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Comparative hematological changes in malarial infection by *P. vivax* and *P. falciparum*: Observations from the endemic region of Mangalore, India

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Abstract

Purpose of the Study: Malaria causes significant mortality and morbidity in endemic countries. The present study is aimed to evaluate certain hematological changes (RDW, platelet count and volume, total WBC and its differential count) in patients with malaria (*P. vivax* and *P. falciparum* only) and correlating these variations to the type of malaria.

Methodology: 60 vivax malaria and 60 falciparum malaria patients approaching our hospital set-up were studied using purposive sampling technique. The diagnosis and the type of malaria were confirmed by thick and thin blood smears. The blood counts for the above mentioned hematological parameters were assessed by ABX Pentra XL 80 automated blood counter.

Results: On comparing the vivax malaria against the normal controls, highly significant levels of thrombocytopenia ($p=0.0001$), increase in platelet volume ($p=0.0001$), leucopenia ($p=0.004$), monocytosis ($p=0.0001$), eosinopenia ($p=0.0001$), basophilia ($p=0.0001$) and atypical lymphocytosis ($p=0.0001$) were observed, the changes in the other parameters remaining insignificant. However, while comparing falciparum malaria against the normal controls, highly significant levels of thrombocytopenia ($p=0.0001$), increase in platelet volume ($p=0.002$), leucopenia ($p=0.019$), neutrophilia ($p=0.0001$), lymphocytopenia ($p=0.0001$), monocytosis ($p=0.0001$), eosinopenia ($p=0.0001$), basophilia ($p=0.0001$) and atypical lymphocytosis ($p=0.0001$) were observed, the changes in the RDW values remaining insignificant. The increase in the RDW counts were more significant ($p=0.03$) in falciparum malaria as compared to vivax. A highly significant level of neutrophilia ($p=0.003$) and lymphocytopenia ($p=0.0001$) was observed in falciparum malaria. However, the degree of eosinopenia was highly significant ($p=0.001$) in vivax as compared to the falciparum variant of the infection. The other parameters did not show significant differences in the values obtained for the two infections.

Conclusions: Both vivax and falciparum malaria can cause significant hematological changes with a comparatively higher frequency of neutrophilia and lymphocytopenia in falciparum malaria and a higher frequency of eosinopenia in vivax malaria. These characteristic hematological changes should be considered in the diagnosis of malaria and the type of malaria.

Keywords: *Plasmodium vivax*, *Plasmodium falciparum* and hematological changes

Introduction

Malaria is a very common protozoal infection of the tropical and sub-tropical regions, particularly Africa and Asia. The causative agents include the parasites, *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* and are transmitted by the bite of the female Anopheles mosquito [1]. Despite advances in knowledge, malaria continues to cause significant morbidity and mortality worldwide. Apart from increased travel and inadequate prophylaxis, drug resistance has significantly hampered the control of its transmission. The disease has sought global concern, as there are over 40% of the world population living in malaria endemic areas and roughly 300-500 million clinical cases are reported per year of which about 1.5-2.7 million eventually succumb to it every year, mainly children [2].

The mortality rate is usually high (about 20%) in severe malaria (where parasitemia is more than 5%) [3].

The disease may manifest in many forms, depending on the type of malarial parasite transmitted, the most dangerous being *P. falciparum* as its incidence is almost always associated with complications. Fever with chill and rigors remains to be a common manifestation (91% of the patients) seen in all types of malaria, which in vivax is of intermittent nature. Another relatively common finding is splenomegaly detected in 59-73% individuals with vivax and falciparum malaria. Thrombocytopenia was the leading (80% of infected patients) hematological alteration associated with both the Plasmodium species. Other symptoms include malaise, mild diarrhea, jaundice headache and vomiting [4]. In Mangalore (Figure 1), till early 1990 malaria was a restrained infection and medical records show that between 1930 and 1948 over 50,000 people were affected by this disease and more than 2,000 people died. However during the years 1991 to 2008 more than a lakh of people have been affected and in the year 1996 the district was considered to be enlisted among the hyper endemic zones in India for Malaria. Reports indicated that malaria is on the sixth place of the high propensity to become a high endemic zone with over 5.7 percent of its population affected by malaria at any given time [5, 6].

