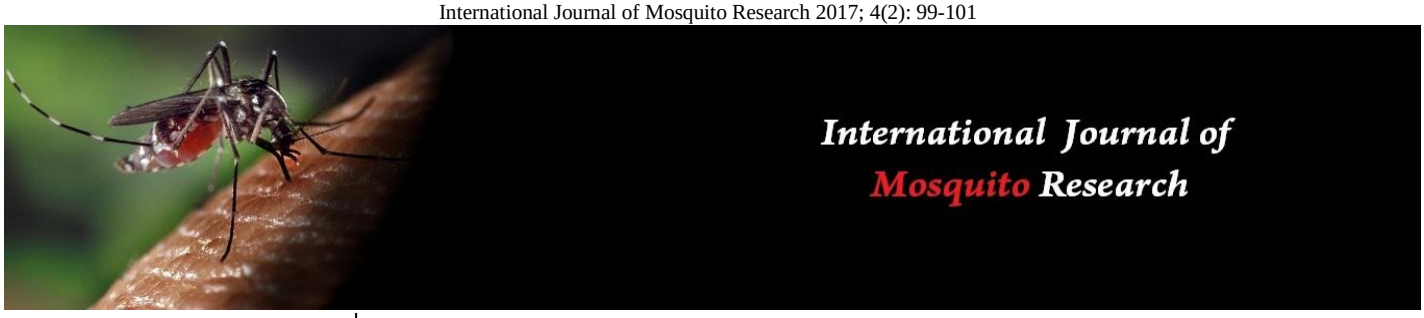

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Chloroquine drug response and resistance in patients with malaria in Khyber Pakhtunkhwa, Pakistan

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Abstract
Malaria is caused by infection with protozoan parasites belonging to the genus Plasmodium transmitted by female Anopheles species mosquitoes. The current study was designed to find resistance and response of chloroquine drug to malaria patients in Thall scout hospital, Khyber pakhtunkhwa, Pakistan from January 2011 to march 2015. The age of adult male patients having positive vivax malaria was 18 to 40 years. Both thick and thin slides were used for the diagnosis and species determination of malaria. The total number of patients included in the study were 518. Out of the 518 patients, 374 (72.2%) were treated with chloroquine and the remaining 144 (27.8%) were given arthemether/lumafantrine combination. 374 patients having positive malaria symptoms was treated with chloroquine, 171 (45.72%) were asymptomatic after 24 hours, 98 (26.2%) after 48 hours, 78 (20.86%) after 72 hours, while 27(7.22%) were found to be resistant to chloroquine. Out of the 144 patients having positive malaria treated with artemether/lumafantrine 62 (43.06%) were asymptomatic after 24 hours, 65(45.14%) after 48 hours, 13 (9.03%) after 72 hours while 4 (2.78%) had still positive symptoms of malaria.

Keywords: Chloroquine Drug, Malaria, Artemether, Plasmodium

1. Introduction
Despite intensive efforts at eradication, malaria remains a major public health problem. The World Health Organization (WHO) estimates that 300–500 million people are afflicted each year [1, 2]. Malaria is transmitted to people throughout tropical and subtropical areas, where 40% of the world's population are at risk of infection. According to world health organization (WHO), about 1.6 million cases of malaria are occurring in Pakistan [3]. Women are at increased risk from malaria during pregnancy, and, for unknown reasons, this risk is greatest during the first pregnancy [4]. Malaria causes symptoms that typically include fever, fatigue, vomiting, and headaches. In severe cases it can cause yellow skin, seizures, coma or death [5]. The disease is transmitted by the biting of mosquitos, and the symptoms usually begin ten to fifteen days after being bitten. If not properly treated, people may have recurrences of the disease months later [6] Approximately 67% malaria cases are caused by vivax species, while the falciparum is responsible for the remaining third Plasmodium vivax dominant on falciparum all over the world [7]. In all uncomplicated cases of malaria, chloroquine was the drug of choice for more than fifty years [8]. With the emergence of Plasmodium parasites resistant strains, the efficacy of different anti-malarial drugs have been questioned. Studies conducted in most part of the Asia, mainly from Indonesia have reported *p. vivax* resistance to chloroquine [9, 10]. In Pakistan, *P. falciparum* resistance to chloroquine is almost established [11, 12]. Reports of different studies carried out during 2006 in Pakistan showed that *p. vivax* is still sensitive to chloroquine, but some resistance is also found [13]. For the treatment of *P. falciparum* malaria, chloroquine is no longer recommended therefore the use of SP+Artesunat for the treatment of uncomplicated *P. falciparum* malaria is a first line therapy was started in 2008 in Pakistan [14]. But still in some part of the world, mostly African countries, fever in children is treated with anti-pyretic, home remedies and chloroquine [15] Studies in Sub Sarahan Africa have shown such home based treatment to be effective in children with fever [16, 17]. In our study, we treated all diagnosed cases of vivax malaria with chloroquine and arthemether/lumafantrine.

With clinic improvement of these patients with both group of drugs, we presumed that vivax malaria in this part of Pakistan is sensitive to chloroquine yet some resistance has developed.

2. Materials and methods

2.1 Study site and duration of study

The study was conducted in Thall scouts hospital, frontier corps (FC), North Wazirstan agency, Kuram Agency and Oragzai agency, Khyber Pukhtunkhwa province of Pakistan. This study was conducted from January 2011 to March 2015.

