Assessment of Therapeutic Efficacy of Anti Malarial Drug (Chloroquine) against *Plasmodium Vivax* Malaria in Kanchanpur District

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Abstract

Introduction The control of malaria relies mainly on chemoprophylaxis and use of mosquito bed nets. The emergence of resistance of parasites to anti malarial drugs and vector insecticides respectively has exacerbated the problem of control. It is used for treatment of laboratory confirmed plassmodium vivax and clinical malarial cases. Unfortunately, resistance to this drug has alarming proportion in most countries affected by *Plasmodium falciparum* and *Plasmodium vivax*.

Objective Assessment of therapeutic efficacy of anti malarial drug (chloroquine) against *Plasmodium vivax* malaria in Kanchanpur district

Methods A prospective study using standard protocol of WHO 14 days *in vivo* drug efficacy test (WHO, 2001) was carried out during June – October 2005 in Kanchanpur district. Two village development committees were selected, based on the diseases endemicity. Patients visiting health post confirmed with *P. vivax* malaria were treated with standard dose of chloroquine 25mg/kg and followed up to 14 days.

Result A total of 374 slides were collected from two sentinel sites (Jhalari -01 and Krishnapur – 02). Out of 374, 154 cases (41.17%) were confirmed with *P. vivax*. The slide positivity rate was 36.13 and 50 percentages respectively. Ninety two (59.74 %) cases (47 cases from site -01 and 45 cases from site 02) were enrolled in 14 days *in vivo* test. In all 84 cases, the chloroquine at a dose of 25 mg/kg was found to be 100 percent effective . No treatment failure was recorded.

Conclusion This finding indicates that the chloroquine at a dose of 25mg/kg body weight should be continued as a first choice treatment of vivax malaria in Kanchanpur district. However, sentinel sites for monitoring *Plasmodium vivax* sensitivity to chloroquine should be established for regular assessment of treatment policies in Kanchanpur district.

Key words Chloroquine, Plasmodium vivax, Therapeutic efficacy, Kanchanpur.

Introduction

Malaria is major public health problem and cause of suffering, premature death in tropical and subtropical countries including Nepal. Nearly 40 percent of the world's population lives in the region where malaria is endemic and 300-500 million cases of clinical diseases per year with 1.5 to 2.5 million death[1].

In Nepal, out of the total population of 21.1 million; approximately 15.3 million Nepalese people are residing in the areas from where indigenous malarial cases reported[2]. However, the number of reported malaria cases in Nepal has dramatically decreased from over 23 thousand since 1994 with 5-20 percent due to *Plasmodium falciparum*[3]. The control of malaria relies mainly on chemoprophylaxis and use of mosquito bed nets[4].

The emergence of resistance and rapid spread of of parasites to antimalarial drugs and vector to insecticides respectively has exacerbated the problem of control.

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Chloroquine is the most common and cheapest antimalarial drugs available at the peripheral level (sub – health post and health post with out lab facilities). It is used for treatment of laboratory confirmed *Plasmodium vivax* and clinical malarial cases. Unfortunately, resistance to this drug has alarming proportion in most countries affected by *Plasmodium falciparum* and vivax malaria. In such condition, there is urgent need to assess drug policy and have proven extremely useful for obtaining the information to develop or modify the treatment policies.

Methodology

A prospective study using standard protocol of WHO 14 days *in vivo* drug efficacy test (WHO, 2001)[5] were carried out during June – October in Kanchanpur district, hyper endemic zone of Nepal. Two villages development committees (VDCs) were selected, based on disease endemicity. Blood specimens were collected from individual visiting health post who had a presumptive diagnosis of clinical malaria. A diagnosis of clinical malaria would be based on fever >38^{0}C. history of fever in the last 48 hours and no other evident cause of fever.