Mortality rate is usually high in severe malaria and more so when both *Plasmodium falciparum* and *Plasmodium vivax* are the parasites involved [7, 8]. Hematological changes are the most common complications in malaria and play an important role in these fatal complications [8]. The hematological abnormalities that have been reported to invariably accompany include anemia, thrombocytopenia, and atypical lymphocytosis and rarely disseminated intravascular coagulation [9]. Leucopenia, leukocytosis, Neutropenia, Neutrophilia, Eosinophilia and monocytosis also have been reported [9, 10]. Of these, thrombocytopenia is a common feature of acute malaria and occurs in both *P. falciparum* and *P. vivax* infections regardless of the severity of infection albeit with variations in the degree of nadir with the gradation of endemicity and health of the patient [11].

With regard to the malarial pathogenesis while *P. vivax* is known to cause low parasitemia, mild anemia and in rare instances splenic rupture and nephritic syndrome, *P. falciparum* infestations cause a high level of parasitemia, severe anemia, cerebral symptoms, renal failure, pulmonary edema and even death. The high grade of anemia is explained by the rupture of red blood cells (RBCs) followed by the release of merozoites in blood or destruction of non deformable peripheral RBCs (PRBCs). During diapedesis, ingestion/ destruction of PRBCs by macrophages/Ig dependent mechanism/ NK cells, destruction of non infected RBCs by immune mechanisms or by dyserythropoiesis due to release of inflammatory cytokines [12].

The red cell distribution width (RDW) also significantly varies. On arrival to the hospital, a patient presenting with a higher RDW (increased population dispersions of red cell volume) can act as an indicator of malaria. The increased RDW correlates to an increase in the number of macrocytes. This increase may aid in the diagnosis of vivax malaria in the malaria endemic areas [13, 14]. The most drastic and devastating changes are of those associated with platelets. Thrombocytopenia is a common finding in both vivax and falciparum malaria and its levels determine the prognosis of the patient. Platelet survival is reported to be reduced to 2-4 days in severe falciparum malaria. The platelet count is usually inversely related to the degree of parasitemia [15-17].

Abnormal thrombopoiesis, earlier attributed to this low platelet count has been ruled out from the cause of this condition as normal to increased number of megakaryocytes have been seen in the bone marrow. Hence the only likely explanation is that it is due to peripheral destruction of the platelets as evidenced by decrease in platelet survival time to less than half of the normal [17].

Many theories have been suggested to explain this, of which one is the non-immune mechanism [18]. However this has not gained sufficient recognition due to inconsistent findings. Also platelet associated Ig G, and Ig G coated platelets have not been consistent findings. A possible reason for the thrombocytopenia could be the enhanced splenic uptake or sequestration and in patients with DIC, the reduced counts have been attributed to the consumptive coagulopathy [19-23]. The immune mediated theory of thrombocytopenia suggests that IgG forms a complex with the malaria antigen which binds to and damages the circulating platelets which are eventually removed from the circulation. Another possible mechanism is that platelets engulf malarial parasites and get destroyed in the process and the damaged platelets are thus removed from the circulation. The level of thrombocytopenia could be as low as 10,000 to 20,000/ul [17, 23, 24].

Platelets are said to be invaded by the malarial parasites during the days of acute infection and these are bound to a high level of IgG which are destroyed by the spleen. This returns to normal as the platelet level increases [24, 25]. Irrespective of the levels of thrombocytopenia, bleeding tendencies have not been reported. This could possibly be so as platelets during malaria are hyperactive and thus enhance the hemostatic responses [16, 26]. Apart from the platelet counts, the results obtained in regard to the platelet volumes have also been consistent. The mean platelet volume has been reported to be significantly higher in patients suffering from malaria. This is probably due to the early release of platelets from the bone marrow in response to peripheral destruction of platelet [27, 28].

The findings in regard to the total WBC count in patients with malaria have been more or less inconsistent. Mild leukocytosis and leucopenia have been observed varying with different clinical settings. Leukocytosis is more often seen in patients with severe falciparum malaria and is associated with bad prognosis. This could be attributed to the TNF α levels. The other common changes observed is monocytosis [19, 21, 27, 29]. Eosinopenia has also been a common finding which is usually reversed by chemotherapy during which a rebound eosinophilia is seen which correlates or predicts a successful hematological recovery [30]. The blood smears have also revealed mild to moderate atypical lymphocytosis in these patients [19, 21, 29, 31].

