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A Study of Patients in Malaria and Complicated Malaria

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Abstract

Background: *Malaria is a very common infectious disease and multiple studies have reported thrombocytopenia as one of the common haematological abnormalities associated with it Increasing association between the disease severity, its pathology and platelet indices is being suggested . This study aimed to attempt an association between the myriad manifestations of malaria, their severity and correlation with platelet count.*

Methods: *This study was carried out as an observational study on patients admitted with the diagnosis of Malaria in the general medicine wards of Pt BRAM Medical College, Raipur between 2005-2008. Diagnosis of malaria was considered if either of the investigations-peripheral smear, antigen based rapid diagnostic card tests or quantitative buffy coat method (QBC) were positive. Coulter LH 756 was used to measure platelet counts. Platelet counts less than 1,50,000/mm3 were taken to be abnormal. Biochemistry and other pertaining investigations were done to ascertain the presence of any other complications. All the parameters at the time of hospitalization were considered for data analysis*

Results: *Of the 105 patients included in the study, majority were of male gender (82%) with an average mean age of 38 years.*

50 % of patients had tested positive for plasmodium Falciparum, 48% had Plasmodium Vivax and 2% had mixed Plasmodium Vivax and Falciparum infections.

As per the WHO criteria on management of severe malaria (2008), only 14% of patients infected with plasmodium falciparum had severe disease while the majority (36%) had non-severe disease. Both Plasmodium Vivax and Falciparum had equal incidence of thrombocytopenia but significantly lower platelet count were seen in patients with mixed Pl Vivax and Pl Falciparum infections and in those cases who met any one or more of the WHO criteria for severe malaria, though not all associations were statistically significant.

Conclusions: *In our study group, Thrombocytopenia was a very common haematological abnormality . However a statistically significant association between severity of platelet count and the species of malaria (Vivax vs Falciparum) was not seen. However, lower platelet counts were seen in patients meeting one or more of the WHO criteria of severe malaria. This association was most significant when renal impairment and parasitemia were taken into consideration. However, since a single reading of different parameters at the time of inclusion was taken, this association could not be definitely proved and thus needs further larger and prospective studies before appropriate conclusions can be drawn.*

Introduction

As per the WHO Malaria report 2008, around 1.8 million confirmed cases of malaria are reported annually in the Indian subcontinent, 53% of which are Plasmodium Vivax cases, 47% are Plasmodium Falciparum and only 0.2% cases have mixed infections. The disease is purported to have a case fatality rate of about 0.8%.

Traditionally it was thought that infections with Pl Vivax had a much benign course when compared to Pl. Falciparum. But increasing data and studies are indicating towards infections with Pl Vivax

having increased mortality and morbidity which is equal and comparable to that seen with Pl Falciparum. The emerging chloroquine resistance has further confounded the scenario.

Multiple recent studies have documented incidence of thrombocytopenia in Plasmodium infections (Erhabor et al, Lee et al, Pongponratn et al, Jadhav et al) and some have speculated on possible association between platelet counts and Pl Falciparum severity (Gerardin et al, Srichaikul et al) but the data about a probable association in Pl Vivax infections, especially in Indian sub-continent is scarce and conflicting. (Makkar RP et al, Kochar et al, Sina B et al).

With this background, this observational study was attempted to determine the clinical profile of the patients infected with the Plasmodium as well as the predictors of outcome with regards to the complications and manifestations, with special emphasis on platelet counts.

Methods

This study was carried out as an observational study on patients admitted into the general medicine wards of Pt BRAM Medical College, Raipur between 2005 August and November 2008, with a diagnosis of fever, clinical suspicion of malaria and testing positive for Malaria (Peripheral smear-thin and thick blood smear using Giemsa stain, QBC for malarial parasites or the rapid species specific antigen based diagnostic card tests for malaria).

Informed consents were taken either from the patient or from the relative in those with obtundation. The data pertaining to demographics, relevant clinical, microbiological, biochemical and haematological investigations were entered into a pre-structured format.

Patients with known chronic liver disease, chronic kidney disease, coagulation or bleeding disorders, Iron deficiency Anemia , HIV positive status and other coincidental infections that might confound the reports ,like enteric fever and viral hepatitis were excluded from the study.

Biochemistry investigations like Bilirubin, Liver enzymes, Blood urea, creatinine, Plasma glucose, Arterial blood gas analysis, coagulation parameters like APTT and PT-INR, and Xray chest were done in all subjects, as and when relevant .Species of plasmodium was identified by thick smear.

