Study of Clinical and Laboratory Behavior of Thrombocytopenia In Acute Febrile Illness

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ABSTRACT

OBJECTIVE: The study was carried out to document the clinical and laboratory behavior of thrombocytopenia in acute febrile illness.

METHODS: Consecutive subjects of fever of 7 days' duration and thrombocytopenia were included. Patients with localizing causes like Pneumonia, Meningitis, skin or subcutaneous infections; patients with bleeding disorders were excluded. Complete blood count of all subjects was done on day 1. Platelet count was repeated on day 7 determine **RESULTS:** Significantly more subjects with platelet count below 20000/l had bleeding manifestations due to thrombocytopenia. Statistically significant (p0.01) difference in the mean platelet count on days 1 and 7 was observed, even in those subjects who did not receive specific replacement therapy (63306+/-33287 on day1,168889+/-62490 on day 7).

CONCLUSION: Thrombocytopenia in acute febrile illness is well tolerated, though bleeding manifestations significantly occur below 20000/l. Statistically significant improvement in platelet count occurs on day 7 even without replacement therapy.

INTRODUCTION

In clinical practice, many infectious diseases present as fever and thrombocytopenia. In the tropics, diseases that commonly present as fever and thrombocytopenia are malaria, both falciparum and vivax, Dengue, Leptospirosis, rickettsial infections and viral fevers (1). In these conditions, thrombocytopenia occurs due to immune destruction, bone marrow suppression, DIC and sometimes due to hypersplenism or drugs (1). Presence of thrombocytopenia in an acute febrile illness in the tropics increases the possibility of malaria (2, 3). Thrombocytopenia manifests commonly as hemorrhages in the skin (petechiae, purpurae or ecchymosis), from the mucosal surfaces (epistaxis, bleeding gums etc) and rarely into the internal organs (4) There is no linear relationship between the bleeding manifestations and the levels of platelet count. Bleeding is occasional when count is above 40000/l, common but not invariable when count is below 30000/l-40000/l, while it is usual and severe below 10000/l (4). Thrombocytopenia in these conditions may be transient (5, 6, 7), but if severe, may produce life-threatening bleeding. Hence the present study was undertaken to study the clinical profile of thrombocytopenia in acute febrile illness and its behavior during hospital stay.

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METHODS

After their consent, patients presenting with fever of less than 7 days' duration and thrombocytopenia who were admitted to wards during the period from October 2010 to December 2010 were included in the study. Patients in whom a localizing cause could be determined (pneumonia, meningitis, skin and sub-cutaneous infections etc); patients with history or clinical features suggestive of chronic liver disease and those with history of bleeding disorder, thrombocytopenia or purpura were excluded. Patients with history of intake of drugs like Septran, Thiazides or chemotherapeutic agents were excluded.

Detail history was taken and clinical examination for bleeding manifestations was done. Besides routine investigations, a complete blood count was done by automated cell counter on the day of admission (day 1). Hemoglobin values below 10 gm% and total

leukocyte counts below 4000/l and 1, 50,000/l were used to define anemia, leucopenia and thrombocytopenia respectively (4). Leucocytosis was defined as total leucocyte count above 11000/l. Thrombocytopenia was further categorized as mild (50,000/l-1, 50,000/l), moderate (20,000/l-50,000/l) and severe (20,000/l). Patients were followed up over a period of seven days or till discharge. Relevant therapy for treatment of acute febrile illness as well as for the bleeding manifestations was continued and noted. A repeat platelet count was done on day seven.

RESULTS

Total 36 subjects were included in the study. Mean age of the subjects was 35+/- 19.90 years, there were 24 males and 12 females; the male: female ratio being 2:1. 22 (61.11%)) subjects were diagnosed as malaria on the basis of detection of malaria parasite in the peripheral smear and /or detection of malaria antigen by rapid diagnostic tests. In further 6(16.67%) subjects, anti-malarial treatment was given on clinical suspicion of malaria and they responded to the treatment. 6(16.67%) subjects had antibiotic responsive fever whereas 2(5.55%) subjects received both anti-malarial treatment and antibiotics.

Of the total 36 subjects with thrombocytopenia, suppression of another cell line in the form of either anemia or leucopenia was seen in 16(41.67%) subjects whereas the entire three cell lines were suppressed in 15(36.36%). Total 27(75%) subjects had anemia whereas 19(52.78%) subjects had leucopenia, 2(5.56%) subjects had leucocytosis. Of the total 22 subjects with malaria, 14(63.64%) subjects had anemia, 9(25%) had leucopenia and 1(2.78%) had leucocytosis. The mean hemoglobin value was 8.1+/-2.5 gm% with a range of 3.6gm%to 12.6gm% and the mean leukocyte count was 4781+/-2936/l ranging from 1100/l to14800/l. The mean platelet count on day1 was 63306+/-33287/l (Table1) with a range of 11000/l to 125000/l.