2.2 Study Design

Only adult male with vivax malaria and who had positive malaria symptoms were included in the study. Malaria was confirmed by doing both thick and thin slides. The tests were performed by expert technicians who were being trained in combined military hospitals. All the patients with vivax malaria were admitted in the hospital and a standard dosage of chloroquine was given. The patients remain admitted in the hospital till they were asymptomatic for at least 48 hours.

2.3 Drugs Used

Treatment outcome was evaluated by modifying the WHO protocol, which are used for measuring anti-malarial drug efficacy. Such modified protocols have been used in some other studies also [18]. We defined treatment failure (TF) as recurrence of fever on day 3 to 14. In the absence of fever, on day 3 to 14 was defined as adequate clinical response (AR), without meeting any of the criteria of treatment failure. Fever was defined as an auxiliary temperature of more than or equal to 37.5 ^{0}C we also studied the malaria parasite density in blood of patients before and after treatment under microscope.

3. Results

When the Chloroquine and Arthemete/Lumafantrine drugs are given to the malaria patients they show the response in three days are shown in table 1.

The clinical response to both drug groups was different after 3 days of treatment. There were different symptoms noted in all malaria patients, which were fever, headache, anorexia and nausea etc.

Table 1: Response of the Chloroquine and Arthemete/Lumafantrine drugs

Drugs used	24 hrs	48hrs	72hrs	Resistant patients	Total
Chloroquine	171(45.72%)	98(26.20%)	78(20.86%)	27(7.22%)	374
Arthemete Lumafantrine	62(43.06%)	65(45.14%)	13(9.03)	4(2.78%)	144

Of the total 518 patients having positive malaria 374 patients were treated with chloroquine in which 171 (45.72%) were asymptomatic after 24 hours, 98 (26.2%) after 48 hours, 78(20.86%) after 72 hours while 27 (7.22%) shows resistance to chloroquice even after 72 hours, although these 27 patient's symptoms were not as so much worse after three days of treatment as was on the time of admission to hospital on first day, but these malaria patients were still having positive malaria sign and symptoms which were put on alternative medication to get quick recovery. Of the total 144 patients treated with artemether/lumafantrine, 62(43.06%) were asymptomatic after 24 hours, 65 (45.14%) after 48 hours and 13 (9.03%) 72 hours and 4(2.78%) had still positive symptoms of malaria which were treated with alternative medicine to get quick recovery.

4. Discussion

In many parts of the world, chloroquine has been used in both prophylaxis and treatment of malaria. It is the cheapest and easily available drug. *P. vivax* resistance to chloroquine has been reported in the pacific [9], part of Asia [19, 20] and Latin America [21] but very little observed in Afghanistan and Pakistan [22] and *P. vivax* remains sensitive to chloroquine in India [23, 24]. The ratio of *P. falciparum* to vivax has changed since 1.1:1 in 1999 to 0.8:1 in 2001. This increase in *P. vivax* emergence can be attributed to: change in anopheles fauna, the effective treatment response of *P. falciparum* to new drugs and emergence of vivax malaria resistance to chloroquine [25] Emergence of chloroquine resistance strains is not the only cause of treatment failure [26]. Treatment failure could also be due to poor drug quality, malabsorption of drug, relapse of malaria, recrudesce of parasitemia and low drug level of drug [27].

Our study showed 92.78% sensitivity and 7.22% resistance of vivax malaria to chloroquine. Other studies done on vivax sensitivity to chloroquine in different parts of Pakistan [13, 22], India and Afghanistan [23, 24] also showed little resistance of vivax to chloroquine. Although their results show very little resistance as compared to our study, indicated the increasing trend of chloroquine drug resistance in Pakistan.

In our study, we studied various symptoms of malaria which were noted during therapy and relieve of malaria symptoms disappear which was further confirmed by analyzing patient's blood under microscope with decrease in parasite density. Symptoms like body aches, headache, nausea and vomiting were all included in our study. Each group of patients was treated with only chloroquine or lumafantrine/artemeter, along with anti-pyretic and in some cases these patients were hydrated with intravenous fluids. All the patients responded to this treatment without any complication. The total cost of this treatment was less than 200 rupees as compared to those who were treated in private clinics where the cost was more than thousand rupees. Most of those patients were treated with parental chloroquine, intravenous fluids and multivitamins.

We observed during the study that the incidence of vomiting with chloroquine could be reduced by first settling down fever and once the fever is settled then to start oral chloroquine. In addition, some patients could not tolerate taking four tablets of chloroquine at a time. So give patients two tablets of chloroquine and then to wait for 4 to 5 minutes and then to give the two tablets were well tolerated by the patients. The most common adverse effects observed with chloroquine therapy were itching and gastritis, which responded well to chlorpheneramine and H2 blocker drugs. Though we observed excellent clinical response of vivax malaria to chloroquine, it resulted in significant loss of working days, which is of great concern in military, and Paramilitary set up.

5. Conclusion

From our study, we concluded that vivax malaria is getting

resistance to chloroquine in this part of Pakistan. Though, chloroquine is a very effective drug, but still there is a need for monitoring its efficacy against vivax malaria in Pakistan

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