All patients, at the time of hospitalization, had their baseline platelet counts assessed using the Coulter LH 756 Analyser. A simple classification of thrombocytopenia was done, with counts above 150 x 10^9/l platelet count as normal, between 150-100 x 10^9/l as mild thrombocytopenia and < 50 x10^9/l as severe thrombocytopenia.

As per the World Health Organization Definition of Severe Malaria of 2000 (WHO, 2000), patients with Falciparum infections were classified into non-severe and severe falciparum malaria.

Patients were put into the category of Severe Malaria if their profile showed occurrence any one or more of these laboratory or clinical features:

Major Criteria	**Other Criteria**
Unrousable coma Generalized convulsions > 2 episodes within 24 hours or evidence of continued seizure activity. Haematocrit <15% or Haemoglobin < 5 g/dl, normochromic, normocytic; Urine output < 400 ml/24 hours not improving with rehydration or serum creatinine> 3 mg/dl Non-cardiogenic pulmonary oedema or acute respiratory distress syndrome Blood glucose <40 mg/dl or 2.2 mmol/l 7) Systolic pressure < 80 mmHg with circulatory failure 9) Spontaneous bleeding and laboratory evidence of disseminated intravascular coagulation 10) pH <7.25 or serum bicarbonate < 15 mmol/l; venous lactate level <5 mmol/l 11) Macroscopic haemoglobinuria.	Impaired consciousness but arousable Extreme weakness Serum bilirubin >3 mg/dl Parasitemia level >5%.

Results

Of the one hundred and five patients initially incorporated into the study, three were excluded after detailed evaluation. Of the rest one hundred and two case subjects, 82% were of male gender and none of the female patients (18%) were pregnant. The mean age group along the study population was 38 years.

Figure 1: Mean age group in Pl Vivax and Pl Falciparum infection

Sr No.	Mean Age (yrs)	Category
1	36.4±12.7	Pl. Vivax
2	39.9±13.2	Pl. Falciparum

Figure 2: Gender Distribution in Pl. Vivax and Pl. Falciparum infection

Gender	Pl.Vivax	Pl Falciparum	Mixed
Male	43 (88%)	37(73.3)	2
Female	6(12%)	13 (26.7)	0

Forty nine (48%) had Plasmodium Vivax infection , two patient had mixed Pl Vivax and Falciparum infection while the rest fifty one had Plasmodium Falciparum.

Thirty six % (37) had non-severe Pl Falciparum infection while fourteen % (14) met the WHO 2000 criteria for Severe Falciparum infection. None of the patients with Plasmodium Vivax showed any of the signs or laboratory features of Severe Malaria.

Figure 3: Distribution of patients in Pl. Vivax and Pl .Falciparum infection

S No	Species	Number of patients(n)	Percentage (%)
1)	Pl Vivax	49	48
2)	Pl Falciparum- Non severe	37	36
3)	Pl Falciparum- Severe	14	14
4)	Mixed	2	2

Amongst the study group, the mean duration of illness varied from 6.2 days in Pl Vivax infection to 6.1 days in Pl Falciparum infection to 7.6 days in those with mixed Pl Vivax and Pl Falciparum infections.

Figure 4: Mean duration of illness in days with Pl Vivax and Pl Falciparum infection

S No	Pl Vivax	Pl Falciparum	Mixed Infection
Mean duration of illness(days)	6.2±4	6.1±38	7.6±5.2

Again in the study group, the mean platelet counts were analysed as per the infecting Plasmodium species. It was $84x10^9/l \pm 42$ in patients with Pl Vivax as compared to $96x10^9/l \pm 62$ in uncomplicated falciparum and $49x10^9/l \pm 22$ in those with mixed infections. The difference was statistically significant (p=0.01) in the group with severe Falciparum infection.

Figure 5 (a): Mean platelet count in patients with Pl Vivax and Pl Falciparum infection

Platelet count	Pl Vivax	Pl Falciparum uncomplicated	Pl Falciparum Complicated	Mixed Infection
Mean	$84x10^9/l \pm 42$	$96x10^9/l \pm 62$	$49x10^9/l \pm 22$	$22x10^9/l$
Lowest	$22x10^9/l$	$18x10^9/l$	$12x10^9/l$	$12x10^9/l$
Highest	$245x10^9/l$	$302x10^9/l$	$86x10^9/l$	$32x10^9/l$