Hematological Parameter	Mean	S.D.
Hb (gm %)	8.1	2.5
TLC (per liter)	4781	2936
Day 1 Platelet Count (per liter)	63306	33287

Table 1 showing the mean values of hemoglobin, total leukocyte count and platelet count on day 1

19(52.78%) subjects had mild thrombocytopenia 50,000-1, 00,000), 14(38.89%) had moderate thrombocytopenia (20,000-50,000) and 3(8.33%) had severe thrombocytopenia (20,000). 11(30.565%) subjects had symptoms and signs due to thrombocytopenia. All patients with severe thrombocytopenia had clinically evident bleeding manifestations. 3(21.43%) out of 14 subjects with moderate thrombocytopenia and 5(26.32%) out of 19 subjects with mild thrombocytopenia had clinical manifestations (Table 2).

*Fisher exact test 'p' value 0.023 when manifestations of patients below and above 20000 were compared

Table 2 showing distribution of subjects according to their platelet count and clinical manifestations

Platelet count on day 1	Clinical manifestations of thrombocytopenia	
	At least one symptom and/or sign	None
<20000 (n=3)	3 (100%)	0 (0%)
21000-50000 (n=14)	3 (21.43%)	11 (78.57%)
51000-150000 (n=19)	5 (26.32%)	14 (73.68%)
Total (n=36)	11(30.56%)	25(69.44%)

The patients who were symptomatic for thrombocytopenia were examined for the various manifestations. The most common symptom was cutaneous hemorrhagic rash reported in 5 (45.45%) subjects followed by malena in 4 (36.36%). Bleeding gums and hematuria were the next common symptoms seen in 3(27.27%) subjects and hematemesis, epistaxis and hematochezia were the least common seen only in 2(18.18%) subjects each; 2(16.67%) subjects had more than one symptom. Amongst the various clinical signs, maximum i.e.8 (72.72%) subjects had evidence of cutaneous bleeding in the form of ecchymosis, petechiae or purpura in decreasing order of frequency; 3(27.27%) had bleeding gums and epistaxis was seen in 2(18.18%) subjects.2 (18.18%) subjects had more than 1 sign.

There was no statistically significant difference in the clinical manifestations of the three sub-groups (mild, moderate and severe thrombocytopenia). However when a cut-off value of 20000 was considered, a statistically significant difference was observed in the symptoms and signs of subjects with platelet count

below and above 20000 (Fisher exact test, 'p' value 0.023). Significantly more subjects with platelet count below 20000/l had bleeding tendencies.

Platelet count showed incremental trend on serial estimation. To determine its trend and behavior, platelet count on days 1 and 7 were compared. However, 9 subjects received therapeutic intervention either in the form of blood transfusion or platelet concentrates. Of the 2 subjects who received platelet concentrates, one had oral mucosal bleeding with hematoma over the tongue while the other subject had significant hematochezia. Both had platelet count below 20000/l. The remaining 7 subjects were given replacement therapy (blood transfusion) for severe anemia. Since these patients had received therapeutic intervention which could have confounded the results, these were excluded. Thus platelet count of only 27 remaining subjects was compared at baseline and after 7 days. The mean platelet count on days 1 and 7 was 68148+_34224 and 168889+_62490 respectively (Table 3). The difference was found to be statistically significant ('t' value-9.095, 'p' value 0.01). (Table 3, Figure 1)

Table 3 showing comparison of platelet count on days 1 and 7

Platelet Count	Mean	S.D.	t value	p value
Day 1	68148	34224	9.095	P<0.01
Day 7	168889	62490		Significant

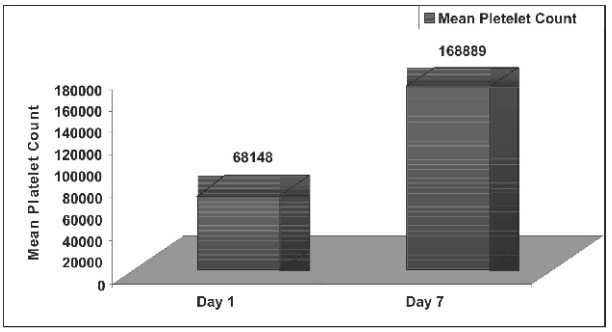

Figure 1 showing comparison of platelet count on days 1 and 7

DISCUSSION

In our series, there were maximum i. e. 22(61.11%) subjects of malaria. Number of cases of malaria starts increasing after the month of June; the peak levels occurring from September to November and a decline occurring later on (1, 8). This is expected, as the stagnant water during the monsoon season acts as a reservoir and breeding ground for the malarial parasite. Our study was carried out in the months of October to December; probably the reason why almost 61% subjects were found to have malaria. In their studies on patients with acute febrile illness without a localizing cause, Memon et al (3) and Lathia et al (2) observed that 47% (60subjects out of 128) and 38% (70 subjects out of 184) subjects had smear positive malaria respectively.

