World Journal of Medical Sciences 13 (2): 103-106, 2016
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2016.13.2.102164

# Chloroquine Drug Response and Resistance in Patients with Malaria in Khyber Pakhtunkhwa, Pakistan

*[1]Sajid Ali Shah, [2]Nasir Khan, [3]Sulaiman Bahadar, [4]Waseem Shah, [4]Shamsul Ghani, [4]Jan Muhammad, [4]Nazif Qazi, [5]Zarnab Zainab, [6]Rahim Bahadar, [3]Afzal Ahmad and [3]Azam Hayyat*

[1]Army medical college, Rawalpindi, Pakistan
[2]Department of Molecular Biology and Genetics,
Izmir Institute of Technology, Urla, Izmir35000, Turkey
[3]Abbottabad University of Science and Technology, Abbottabad, KPK, Pakistan
[4]Department of Bioinformatics and Biotechnology, International Islamic University Islamabad
[5]FCPS part 1 General Medicine Ayub Medical College Abbottabad
[6]Department of Pharmacy, COMSATS Institute of Information Technology,
Abbottabad, Khyber PakhtunKhwa, Pakistan

**Abstract:** Malaria is caused by infection with protozoan parasites belonging to the genus Plasmodium transmitted by female Anopheles species mosquitoes. chloroquine is the drugs that is used for the treatment of malaria patients. The current study was designed to find resistance and response of chloroquine drug to malaria patients in Thall scout hospital, KPK, 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 slide were used for the diagnosis and species determination of malaria. Total number of patients included in the study was 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.

**Key words:** Chloroquine Drug · Malaria · Artemether · Plasmodium

## 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 is 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] Approximately67% malaria cases are caused by vivax species while the falciparum is responsible for the remaining third [7]. For 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.

**Corresponding Author:** Sulaiman Bahadar, Abbottabad University of Science and Technology, Abbottabad, KPK, Pakistan.

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. The use of SP+Artesunat for the treatment of uncomplicated p.faciparum malaria is as a first line therapy in Pakistan was started in 2008 [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.

## MATERIALS AND METHODS

**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.

**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 standard dosage of chloroquine was given. The patients remain admitted in the hospital till they were asymptomatic for at least 48 hours.

**Drugs Used:** Treatment outcome were evaluated by modifying 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 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 auxiliary temperature of more than or equal to 37.5 °C we also studied the malaria parasite density in blood of patients before and after treatment under microscope.

## RESULTS

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

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

## DISCUSSION

In many parts of the world, chloroquine has been used in both prophylaxis and treatment of malaria. It is the cheap 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 from 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, 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].

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 |
| Arthemetelumafantrine | 62(43.06%) | 65(45.14%) | 13(9.03) | 4(2.78%) | 144 |

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 shows 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 parasitic density. Symptoms like body aches, headache, nausea and vomiting were all included in our study. Each group of patients were 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 thousands rupees. Most of those patients were treated with parental chloroquine, intravenous fluids and multi vitamins.

We observed during the study that 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 giving 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 Para military set up.

## 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.

## REFERENCES


1. Olliaro, P., J. Cattani and D. Wirth, 1996. Malaria, the submerged disease. JAMA., 275: 230-33.
2. WHO., 1995. In Control of Tropical Diseases (CTD): Malaria Control. Geneva, Switzerland: WHO Off. Inf.
3. WHO: World malaria report, 2012. Geneva: World Health Organization; 2013.
4. Fried, M., N. François, B. Alan, B.J. Bernard and D.E. Patrick, 1998. Maternal antibodies block malaria, Nature, 395: 851-852.
5. WHO. March, 2014. "Malaria Fact sheet N°94". Retrieved 28 August 2014.
6. Caraballo, H., 2014. Emergency department management of mosquito-borne illness: Malaria, dengue and west nile virus. Emergency Medicine Practice, 16(5).
7. D.M.C., 2013. Malaria No More. Islamabad: Directorate of Malaria Control, Ministry of National Health Services.
8. Most, H.I.M., C.A. London, P.H. Kane, E.F. Lavietes, J.M. Schroder and J. Hayman, 1946. Chloroquine for the treatment of acute attacks of vivax malaria. JAMA, 131: 963-967.
9. Rieckman, K.H., D.R. Davis and D.C. Hutton, 1989. Plasmodium vivaxresistance to choloroquine? Lancet, 2: 1183-1184.
10. Guthmann, J.P., A. Pittet, A. Lesage, M. Imwong, N. Lindegardh, M.L. Min, T. Zaw, A. Annerberg, X. de Radigues and F. Nosten, 2008. Plasmodium vivax resistance to chloroquine in Dawei, Southern Myanmar. Trop Med Int Health, 13: 91-983.
11. Khatoon, L., F.N. Baliraine, M. Bonizzoni, S.A. Malik and G. Yan, 2009. Prevalence of antimalarial drug resistance mutations in Plasmodium vivax and P. falciparum from a malaria-endemic area of Pakistan. Am J. Trop Med Hyg, 81: 525-528.
12. Ghanchi, N.K., J. Ursing, M.A. Beg, M.I. Veiga, S. Jafri and A. Martensson, 2011. Prevalence of resistance associated polymorphisms in Plasmodium falciparum field isolates from southern Pakistan. Malar J., 10: 18.