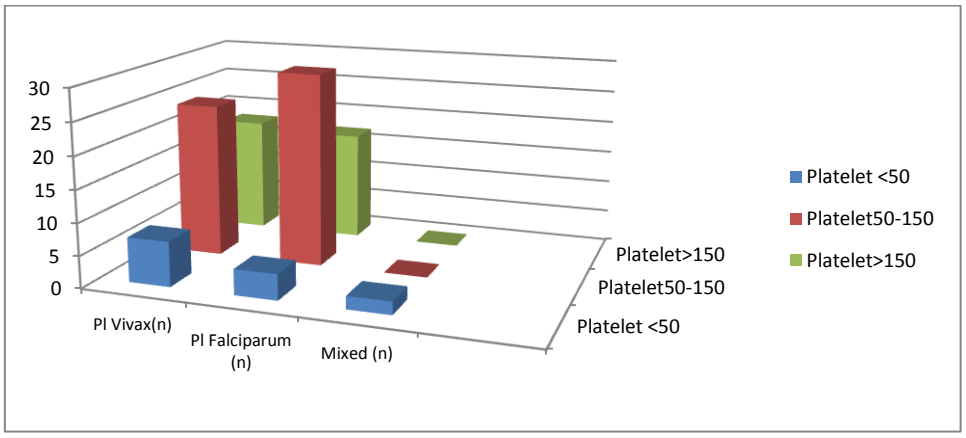

Figure 5(b): Distribution of platelet count in patients with Pl Vivax and Pl Falciparum infection

An inverse correlation was noted between the platelet counts and erythrocyte infection rate in Pl Falciparum infected cases.

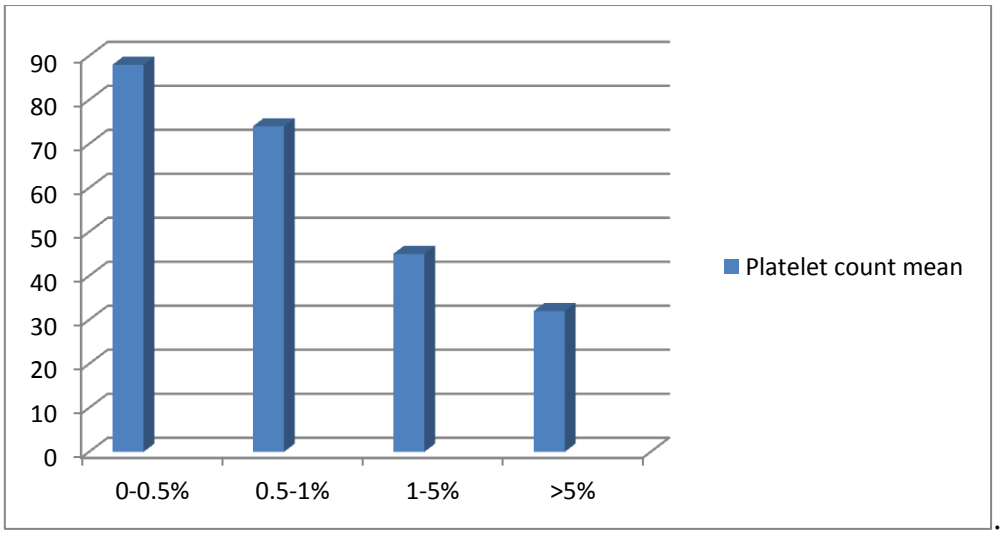

Figure 6: Mean platelet count and percentage of infected erythrocytes in patients with Severe Pl Falciparum infection

The study group was further analysed with emphasis on the complications, if any, noted during the time of hospitalization and association with platelet counts.

Severe thrombocytopenia (Platelet count < 20,000/ul) was seen in 5 patients with Pl Vivax infection and in 9 of those with Pl Falciparum infection. 1 of the cases with mixed species infection also had thrombocytopenia.

Only 1 case with falciparum infection showed abnormal bleeding while jaundice was seen in 27 cases of patients (8 with Vivax and 19 with Falciparum). Renal impairment was seen in 9 cases with Falciparum and 2 with Vivax infections. 1 patient with mixed infection had CNS involvement against 4 with Falciparum and 3 with Vivax infection.

Figure 7: Complications seen in patients with Pl Vivax and Pl .Falciparum

Charachteristic abnormality	Pl Vivax N(%)	Pl Falciparum N(%)	Mixed Infection N
Severe Thrombocytopenia (<20,000/ul)	5(10.2)	9 (18)	1
Abnormal bleeding	None	1(11)	None
Jaundice (>3mg/dl)	8(16.3)	19(38)	1
Renal Failure (>3mg/dl)	2(4.08)	9(18)	1
CNS involvement	3(6.1)	4(8)	1
ARDS	2(4.06)	7(14)	1
Acidosis	3(6.1)	9(18)	1
Circulatory collapse	1(2.08)	4(8)	0
Death	1(2.08)	3(6)	0

Further analysis was done to attempt a correlation between the incidence and degree of thrombocytopenia in patients with Pl Falciparum infection and meeting the WHO 2000 criteria of complicated malaria.

