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Drug Utilization Study of Anti-malarial in a Tertiary Care Teaching Hospital.

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Abstract

National Drug Policy on Malaria has been adopted by the Ministry of Health and Family Welfare, Govt. of India in 2010 to guide the medical professionals on the current method of diagnosis and treatment based on the national drug policy. A retrospective study was performed using data of confirmed malarial adult in-patient records in a tertiary care teaching hospital. Adherence to antimalarial prescribing behavior according to guidelines was assessed and discussed. A total of 60 patients with positive *P.vivax* infection were included in our study. All the patients were thrombocytopenic on admission but severity was found only in 6 (10%) patients because of elevated bilirubin and creatinine. Artesunate plus sulfadoxine-pyrimethamine (A+SP) with other antimalarials was most frequently prescribed among antimalarial agents (in 58 cases, 96.66% of the total) for suppressing acute attacks. As per the guidelines, the standard regimen for treating *P.vivax* infection is chloroquine and primaquine which was the least antimalarial combination prescribed 2 (3.33%) in present study. Our study reveals that most of the *P.vivax* cases were treated parenterally considering as severe *P.falciparum* malaria which usually deviates from the given WHO and National guidelines. Chloroquine prescribing was drastically reduced. Healthcare providers should be encouraged to comply with the current therapeutic guidelines.

Key Words

Antimalarial combinations, thrombocytopenia, adherance.

Introduction

Malaria is one of the most important transmissible diseases in humans. There is an intimate relationship between the malaria parasites and the blood. The obvious advantages to parasites of intra-erythrocytic parasitism are that it offers them protection from the host's defense mechanisms and transport through the blood stream to where they can be taken up in the peripheral circulation by blood sucking female anopheline mosquitoes[1]. It is estimated to be directly responsible for around one million deaths annually worldwide [2]. *P.vivax* causes up to 65% of malaria in India and is becoming increasingly resistant to malaria drugs[3]. Thrombocytopenia is a common feature of acute malaria and occurs in both *P.vivax* and *P. falciparum* infections regardless of severity of infection. Early investigators suggested that the major coagulation abnormality of malaria was disseminated intravascular coagulation (DIC), but in recent years clinicians have recognized that thrombocytopenia is common and early sign of malaria infections, whereas DIC is rare[4]. Both non-immunological as well as immunological destruction of platelets have been implicated in causing thrombocytopenia but the mechanisms involved are still not completely clear[5]. Thrombocytopenia improves with disease resolution and the platelet count is generally normal within seven days but ranged from 2-28 days in one series[6]. A revised National Drug Policy on Malaria has been adopted by the Ministry of Health and Family Welfare, Govt. of India in 2010 to guide the medical professionals on the current method of diagnosis and treatment based on the national drug policy[7]. There is scarcity of literatures on drug utilization of antimalarials in various hospital settings, thus by keeping and considering such challenge in mind the present study was conducted at a tertiary care teaching hospital that caters the treatment need of both rural as well as urban population. The present study evaluates the adherence to the WHO and National (India)

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guidelines for the prescribing of antimalarials for treating *P.vivax* malaria patients.

Materials and Methods

The study was carried out by the Clinical pharmacy department in Bharati Hospital and Research Centre (tertiary care teaching hospital), Pune (India). All adult in-patients records of infectious diseases were reviewed retrospectively for the duration of June 2010 to May 2011. Among them malaria patients with severe manifestations and evidence of *P.vivax* infection was included in the study. Patients who showed evidence of mixed infections and *P.falciparum* infection were excluded from the study. During the study duration total 326 patient's infectious case files were reviewed. Patients with *P.vivax* infections of age ≥ 18 years of either gender were involved in the study who was receiving antimalarial treatment for infection. Any patients with age < 18 years, pregnant women, patients with co-morbid conditions like hematological complications, diabetes, renal disease and hepatic disease were excluded from the study. Using data of confirmed *P.vivax* malarial adult in-patient records, information on age, gender, duration of hospital stay, presenting complaints, laboratory data, diagnostic tests performed (peripheral thin film blood smear and rapid malarial test) and medications prescribed were documented in the patient profile form designed for the study. Further, disease distribution as per gender, hematological changes including hemoglobin, total leukocyte count, differential count, platelet count and glucose-6-phophatase dehydrogenase deficiency, hepatological changes including aspartate transaminase, alanine transaminase, total bilirubin, direct bilirubin, total protein, albumin, other laboratory parameters like serum creatinine, and form of *P.vivax* parasite were assessed. Also, severity of thrombocytopenia associated with *P.vivax* was classified according to the protocol used by Memon et al. i.e. mild (<150,000 to >50,000), moderate (<50,000 to >20,000) and severe (<20,000) and type of drug regimen prescribed to patients was assessed.

