Cause of death in one case was severe bleeding due to snake bite, probably associated with VICC. The other was diagnosed with hemophagocytic syndrome

Symptoms	Undiagnosed (n=6)	Acute lymphocytic leukemia (n=6)	Dengue(n=73)	Enteric(n=14)	Enteric and dengue combined (n=4)	Malaria(n=4)	Miscellaneous (n=12)	Sepsis (n=6)	Total	P value
Fever	6 (100%)	6 (100%)	73 (100%)	14 (100%)	4 (100%)	4 (100%)	7(58.33%)	6 (100%)	120 (96%)	0.0001
Cough	2(33.33%)	1(16.67%)	28(38.36%)	3(21.43%)	3 (75%)	2 (50%)	4(33.33%)	5(83.33%)	48(38.40%)	0.157
Vomiting	5(83.33%)	2(33.33%)	46(63.01%)	12(85.71%)	3 (75%)	3 (75%)	5(41.67%)	5(83.33%)	81(64.80%)	0.177
Myalgia	1(16.67%)	4(66.67%)	43(58.90%)	7 (50%)	2 (50%)	2 (50%)	8(66.67%)	1(16.67%)	68(54.40%)	0.271
ABD pain	4(66.67%)	1(16.67%)	39(53.42%)	10(71.43%)	3 (75%)	2 (50%)	7(58.33%)	1(16.67%)	67(53.60%)	0.221

Table-1: Comparison of symptoms based on etiology

Platelet count (per cubic mL)	At admission (n=125)	Repeat 1 (n=125)	Repeat 2 (n=100)	Repeat 3 (n=61)	P value
<=10000	4	1	1	5	
	(3.20%)	(0.80%)	(1%)	(8.20%)	
11000-20000	12	16	6	4	
	(9.60%)	(12.80%)	(6%)	(6.56%)	
21000-50000	40(32%)	24(19.20%)	13(13%)	3(4.92%)	<.0001
51000-100000	61	63	43	13	
	(48.80%)	(50.40%)	(43%)	(21.31%)	
>100000	8	21	37	36	
	(6.40%)	(16.80%)	(37%)	(59.02%)	
Mean ± SD	58720 ±36270.18	72149.6 ±40181.79	93690 ±48566.04	99096.72± 47241.83	<.0001

Table-2: Platelet count trend on repeat analysis

Diagnosis	Death (n=9)	Discharged (n=116)	Total	P value
Undiagnosed	0 (0%)	6 (100%)	6 (100%)	
All	0 (0%)	6 (100%)	6 (100%)	
Dengue fever	0 (0%)	40 (100%)	40 (100%)	
DHF	0 (0%)	23 (100%)	23 (100%)	
DSS	4 (40%)	6 (60%)	10 (100%)	
Enteric Fever	0 (0%)	14 (100%)	14 (100%)	
Enteric/Dengue co infection	0 (0%)	4 (100%)	4 (100%)	
Malaria	0 (0%)	4 (100%)	4 (100%)	
Miscellaneous	2 (16.67%)	10 (83.33%)	12 (100%)	<.0001
Sepsis	3 (50%)	3 (50%)	6 (100%)	

Table-3: Etiology and disease wise mortality

Parameters	Not transfused (n=103)	Transfused (n=22)	Total	P value
Bleeding Absent	50 (48.54%)	4 (18.18%)	54 (43.20%)	
Bleeding Present	53 (51.46%)	18 (81.82%)	71 (56.80%)	0.01
Death	3 (2.91%)	6 (27.27%)	9 (7.20%)	
			116	0.0009
Discharged	100 (97.09%)	16 (72.73%)		
			(92.80%)	
Non anemic	70 (67.96%)	9 (40.91%)	79 (63.20%)	
Anemic	33 (32.04%)	13 (59.09%)	46 (36.80%)	0.017

Table-4: Association of various parameters with transfusion

Transfusion	Death (n=9)	Discharged (n=116)	Total	P value
No	3 (2.91%)	100 (97.09%)	103 (100%)	0.0009
Yes	6 (27.27%)	16 (72.73%)	22 (100%)	
Total	9 (7.20%)	116 (92.80%)	125 (100%)	

Table-5: Association of transfusion with mortality

(Table 3).