The mean platelet count was 46.8 x 10^9/dl in Falciparum cases without features of DIC against 22 x 10^9/dl in the patient with DIC. Abnormal Bilirubin levels were not found to have any significant statistical association with platelet

counts 60.2 x 10^9/dl in those without jaundice against 52 x 10^9/dl in those with jaundice .Of the three cases of severe Falciparum malaria who died, platelet count was 36 x 10^9/dl against 43.5 x 10^9/dl in those who survived the disease.

Figure 8: Complications seen in patients with Pl .Falciparum and comparison with platelet counts

Characteristic complication	No of patients *with* the complication N(%)	Mean platelet count in patients *without* this complication (no X $10^{9/dl}$)	Mean platelet count in patients *with this* complication (no X $10^{9/dl}$)	P value
Abnormal bleeding	1(11)	46.8	22	0.06
Jaundice (>3mg/dl)	19(38)	60.2	52	0.3
Renal Failure (>3mg/dl)	9(18)	49.1	19.3	0.03
CNS involvement	4(8)	43.2	32.5	0.6
ARDS	7(14)	68.4	36	0.2
Acidosis	9(18)	55.4	32	0.2
Circulatory collapse	4(8)	48.3	28	0.1
Death	3(6)	43.5	36	0.6

Discussion

In our study group, male preponderance was seen with 82% being male patients and the mean age was 38 years. Similar findings have been reported in other studies (Jadhav et al, 2004, Kochar et al, 2005 & Makkar et al, 2002). This could be attributed to the demography in the local area, where young males being more outgoing and the dominant bread winner tend to develop exposure to insect bites more and approach hospital care more promptly.

We further found that 66.6% of our Pl Falciparum cases and 63.3% of Pl Vivax cases had thrombocytopenia. The traditional concept of higher association of thrombocytopenia with Pl Falciparum infections have been questioned in several other national and international studies. (Erhabor et al, 2006, Jadhav et al, 2004, Sina B et al, 2002, Srichaikul et al, 1975, Kelton et al, 1979).This was in accordance with the findings in our study, namely that thrombocytopenia has equal prevalence in both Plasmodium species.

The mean platelet count in our study was 84,000 ± 42 x 10^9/l in our Pl Vivax cases , 96,000 ± 62 x 10^9/l in our simple Pl Falciparum infections, 49,000 ± 20 x 10^9/l in our severe Pl Falciparum cases while both our mixed Plasmodium infected cases had platelet counts < 50,000 x 10^9/l. These were comparable to Indian studies by Jadhav et al, 2004 and Sina B et al, 2002. There were 7 cases of Pl Vivax infections in our study, who had platelet counts <50 x 10^9/l, but none had any bleeding tendencies and all made complete recovery. Similar findings have been reported by Ladhani et al in 2002.

The mean platelet counts in patients with complicated malaria were compared with those having non-severe disease. In patients with cerebral malaria, the mean platelet count was 32.5 x 10^9/l against 43.2 x 10^9/l which was statistically insignificant. Similar findings were seen with regards to DIC, Jaundice, Acidosis, ARDS, circulatory collapse and death.

However statistically significant thrombocyto-penia was seen in patients with renal Impairment when compared with those without severe malaria and associated renal impairment. Studies with similar findings have been reported by Reyburn et al and Jadhav et al. Further, higher parasitemia rates in our Falciparum cases had lower platelet counts in a statistically significant manner.

A possible explanation for these preferential low platelet counts in some but not the other complications of Plasmodium infections could be due to varying affinity and subsequent sequestration of the infected erythrocytes in some vascular beds or probable platelet antibody effect. (Ohtaka et al, 1993, Touze et al,1990)

To summarize, incidence of thrombocytopenia was similar in Plasmodium Vivax and Falciparum infections, but very low platelet counts were seen in patients fulfilling the WHO 2000 criteria of severe Pl Falciparum infection, though statistical significance could be proved only in those with renal impairment

This study was limited by the fact that only one time values of platelet counts and other relevant haematological and biochemical parameters were taken, at the time of hospitalization and sequential follow-up and treatment effects and course during hospital stay were not assessed. More detailed and expansive studies are needed to ascertain the myriad implications and correlations of platelet count with Plasmodium infections.

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