Results and Discussion

Out of 326 patient's infectious case files 76 malarial case files were reviewed. Among which *P. falciparum* causative parasite species was found in 16 cases (21%) and *P.vivax* in 60 cases (79%). The mean age of the patients was found to be 33 yrs and mean hospital stay was 5 days (Table 1). In case of hematological abnormalities, the hemoglobin of the study population was found to be deranged varying within the range of 6.2-14.9 gm/dl. Also, wide variation is observed in WBC count ranging from 2300-24000 cells/mm^3. Also among WBC cells, large variations were seen with respect to neutrophils, eosinophils, lymphocytes, monocytes as shown in Table 2. In the study population, malaria associated hepatic abnormalities in laboratory parameters were depicted in Table 3. Deviation from normal range was observed with AST, ALT, bilirubin total, bilirubin direct, total protein and albumin. Mean serum creatinine was found to be 1.17 ± 1.1mg % between range of 0.5 – 6.9mg%. G6PD reports were analyzed and among all patients least G6PD noted as 2.6 U/gHb while the maximum value of G6PD was found to be 22.6 U/gHb with mean range of 11.61 U/gHb (Table 4). The trophozoite form of *P.vivax* parasites was found to be accountable for causing malaria in most of the patients 34 (56.66%) (Figure1). 44 cases (73.33%) do not show any major finding in USG abdomen and pelvis reports (Figure 2). Severity to malaria was only found in 6 (10%). On the day of admission all the patients were thrombocytopenic among which 4 (6.66%) patients were found with severe thrombocytopenia and 28 (46.6%) patients were found for both mild and moderate thrombocytopenia. The severity of thrombocytopenia resolves with treatment progression (Figure 3). Artesunate plus sulfadoxine-pyrimethamine (A+SP) with other antimalarials was most frequently prescribed among antimalarial agents (in 32 cases, 54% of the total) for suppressing acute attacks. The prescribing behaviour was evaluated by classifying each A+SP case into three groups: A+SP in combination with doxycycline and primaquine in group one 48 (80%), A+SP with chloroquine and primaquine in group two 8 (13.33%) and A+SP with doxycycline in group three 2 (3.33%). The least antimalarial combination recorded was chloroquine plus primaquine with doxycycline in 2 (3%) cases (Figure 4). Only 2 (3.33%) patients were not prescribed with primaquine as they were G6PD deficient. In this study, the major derangements were observed in hematological and hepatic laboratory parameters. In agreement with the findings, decrease in hemoglobin in 34(56.67%) cases of the present study population