Among children with bleeding manifestations, the most common etiology was Dengue fever. But those patients with enteric fever had a higher incidence of bleeding compared to dengue fever. In fact, co infection of Enteric and Dengue had the highest incidence of bleeding.In children with Dengue, counts less than 20,000 had high association with bleeding, while in enteric fever there was no such correlation observed. Standard protocols were followed in transfusing blood products to children in the present study. Majority of them received packed red blood cells and platelets, while a few patients were transfused with whole blood and colloids. The cause for most transfusions was found to be severe shock with bleeding manifestations requiring plasma expansion, while few children were transfused prophylactically in view of drastically decreasing platelet counts.

81.82% of patients with bleeding manifestations were transfused ($p<0.05$). Among the bleeding manifestations, children with GI bleed had a significantly increased need for transfusions ($p<0.05$). There was an association between

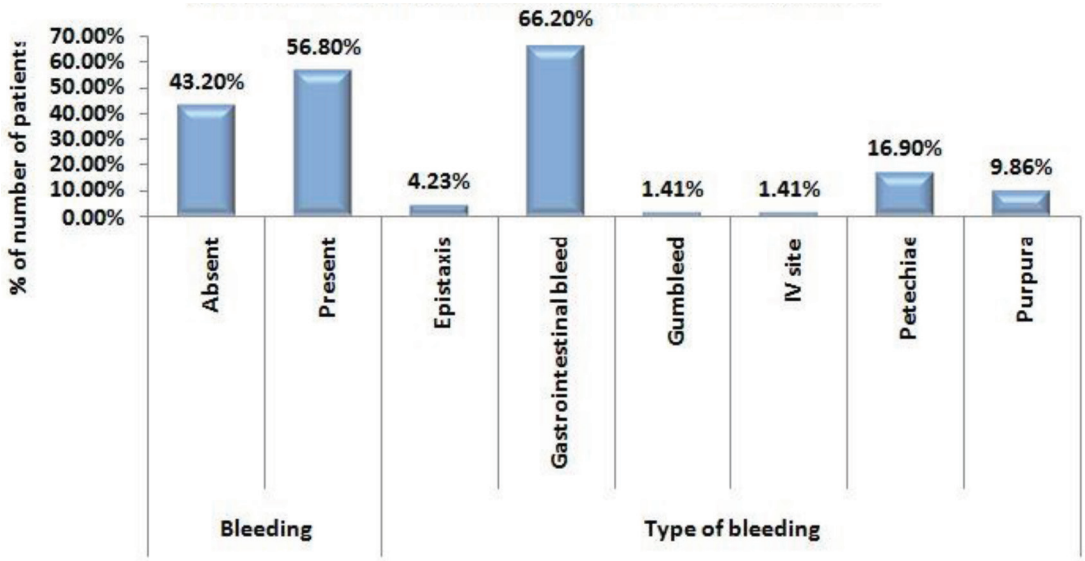

Figure-1: Distribution of type of bleeding

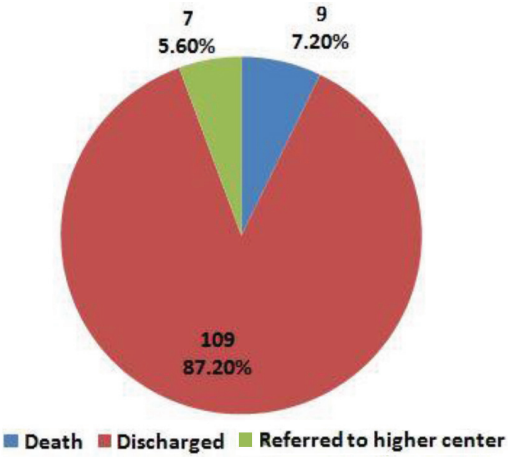

Figure-2: Outcome of children with new onset thrombocytopenia

need for transfusion and mortality which is statistically significant ($p<0.05$). Transfusions have not significantly altered the outcome because all the poor predictors of mortality also had significant association with the need for transfusions (Table 4) (Table 5).