13. Leslie, T., M.I. Mayan, M.A. Hasan, M.H. Safi, E. Klinkenberg, C.J. Whitty and M. Rowland, 2007. Sulfadoxine-pyrimethamine, chlorproguanil-dapsone, or chloroquine for the treatment of Plasmodium vivax malaria in Afghanistan and Pakistan: a randomized controlled trial. JAMA, 297: 2201-2209.
14. WHO: World Malaria Report, 2008. Geneva: World Health Organization; 2009.
15. McCombie, S.C., 2002. Self-treatment for malaria: the evidence and methodological issues. Health Policy Plan, 17: 333-344.
16. Pagnoni, F., N. Convelbo, J. Tiendrebeogo, S. Cousens and F. Esposito, 1997. A community-based programme to provide promt and adequate treatment of presumptive malaria in children. Trans R Soc Trop Med Hyg, 91: 512-517.
17. Kidane, G. and R.H. Morrow, 2000. Teaching mothers to provide home treatment of malaria in Tigray, Ethiopia: a randomised trial. Lancet, 356: 550-55.
18. Müller, Olaf, Maurice Yé, L.R. Valérie and S. Ali, 2009. Malaria in sub-Saharan Africa." Lancet, 37: 9658: 122.
19. Phan, G.T., P.J. de Vries, B.Q. Tran, H.Q. Le, N.V. Nguyen, T.V. Nguyen, S.H. Heisterkamp and P.A. Kager, 2002. Artemisinin or chloroquine for blood stage Plasmodium vivax malaria in Vietnam. Trop Med Int Health, 7: 858-864.
20. Kurcer, M.A., Z. Simsek and Z. Kurcer, 2006. The decreasing efficacy of chloroquine in the treatment of Plasmodium vivax malaria, in Sanliurfa, south-eastern Turkey. Ann Trop Med Parasitol, 100: 109-113.
21. Soto, J., J. Toledo, P. Gutierrez, M. Luzz, N. Llinas, N. Cedeno, M. Dunne and J. Berman, 2001. Plasmodium vivax clinically resistant to chloroquine in Colombia. Am J. Trop Med Hyg, 65: 90-93.
22. Awab, G.R., S. Pukrittayakamee, M. Imwong, A.M. Dondorp, C.J. Woodrow, S.J. Lee, N.P. Day, P. Singhasivanon, N.J. White and F. Kaker, 2010. Dihydro artemisininpiperaquine versus chloroquine to treat vivax malaria in Afghanistan: an open randomized, non-inferiority, trial. Malar J., 9: 105.
23. Nandy, A., M. Addy, A.K. Maji and A.K. Bandyopadhyay, 2003. Monitoring the chloroquine sensitivity of Plasmodium vivax from Calcutta and Orissa, India. Ann Trop Med Parasitol, 97: 215-220.
24. Valecha, N., H. Joshi, A. Eapen, J. Ravinderan, A. Kumar, S.K. Prajapati and P. Ringwald, 2006. Therapeutic efficacy of chloroquine in Plasmodium vivax from areas with different epidemiological patterns in India and their Pvdhfrgene mutation pattern. Trans R Soc Trop Med Hyg, 100: 831-837.
25. Vijaykadga, Saowanit, Alisa P. Alker, Wichai Satimai, John R. MacArthur, Steven R. Meshnick and Chansuda Wongsrichanalai, 2012. "Delayed Plasmodium falciparum clearance following artesunate-mefloquine combination therapy in Thailand, 1997–2007." Malaria journal, 11(1): 1-10.
26. Tsige, K., B. Ketema, B. Tarekegn and P. Beyene, 2009. Chloroquine-resistant Plasmodium vivax malaria in Serbo town, Jimma zone, south-west Ethiopia." Malaria journal, 8(1): 177.
27. Djimde, A.A., K.D. Ogobara, T. Ousmane, B.G. Ando, K. Kassoum, D. Yacouba, N. Safiatou, C. Drissa, K.K. Abdoulaye, C. Yacouba, T. Mamadou, F. Bakary, D. Alassane, A.D. Dapa, E.W. Thomas, K. Dominic and V.P. Christopher, 2003. Clearance of drug-resistant parasites as a model for protective immunity in P. Falciparum malaria. Am J Trop MedHyg, 69: 558-563.