was found, and other studies have also reported a decrease in haemoglobin occurring during infection with the major species of malaria[8]. The mechanical destruction of parasitized red blood cells reduced red blood cell (RBC) production in the bone marrow, phagocytosis of uninfected RBCs and autoimmune destruction of RBCs are some of the mechanisms known to cause anemia during malaria. The hematological analysis of this study have shown that majority of malaria infected patients are presented with total white blood cell counts within the normal range 40(66.67%), but deranged value was observed in 20 (33.33%) ranging from 2300-24000 cells/mm^3 and most were thrombocytopenic. This result compliment with a study conducted by Walter RJ Taylor et al,[6]. Leucopenia was observed only in 16 (26.67%) patients of *P.vivax* in our study, although Deata Kassa et al had observed leucopenia only in falciparum patients while Meek et al reported leucopenia in vivax malaria patients[9,10]. An increase in neutrophils count 22 (36.66%) in our study was found consistent as reported by Toure-Bolde A et al and no increase in monocytes were observed[11]. Also, no decrease in eosinophils count was found in our study while this had been observed by Elhassan IM et al,[12]. Among the various hematological changes in malaria, thrombocytopenia is the most consistent one, which occurs in more than half of the patients where as in our study on the day of admission all patients were thrombocytopenic among which only 4(6.67%) patients were severely thrombocytopenic[13]. Our results were generally comparable with those of most of the studies, thus signifying the association of thrombocytopenia with malaria caused by *P.vivax*[13,14,15]. The precise mechanism behind thrombocytopenia, however, remains unclear. Both the immunological as well as the non-immunological destruction of platelets have been implicated[13]. In most the studies, thrombocytopenia was neither associated with the severity of the disease or death in malaria[16,17]. It usually disappears with the treatment of the disease and requires no treatment for itself[18]. Another major derangement in laboratory parameters was observed in hepatic parameters assessment. Jaundice in malaria is multifactorial. It is believed to occur as a result of intravascular hemolysis of parasitized erythrocytes, hepatic dysfunction, and possibly due to microangiopathic haemolysis associated with disseminated intravascular coagulation. Most patients have unconjugated bilirubinaemia due to haemolysis; conjugated bilirubin may predominate due to hepatocyte dysfunction. Incidence of raised serum bilirubin has been reported in 34(57%) patients in a study conducted by Nitya Nand et al,[19]. Similarly, in our study 30 patients were found with elevated serum bilirubin among which 4 were found with jaundice (serum bilirubin > 3mg/dl) according to guidelines. They also reported elevated transaminases which are consistent with our study as 12(20%) patients were found with elevated AST and 6(10%) patients were found with elevated ALT. According to the guidelines for diagnosis and treatment of malaria in India, 2011 serum creatinine > 3 mg/dl is considered as renal failure leading to severe malaria; similarly in our study 8(13.33%) patients were found with elevated serum creatinine among which only 2(3.33%) patients were found to be with serum creatinine > 3 mg/dl. The elevated findings of serum creatinine were found consistent with a study Nitya Nand et al,[19]. As per WHO and National guidelines for diagnosis and treatment chloroquine monotherapy (25 mg base/kg body weight over 3 days) is recommended as the standard treatment for *P.vivax* malaria, because the parasite remains sensitive to chloroquine in much of the world and for preventing relapse primaquine (0.25 or 0.5 mg base/kg body weight in a single daily dose for 14 days) is used as a supplement to the standard treatment for the purpose of eradicating dormant parasites in the liver called as hypnozoites[7, 20]. While in our study, 58(96.66%) patients received artesunate plus sulphadoxine-pyrimethamine combination with other antimalarials as a standard treatment for *P.vivax* patients, this prescribing behavior may be a rational one and does not deviate from WHO and National guidelines for diagnosis and treatment of malaria. Because, artemisinins when combined with sulphadoxine-pyrimethamine, have provided excellent cure rates in both chloroquine sensitive and chloroquine resistant strains of *P. vivax* to reduce the emergence of resistance through mutation for pyrimethamine by *P.vivax*. [20, 21] Treatment failure with chloroquine in *P.vivax* malaria is rare in India but still in our study only 2(3.33%) patients were found to be prescribed according to the guidelines[7]. In our study, 8 patients (13.33%) were prescribed with artesunate plus chloroquine along with other antimalarials, such combination was also studied in one study carried

out by Colin J. Sutherland et al in *P.falciparum* but chloroquine plus artesunate is not sufficiently efficacious to justify its introduction as a replacement for chloroquine monotherapy[22]. There is no extensive literature available on the use of such antimalarial drug combination in *P.vivax* malaria. So, it is questionable in terms of cure rate to use artesunate along with chloroquine in *P.vivax* infected patients.

Conclusion

In our study, we report thrombocytopenia to be the most common finding in patients with confirmed malaria cases of *P.vivax* species. First-line treatment of uncomplicated *P.vivax* malaria as per the National Malaria policy which specifies the combination of chloroquine and primaquine (14 days) has been drastically reduced and a change in prescribing behaviour was observed as all the confirmed *P.vivax* cases were treated with artesunate in combination with other antimalarials and the cure rates was good with resolving thrombocytopenia. The antimalarial combinations prescribed were in line with the guidelines but keeping the financial constraints in mind chloroquine prescribing should be emphasized.