DISCUSSION

Age wise incidence: The present study shows the highest incidence of thrombocytopenia is amongst the 6-10 years age group, with a mean age of 6.56 years. Gender wise distribution: There is no particular gender predilection. Incidence: The incidence of thrombocytopenia is 15.96% .

Platelet trend among subjects: 32.39% of children had platelet counts between 21,000-50,000 and 40.85% children had between 50,000 - 1,00,000. Children having platelet counts below 20,000 had a high risk of mortality compared to the other groups. Mortality: Mortality in the present study is 7.1% with DSS contributing to 44.4% of deaths. Mortality is highest among infants (45.5%) and younger children (<5 years).

Comparison of etiology of Thrombocytopenia: The commonest etiology for newly diagnosed thrombocytopenia was Dengue infection(58.4%). The total patients under study were 125 among which the total cases of dengue fever were 73, which constituted for more than 50% (58.4%) of the total cases. So a detailed analysis of dengue infection was performed. Dengue fever with or without hemorrhage (DF) was most common presentation constituting 50.4%. Dengue shock syndrome (DSS) comprised of only 8% of cases with thrombocytopenia, but had the highest mortality rate of 44.4%.The major reason for higher incidence of deaths among children with Dengue shock syndrome could be attributed to the high baseline micro vascular permeability in children[11]. The present study also showed that early monitoring and appropriate fluid management can prevent the children from developing Dengue shock syndrome.

Platelet counts had no correlation to the bleeding manifestations in dengue; majority of bleeding manifestations in the present study were observed in patients with counts more than 20,000. Bleeding in dengue is multifactorial. Reduced platelets and fibrinogen are the two most prominent hemostatic defects responsible for bleeding in DHF. Gomber et al[13] defines 36.3% as the cut-off hematocrit value for Dengue Hemorrhagic Fever; the hematocrit values below this mean are associated with a significantly poor outcome in their study group.

The incidence of co infections in the present study is low (3.2%). Hepatomegaly is present in almost 40% of children with Enteric Fever/Dengue co-infection. USG abdomen findings in the form of gallbladder wall edema and ascites is seen in 23.3% and splenomegaly in 17.8% of dengue cases.

Lab parameters in association with thrombocytopenia: Leucopenia is associated with 36% of cases of thrombocytopenia and dengue fever has the highest number of cases with leucopenia (38.6%). The mean hematocrit in the present study is 36.05%, mean hemoglobin is around 10.99% and the values below this mean suggested poor outcome. The liver function tests were deranged in 24.6%.

Serological investigations in dengue infection: The present study showed 34.2% NS1 positivity, 86.3% IgM positivity

and 53.4% showed rise of IgG.. All three serological investigations were very useful in identifying both primary and secondary infection. Triple positivity was seen in 12.3% of the cases. Majority of the cases had IgM positivity which shows that the clinical presentation is more during the active phase of the disease

Predictors of Mortality: Altered sensorium, shock, tachycardia, tachypnea, abdominal distension, GI bleed, the requirement of inotropic support, mechanical ventilation (50%) and seizures were significantly associated with increased mortality. Early identification of shock is of utmost importance as the outcome of a patient with DSS depends on the duration of shock.

Bleeding Manifestations: Bleeding manifestations were seen in a total of 71 patients (56.8%). Gastrointestinal (GI) bleed in the form of hematemesis or malena was the commonest bleeding manifestation associated with thrombocytopenia, seen in total of 47 patients which is around (37.6%). Children with counts between 11000 to 20000 had the highest number of bleeding manifestations followed closely by children with counts less than 10,000. The overall mortality among children with bleeding manifestations is 7.1%.

Transfusion Requirements: In spite of several studies, there are no clear evidence based guidelines for transfusions in children with thrombocytopenia. 17.6% children in the present study required transfusions. Most of the patients who require transfusion in the present study were DSS patients. Transfusion requirements are more in those patients who had bleeding manifestations in one or the other form and with associated anemia. The mean platelet count of transfused patients was 26,000/μL. Yet 66% mortality was seen in the transfused patients, which was statistically significant.