Falciparum malaria has been characterized by a higher WBC count, higher lymphocyte count and lower monocyte counts and these are associated independently with mortality. Severity of malaria depends on the host response to malaria by the production of TNF α and IFN γ and an excessive secretion of these cytokines by the increased number of lymphocytes are said to contribute to the severity of the disease. Uncomplicated malaria is usually associated with lymphocytopenia. This is claimed to be either due to the redistribution of the lymphocytes especially T lymphocytes to the site of the inflammation and /or due to apoptosis of T lymphocytes brought about by extremely elevated levels of Fas (death ligand). The levels of which

then gradually decrease on treatment simultaneous with the obvious elevation of the lymphocyte count [26, 32, 33].

The quantitative estimation of the hematological changes and thrombocytopenia in particular is also of help to the physician in deciding the treatment regimen and the possible requirement of platelet infusions if necessary. In this study, we aim to evaluate the hematological changes that occur in falciparum and vivax malaria as these variations frequently aid in the early diagnosis of this infection. The present study was carried out with a objective to assess the alterations in the WBC count and distribution, platelet count and volume and RDW in malaria caused by vivax and falciparum.

Materials and methods

This was a hospital based study and was carried out during June to July 2009 at Father Muller Medical College after obtaining the permission from the Hospital Ethics Committee. The data were collected from the Pathology Laboratory of the hospital from the clinically confirmed cases of malaria. The factors considered were that the patients with peripheral blood smears positive for either *P. falciparum* or *P. vivax* with all the hematological parameters also evaluated by ABX Pentra XL 80 automated blood counter was recorded. The exclusion criteria included was patients positive for other malaria species (excluded by examination of morphology of malarial parasite and patients with a history of intake of anti-malarial drugs prior to blood smear examination. The data from the records were retrieved and entered in excel and analyzed using the Vassar stats Online program. The One-way ANOVA with Bonferroni multiple comparisons was used to compare the statistical significance between the three groups. A p value of < 0.05 was considered significant.

Results

The results are indicated in table 1 and individual parameter is explained here with in detail:

RDW: In the present study, the increase in the RDW values for vivax ($12.99 \pm 1.39\%$). ($p=0.78$) and falciparum ($13.37 \pm 1.31\%$) ($p=0.07$) malaria are not significant as compared to the normal ($12.83 \pm 0.62\%$). But when comparing the two plasmodium species against each other, differences in their RDW values are significant ($p=0.03$).

Platelet count: It was observed that a highly significant level of thrombocytopenia exists in patients suffering from vivax malaria ($85.22 \pm 39.83 \times 10^3/\text{mm}^3$) $p=0.0001$ and in patients suffering from falciparum malaria ($100.82 \pm 67.22 \times 10^3/\text{mm}^3$) $p=0.0001$ when compared to the normal controls ($255.75 \pm 58.41 \times 10^3/\text{mm}^3$).

Platelet volume: In the present study, the mean platelet volume in patients suffering from vivax malaria ($8.93 \pm 0.94 \mu\text{m}^3$) and falciparum malaria ($8.84 \pm 1.08 \mu\text{m}^3$) were found to elevated, and these values were highly significant when compared against the normal ($8.08 \pm 0.55 \mu\text{m}^3$) ($p=0.0001$ and $p=0.002$ respectively). However, the elevation of the mean platelet volume was not significant on comparing the two Plasmodium species against each other ($p=0.50$).

Total WBC count: It has been observed that there exists a highly significant leucopenia in vivax malaria ($5.46 \pm 1.90\%$). and falciparum malaria ($5.94 \pm 2.74\%$). as compared to the normal control ($6.73 \pm 1.58\%$). ($p=0.004$ and $p=0.019$

respectively). However, on comparing the leucopenia between the two different species of malaria, no significant difference was observed ($p=0.74$).

Neutrophils: In the present study, it has been observed that the neutrophil count in vivax malaria ($58.40 \pm 13.01\%$) does not show any significant change ($p=0.09$) when compared to the normal ($54.52 \pm 7.02\%$). However, in falciparum infections, we have observed, a highly significant ($p=0.0001$) neutrophilia ($65.63 \pm 11.40\%$). On comparing the two different infections against each other, the neutrophil percentage was significantly higher in falciparum malaria ($p=0.003$) than the vivax form of the disease.