References

1. Abdalla SH, Pasvol G. Malaria: A hematological perspective. Volume 4. Imperial college press; 2004. p. xii.
2. Greenwood BM, Boding K, Witty CJM, Target GA. Malaria. Lancet. 2005, 365, 1487 – 98.
3. Devi G, Indumathi VA, Sridharan D, Srinivas BP, Sandhya BM. Evaluation of ParaHITf strip test for diagnosis of malarial infection. Indian J Med Sci. 2005, 56, 489 -94.
4. Col. Uttra KM, Devrajrani BR, Shaikh K, Shaikh KR, Shah SZA. Severity of thrombocytopenia and prolonged bleeding time in patients with malaria (A Clinical Study of 162 Malaria Cases). World Appl. Sci. J. 2010, 9 (5), 484 – 488.
5. Makkar RPS, Mukhopadhyay S, Monga A, Gupta AK. Plasmodium vivax malaria presenting with severe thrombocytopenia. Braz J Infect Dis. 2002, 6 (5), 263 – 265.
6. Taylor WRJ, Widjaja H, Basri H, Ohrt C, Taufik T, Tjitra E, et al. Changes in the total leukocyte and platelet counts in Papuan and non Papuan adults from northeast Papua infected with acute *Plasmodium vivax* or uncomplicated *Plasmodium falciparum* malaria. Malaria journal. 2008, 7, 259.
7. Guidelines for diagnosis and treatment of malaria in India 2011; Government of India, 2nd edition, NIMR, New Delhi, pp. 1-14.
8. Erhart LM, Yngyuen K, Chuanak N, Buathong N, Laoboonchai A, Miller RS et al. Hematologic and clinical indices of malaria in a semi-immune population of western Thailand. Am J Trop Med Hyg. 2004, 70(1), 8-14.
9. Kassa D, Petros B, Messele T, Admassu A, Adugna F, Wolday D. Parasito-hematological features of acute *Plasmodium falciparum* and *Plasmodium vivax* malaria patients with and without HIV co-infection at Wonji Sugar Estate, Ethopia. Ethiop. J. Health Dev. 2005, 19(2), 132-139.
10. 10. McKenzie EF, Prudhomme WA, Magill AJ, Forney JR, Permpanich B, Lucas C et al. White Blood Cell Counts and Malaria. The Journal of Infectious Diseases. 2005, 192, 323–30.
11. Taylor WRJ, Widjaja H, Basri H, Ohrt C, Taufik T, Tjitra E. Changes in the total leukocyte and platelet counts in Papuan and non Papuan adults from northeast Papua infected with acute *Plasmodium vivax* or uncomplicated *Plasmodium falciparum* malaria. Malaria Journal. 2008, **7**, 259.
12. i Layla A.M. Bashawri, Ahmed A. Mandil, Ahmed A. Bahnassy, Mirghani A. Ahmed. Malaria: Hematological aspects. Annals of Saudi Medicine. 2002, 22, 372-377.
13. Khan SA, Ali W, Shahmi SN, Luqman M, Latif T. Platelet count in malaria. Pak J Pathol 2008, 19(3), 86-88.
14. Rathod DA, Patel V, Kaur AA, Patel VD, Patel DD. Diagnosis of acute malaria by laser based cell counter with comparison of conventional and recent techniques in Indian scenario. Indian J Pathol Microbiol. 2009, 52, 185-8.
15. Faseela TS, Roche RA, Anita KB, Malli CS, Rai Y. Diagnostic value of platelet count in malaria. Journal of Clinical and Diagnostic Research 2011, 5(3), 464-466.
16. Pascual CC, Kai O, Newton CRJC, Norbertpeshu, Roberts DJ. Thrombocytopenia

in falciparum malaria is associated with high concentration of IL-10. Am J Trop Med Hyg. 2006 Sep, 75(3), 434-436.