In the present study, the diagnosis of malaria was done by peripheral smear examination and/or rapid diagnostic tests. Though detection of the parasite on blood smear is the gold standard for the diagnosis of malaria, Rapid diagnostic tests(RDT) are useful, especially in countries with limited resources having major disease burden(9). Rapid diagnostic tests (RDT) for the diagnosis of malaria are based on the detection of malaria antigens (HRP-2 i.e. Histidine rich protein 2 expressed by Plasmodium falciparum, pLDH i.e. parasite specific LDH expressed by all 4 plasmodium species and Plasmodium Aldolase). Poor sensitivity of the tests is the major limitation, especially for the diagnosis of non-falciparum malaria (9).

Hematological dysfunction affecting all the three cell lines was seen in a significant proportion of subjects. Similar observations have been reported previously (2, 3, 8) The various mechanisms by which this occurs depend upon the etiology. It can occur due to peripheral destruction of the cells (by immune or non-immune mechanisms) or direct suppressant effect on the bone marrow (1, 10). Additionally, consumptive coagulopathy and bleeding might contribute to anemia and thrombocytopenia, especially in malaria (1). In our series, leucocytosis was seen in one subject with malaria. Though leucopenia is more frequent, leucocytosis is sometimes observed in acute plasmodium infection and may suggest co-existing viral infection (5, 11, 12).

The most frequent symptom as well as sign in the present study was cutaneous bleeding tendency. In their studies, Chetan CS et al (13) and Das DRS (14) reported that bleeding gums and subcutaneous bleeding were the most common symptom and sign respectively.

More subjects with mild thrombocytopenia were paradoxically found to have clinical bleeding manifestations in the present study. Fah TS et al looked at the association of duration of fever and thrombocytopenia and observed that thrombocytopenia is common as early as day 3 after the onset of fever (15). Secondly and more importantly the platelet count shows markedly incremental trend after therapy (5, 6, 7). The association of duration of fever prior to hospitalization with the platelet count was not studied in this study. Further, many patients receive empirical therapy prior to hospitalization which could have influenced their platelet count. It is therefore suggested that these subjects were probably included in the study when their count was already recovering.

In the present study, the platelet count showed marked recovery even without specific therapy in the form of replacement therapy. Levels of Thrombopoietin, a key growth factor regulating megakaryopoiesis, show an inverse relationship to the platelet counts in patients with malaria and start rising as early as day 4, normalizing by day14-21 of therapy(6). This results in accelerated platelet production. The rapid increase in TPO serum levels in response to the thrombocytopenia associated with malaria and the rapid recovery within 7 d of initiation of therapy supports the concept of peripheral destruction of platelets early in the course of disease without continuing platelet consumption(6). In viral fevers, similar bone marrow recovery probably results in normalization of platelet count.

Many other studies have reported similar laboratorial behavioral pattern of thrombocytopenia (5,6,7).). However, most of these studies have concentrated on its trend in patients with malaria. Adedapo et al noted a statistically significant improvement in platelet count on day 28(5). Kreil et al observed a linear decline in Thrombopoeitin levels and a concomitant significant increase in platelet count by day 7 in patients with malaria (6). Similarly, Kehinde et al noticed a rising trend on comparison of the platelet count on day 0 and day 14 (Day 0 count 137000/l+/-580000/l, Day 14 count 234000/l+/-969000/l) (7)

However, there are limitations of this study. The main limitation of the present study is undoubtedly its small sample size. Secondly, detail investigations, including bone marrow, to know the etiology were not done. Since this study was carried out in a tertiary care referral hospital, subjects with more severe thrombocytopenia were probably included and hence the might not reflect the true scenario in general population with febrile illness.

CONCLUSIONS

To conclude, malaria is the most common cause of thrombocytopenia in patients with acute febrile illness of less than 7 days' duration, after excluding conditions with a localizing cause like pneumonia. In these subjects, low platelet counts are tolerated well without serious life threatening bleeding manifestations. Significant improvement in the platelet count may be expected by day 7 even without replacement therapy.

If corroborated by larger studies, the results of this study could provide the basis for 'masterly inactivity' for management of mild to moderate thrombocytopenia (above 20000/l) when occurring in the setting of acute febrile illness after exclusion of sepsis and other conditions wherein progressive decline in platelet count is anticipated.

In a society with meager and limited resources, this could help in avoiding inadvertent platelet or blood transfusions in these subjects, a significant proportion of whom might improve with time.

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