Lymphocytes: In the present study, no significant difference was observed in the lymphocyte values in vivax malaria ($30.43 \pm 12.27\%$) as compared to the normal ($34.03 \pm 6.85\%$) ($p=0.067$). However, a highly significant lymphocytopenia was seen in falciparum malaria ($22.26 \pm 9.30\%$) as compared against the normal ($p=0.0001$).

Monocytes: In the present study, a highly significant increase in the monocyte count in vivax ($8.48 \pm 3.98\%$) ($p=0.0001$) and falciparum malaria ($8.71 \pm 3.34\%$) ($p=0.0001$) has been observed as compared to the normal ($5.03 \pm 2.11\%$). Also in this study, the difference in values of monocytes in the two species was not found to be significant ($p=0.71$).

Eosinophils: In the present study, it was observed that there exists a highly significant eosinopenia in vivax ($1.55 \pm 2.25\%$) ($p=0.0001$) and falciparum infections ($1.96 \pm 1.87\%$) ($p=0.0001$) as compared to our normal controls ($5.84 \pm 4.45\%$). Also, when comparing the eosinopenia of the two infections, we observed a highly significant difference in the values of patients infected with vivax and falciparum malaria ($p=0.001$).

Basophils: A highly significant basophilia in vivax ($1.13 \pm 0.69\%$) ($p=0.0001$) and falciparum malaria ($1.36 \pm 1.22\%$) ($p=0.0001$). When compared to the normal controls ($0.57 \pm 0.12\%$). However, this increase was not significant on comparing the two forms of the infection as against each other ($p=0.90$).

Atypical lymphocytes: A highly significant presence of atypical lymphocytes in both vivax ($2.21 \pm 1.29\%$) ($p=0.0001$) and falciparum ($2.77 \pm 2.47\%$) ($p=0.0001$) forms of the infection as compared to the normal ($0.95 \pm 0.37\%$). However, on comparing the two infections against each other, the differences were not significant ($p=0.537$).

Discussion

Malaria continues to be a great health problem in some of the Asian and African countries around the world [28]. Hematological changes associated with malaria infections are well recognized, but the specific changes may vary with the type of malaria [26]. In this study, significant changes have been observed involving RDW, platelet count, platelet volume, Total WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils and atypical lymphocytes.

In the present study an increase in the RDW values was observed. This may be due to the high parasitemia and

increased destruction of RBCs in *P. falciparum* malaria producing more macrocytes (reticulocytes). In patients presenting with malaria a higher RDW can act as an indicator of malaria. The increased RDW is due to the increase in the number of macrocytes [13]. With regard to the platelet count, when compared to the normal controls a highly significant level of thrombocytopenia was observed in patients suffering from vivax malaria and falciparum malaria. This observation is not in agreement to the previous reports where the investigators had observed a moderate thrombocytopenia associated with *P. vivax* infection and mixed infection (*P. vivax* and *P. falciparum*) [28].

Thrombocytopenia has been a common finding in both vivax and falciparum malaria. Its degree is considered by some as relevant to prognosis as platelet survival is reduced in severe falciparum malaria [33]. Low platelet count due to abnormal thrombopoiesis has been ruled out, as evidenced by normal to increased number of megakaryocytes in the bone marrow. Hence the only plausible explanation is that it is due to the peripheral destruction of platelets as evidenced by decrease in platelet survival time to less than half of the normal [17].

In immune mediated thrombocytopenia, Ig G forms a complex with the malarial antigen and the complex binds to and damages the circulating platelets which are then removed from the circulation. Platelets can engulf the malarial parasites and hence get destroyed. Platelet count may fall as low as 10000-20000/ μ l [16, 17, 26]. In spite of a low platelet count, bleeding tendencies have never been

reported. This is because platelets will be hyperactive during malaria and will enhance the homeostatic responses [16, 26] and is in agreement to earlier observations [16].

The mean platelet volume in patients suffering from vivax malaria and falciparum malaria were found to elevated, and these values were highly significant when compared against the normal and is in agreement to earlier reports [27]. It was observed that the mean platelet volume was significantly higher in malaria patients. This probably represents the early release of platelets from the bone marrow in response to peripheral destruction of platelets [27].