17. Ladhani S, Newton CRJC. Letter to the editor. Am J Trop Med Hyg. 2003, 68 (4), 379-380.
18. Katira B, Shah I. Thrombocytopenia in *Plasmodium vivax* infected children. J Vector Borne Dis. 43, 2006, 147-149.
19. Nitya Nand, Aggarwal H, Sharma M, Singh M. Systemic manifestations of malaria. Journal, Indian Academy of Clinical Medicine. 2001, 2(3), 189-194.
20. World Health Organization. Guidelines for the treatment of malaria 2010; 2nd edition, 167.
21. Tjitra E, Baker J, Suprianto S, Cheng Q, Anstey NM. Therapeutic efficacies of artesunate-sulfadoxine-pyrimethamine and chloroquine-sulfadoxine-pyrimethamine in vivax malaria pilot studies: relationship to *Plasmodium vivax* dhfr mutation. Antimicrob. Agents Chemother. 2002, 46(12), 3947-3953.
22. Sutherland CJ, Drakeley CJ, Obisike U, Coleman R, Jawara M, Targett GAT et al. The addition of artesunate to chloroquine for treatment of *Plasmodium falciparum* malaria in gambian children delays, but does not prevent treatment failure. Am J Trop Med Hyg. 2003, 69(1), 19-25.

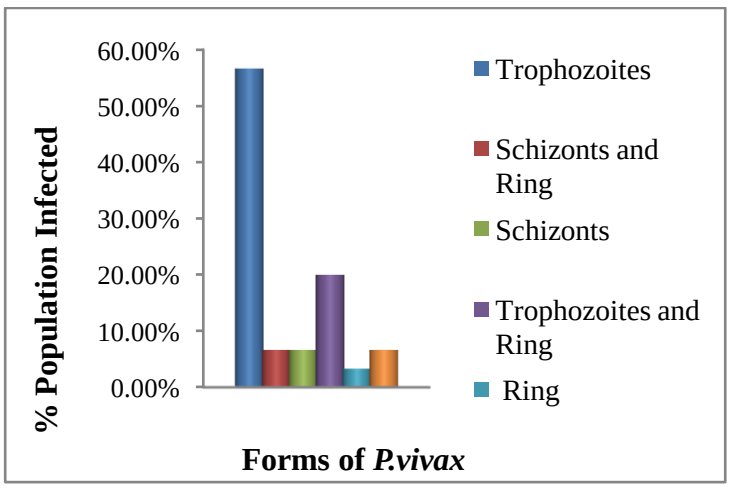

Figure 1: % Population Infected With Various Parasitic Forms of *P.Vivax.*

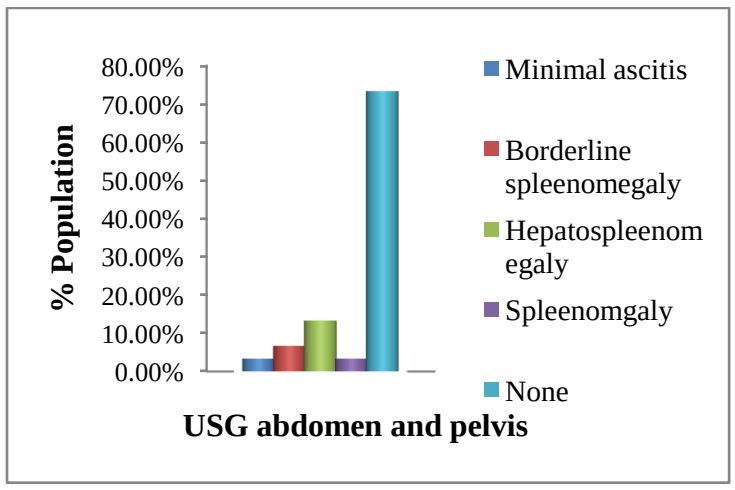

Figure 2: Hepatic and Spleenic Abnormality in % Population According to USG.