Limitations of the study: Considering that the present study was a small scale study (total number of subjects were 125) done in an area with high endemicity of dengue (an infectious disease very commonly associated with thrombocytopenia) most of the comparisons are done based on that, which may not give a clear picture of the entire spectrum of pediatric thrombocytopenia. Serological studies for viral markers have not been done; the observations of the present study are definitely subjected to confounding. Only newly diagnosed thrombocytopenia is taken into consideration rather than already known cases like chronic ITP and hence the spectrum of non-infectious thrombocytopenia could not be studied clearly.

CONCLUSION

Dengue fever is the major cause for newly found thrombocytopenia in the present study. Children with DSS with shock and bleeding manifestations had the worst outcome. DSS managed with careful clinical examination of pulse rate, volume status, fluid resuscitation, vitals monitoring and relying on lab parameters like rise in hematocrit and thrombocytopenia contributed to reducing mortality and morbidity in this group. Pedal edema, altered sensorium, tachycardia, tachypnea, shock, seizures, anemia, increased ESR, severe leucopenia, GI bleed and abdominal distension, intra cranial bleed, platelet counts of < 10000, need for inotrope support and for mechanical ventilation are all associated with increased mortality. Transfusion of blood products is not significantly associated with altering the outcome. There is no role for prophylactic transfusions.

REFERENCES

1. Cotran, Kumar, Robbins. Pathological basis of disease. 8th ed. Philadelphia: W.B. Saunders Company; 2010. p.115
2. Strauss R, Hahn E. Thrombocytopenia in patients in the Medical Intensive Care Unit. Crit Care Med. 2002; 30: 1765- 71
3. Deborah M. Consolini. Thrombocytopenia in Infants and Children. Pediatr. Rev. 2011; 32: 135-151
4. Moreau D, Zahar JR et al. Platelet count decline: An early prognostic marker in critically ill patients with prolonged intensive care unit stay. Chest. 2007; 313: 735-4
5. Ali Jan et al. Thrombocytopenia in children. Hayat Shaheed Teaching Hospital, Peshawar. JPMI vol 18(3)
6. Shruti Agrawal, Anil Sachdev et al. Platelet counts and outcome in the Paediatric intensive care unit. Indian J Crit Care Med. 2008; 12: 102-108
7. Chandrakanta Kumar R, Garima Agarwal et al. Changing clinical manifestations of dengue infection in North India. Dengue Bull, 2008; 32: 118-25
8. Mittal, Faridi, Arora et al. Clinico-hematological profile and platelet trends in children with dengue during 2010 epidemic in North India. IJP. April 2012; 79(4)
9. Fauziah Md Kassim. Use of dengue NS1 antigen for early diagnosis of dengue virus infection, Institute for Medical Research, Kuala Lumpur. Southeast Asian J Trop Med Public Health. May 2011; Vol 42 No.3
10. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Revised and expanded Edition. World Health Organization; 2011
11. Gamble J, Bethell D, Day NPJ et al. Age-related changes in Microvascular Permeability: A significant factor in the susceptibility of children to shock. Clinical Science 2000; 98: 211-6
12. Mitrakul C, Poshyachinda M, Futrakul P, Sangkawibha N, Ahandrik S. Haemostatic and platelet kinetic studies in dengue haemorrhagic fever. American J Tropical Medicine Hygiene. 1997; 26: 975-984
13. Gomber S, Ramachandran VG, Kumar et al. Hematological observations as diagnostic markers in DHF- A reappraisal. Indian Paediatrics 2001; 38: 477-81
14. Predictive markers for DSS. J of Tropical Paediatrics. 2004;50: 301-305
15. Agarwal A, Chandra J, Aneja S, Parwari AK, Dutta AK. An epidemic of dengue hemorrhagic fever and dengue shock syndrome in children in Delhi. Indian Pediatrics. 1998; 35: 727-732
16. Halsted SB et al. Antibody, macrophage, dengue virus infection, shock and haemorrhage - A pathological cascade. Rev Infect Dis. 1989; 11: 830-836

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