In the present study, it has been observed that compared to the normal control a highly significant leucopenia occurs in both vivax and falciparum malaria and are in agreement to previous reports [27, 28]. Leucopenia is an important abnormality in patients with severe falciparum malaria and is associated with a bad prognosis. TNF- α may be responsible for this [19, 21, 27, 29]. Analysis of the individual constituents of the leucocytes showed that when compared to the normal controls, a significant neutrophilia and lymphocytopenia were seen only in falciparum malaria and is consistent with the earlier findings [16, 28]. On a contrary, a significant increase in the monocytes and basophils and a significant decrease in eosinophil counts were observed in both vivax and falciparum malaria and are in agreement to previous observation [28, 29]. Additionally highly significant increases in the number of atypical lymphocytes were observed in both forms of malaria thereby validating the earlier observations [29, 31].

Table 1: Hematological changes in the people infected with *Plasmodium vivax* and *Plasmodium falciparum* in the malaria endemic region of Mangalore, India

	Control	Vivax	Falcifarum
RDW (%)	12.83 \pm 0.62	12.99 \pm 1.39	13.37 \pm 1.31*
Platelet Count (10 ³ /mm ³)	255.75 \pm 58.41	85.22 \pm 39.83 ^a	100.82 \pm 67.22 ^a
Platelet Volume (μ m ³)	8.08 \pm 0.55	8.93 \pm 0.94 ^a	8.84 \pm 1.08 ^a
Total WBC Count (10 ³ /mm ³)	6.73 \pm 1.58	5.46 \pm 1.90 ^b	5.94 \pm 2.74 ^c
Neutrophils (%)	54.52 \pm 7.02	58.40 \pm 13.01	65.63 \pm 11.40 [@]
Lymphocytes (%)	34.03 \pm 6.85	30.43 \pm 12.27	22.26 \pm 9.30 [#]
Monocytes (%)	5.03 \pm 2.11	8.48 \pm 3.98 ^a	8.71 \pm 3.34 ^a
Eosinophils (%)	5.84 \pm 4.45	1.55 \pm 2.25 ^a	1.96 \pm 1.87 ^{a&}
Basophils (%)	0.57 \pm 0.12	1.13 \pm 0.69 ^a	1.36 \pm 1.22 ^a
Atypical Lymphocytes (%)	0.95 \pm 0.37	2.21 \pm 1.29 ^a	2.77 \pm 2.47 ^a

The superscript alphabets indicates comparison between control with vivax and falcifarum a = p < 0.0001; b = p < 0.0004; c = p < 0.02
The superscript symbol indicates inter comparison between vivax and falcifarum * = p < 0.03; @ = p < 0.003; # = p < 0.0001; & = p < 0.001

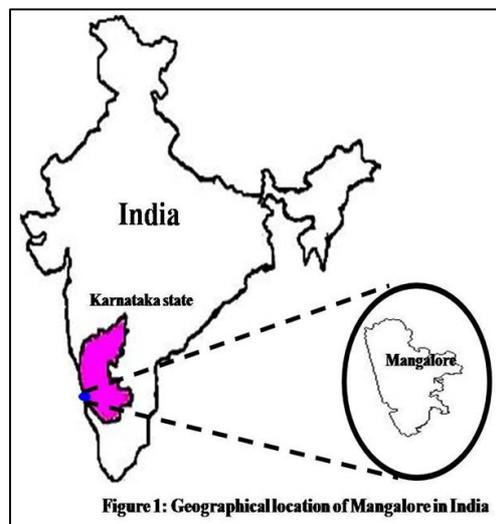


Fig 1: Geographical location of mangalore in India

Conclusion

The results from the present study indicate that patients with vivax and falciparum malaria experience a high degree of thrombocytopenia, increase in platelet volume, leucopenia, monocytosis, eosinopenia, basophilia and atypical lymphocytosis. Additionally, it was also observed that patients with falciparum malaria experienced a high degree of neutrophilia and lymphocytopenia, while *P. vivax* can cause a higher degree of eosinopenia. Together, these observations suggest that the characteristic hematological changes could be an important prognostic indicator in the diagnosis of malaria and the type of malaria.

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