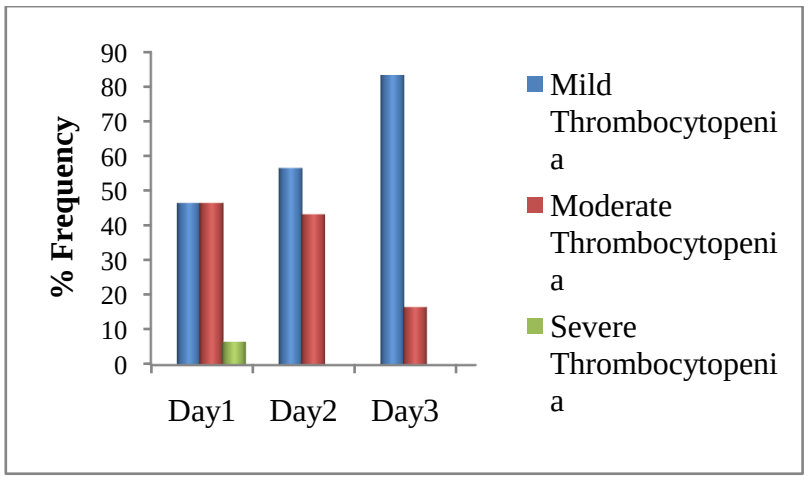

Figure 3: Thrombocytopenia Severity in *P.Vivax* Infected Patients.

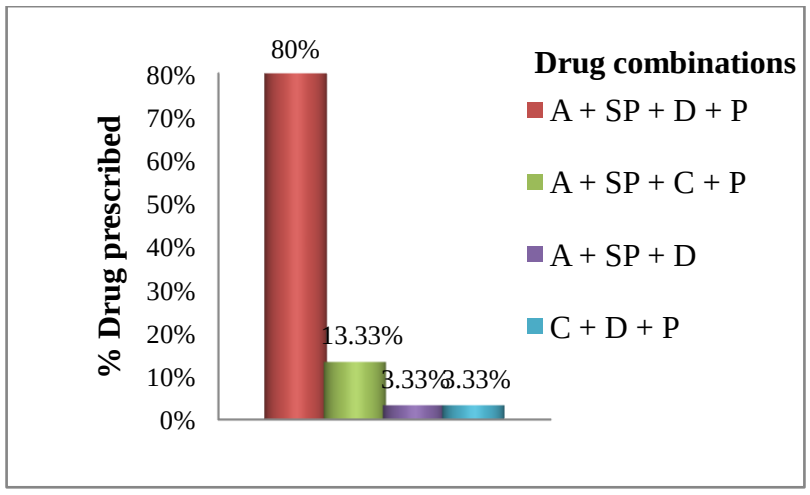

Figure 4: Prescribing Pattern of Antimalarial Drugs. (A= Artesunate; SP= Sulfadoxine-pyrimethamine; D = Doxycycline; C= Chloroquine; P = Primaquine)

Table 1: Patient Characteristics.

PATIENT CHARACTERISTICS	MEAN ± SD, WITH RANGE IN PARENTHESIS
Age (yrs.)	32.9±13.62 (18-65)
Sex **Male (Number, %)** **Female (Number, %)**	 N= 22, (73.33%) N= 08, (26.66%)
Days of stay	5±1.46 (2-9)

Table 2: Hematology.

PARAMETERS	NORMAL RANGE	MEAN± SD, WITH RANGE
Hb (g/dl)	11.5 – 16	11.5 ± 2.1 (6.2-14.9)
WBC (cells/mm^3)	4000 – 11000	5693.33 ± 3989.2 (2300-24000)
Neutrophils (%)	40 – 70	61.63 ± 15.32 (25-85)
Eosinophils (%)	1 – 6	3.8 ± 1.58 (2-10)
Lymphocytes (%)	20 – 45	28.36 ± 12.21 (11-59)
Monocytes (%)	2 - 10	4.1 ± 1.84 (1-8)

Table 3: Liver Function Tests.

PARAMETERS	NORMAL RANGE	MEAN± SD, WITH RANGE
AST (IU/L)	Upto 40	35.1 ± 13.02 (18-68)
ALT (IU/L)	Upto 40	29.26 ± 9.87 (14-55)
Bilirubin total (mg/dl)	0.2 – 1.1	1.35 ± 0.89 (0.3-3.49)
Bilirubin direct (mg/dl)	0 – 0.25	0.541 ± 0.42 (0.12-1.52)
Total protein (g/dl)	6 – 8	6.51 ± 0.73 (4.6-7.8)
Albumin (g/dl)	3.5 – 5	3.62 ± 0.67 (1.09-4.2)

Table 4: Mean Serum Creatinine and G6PD Values.

PARAMETER	MEAN WITH RANGE IN PARENTHESIS
Serum Creatinine (mg %)	1.17(0.5-6.9)
G6PD (U/gHb)	11.61(2.6-22.6)

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