A total 374 fever cases (238 cases from Jhalari-01 and 136 cases from Krishnapur-02) were screened. Out of 374, 154 cases were with *P. vivax*. Ninety two patients (47 from Jhalari and 45 from Krishnapur) confirmed by a positive blood slide for *P. vivax* who agreed to participate were included. Eight cases dropped out and 84 cases completed the study.

Microscopic confirmation was done using both thick and thin smear with standard Giemsa staining method. Patients fulfilling the protocol criteria were enrolled in the study only after obtaining informed consent from them and their guardians. Patients who were positive for malaria but not met the enrollment criteria or no consent to participate in the study were given a standard dose of antimalarial drugs according to the species of parasites.

The enrolled patients *in vivo* tests were administered a strictly supervised standard therapeutic regimen of 25 mg/kg of chloroquine (RD – Chloroquine, Batch No. 772 Royal Drug Limited Nepal) base /kg of body weight as 10 + 10 + 5 mg/kg doses at 24 hours interval with food. Along with blood films clinical information were recorded in a WHO recommended case record form on day 0,1,2,3,7 and 14 or any other day of illness with symptoms of malaria. Patients were excluded from the study if additional antimalaria drug administered diagnosed as mixed infection, development of complicated severe malaria and occurrence of concomittant.

Criteria for interpretation of test result:

Clinical and parasitological results were classified for overall response, classification of both results were classified for over all response, classification of both results were combined and classified in three categories (TS , LTF, ETF)[6].

Quality control and reliability of the activities:

One week training on quality control and quality assurance on microscopy was provided by District Public Health Office with collaboration of USAID before conducting research. Antimalrial drug used in the tests were supplied to the health post by public health system and it was assumed that quality control had been performed prior to supply. In order to ensure reliable result, quality control on the reliability of laboratory work and over all performance of activities was done.

Result

A total of 374 fever cases (238 cases from Jhalari – 01 and 136 cases from Krishnapur -02) were screened. In Jhalari 86 cases were positive with *P. vivax* but in Krishnapur 68 cases were positive with *P. vivax* .Total slide positivity rate is 41.17 percent and slide positivity rate of two sentinel sites were 36.13 and 50 percent respectively. No Pf cases were encountered during the study period.

The observation of symptomatic patterns of representative showed 43 (41.19%) cases of fevers, 41 (48.8%) cases history of fever, 58 (69.04%) cases of headache, and 2 (2.38%) cases of loss of appetite were recorded.

A total of 84 cases had been monitored, among them 45 (53.57%) male and 39 (46.42%) female enrolled. All cases demonstrated a good early clinical as well as parasitological response to treatment. No treatment failure was recorded in any cases during the study period. Similarly, signs and symptoms of malaria were not observed in any case after day 3 with chloroquine treatment but dizziness reported in some cases. Parasite density was found to be 1520-29600/ml. in day.

Table 1: Malaria prevalence in two sites of Kanchanpur district

Descriptions	Site 01	Site 02	Total
No. of screened (tested)	238	136	374
No. of positive (*Plasmodium vivax*)	86	68	154
Pf (*Plasmodium falciparum*)	0	0	0
No.of mixed (Pf+Pv)	0	0	0
Slide positivity rate	36.13	50	41.176

Table 2: Enrollment of participants *in vivo* test of monitoring of therapeutic efficacy of Chloroquine for the treatment of *Plasmodium vivax*

Descriptions	Site 01	Site 02	Total
No. of qualified for study (Total enrolled)	47	45	92
No. of dropped out	3	5	8
No. of completed study	44	40	84
Age range (in years)	7-66	6-56	6-66
Weight range (kg)	17-59	19-58	17-59
With fever	29	14	43
History of fever	15	26	41
Headache	33	25	58
Nausea	0	0	0
Loss of appetite	0	2	2
Parasite density /µl of blood (average)	9520	11635	10375
Range	1520-22240	1520-29600	1520-29600

Fig 1: Symptomatic representation in enrolled patients

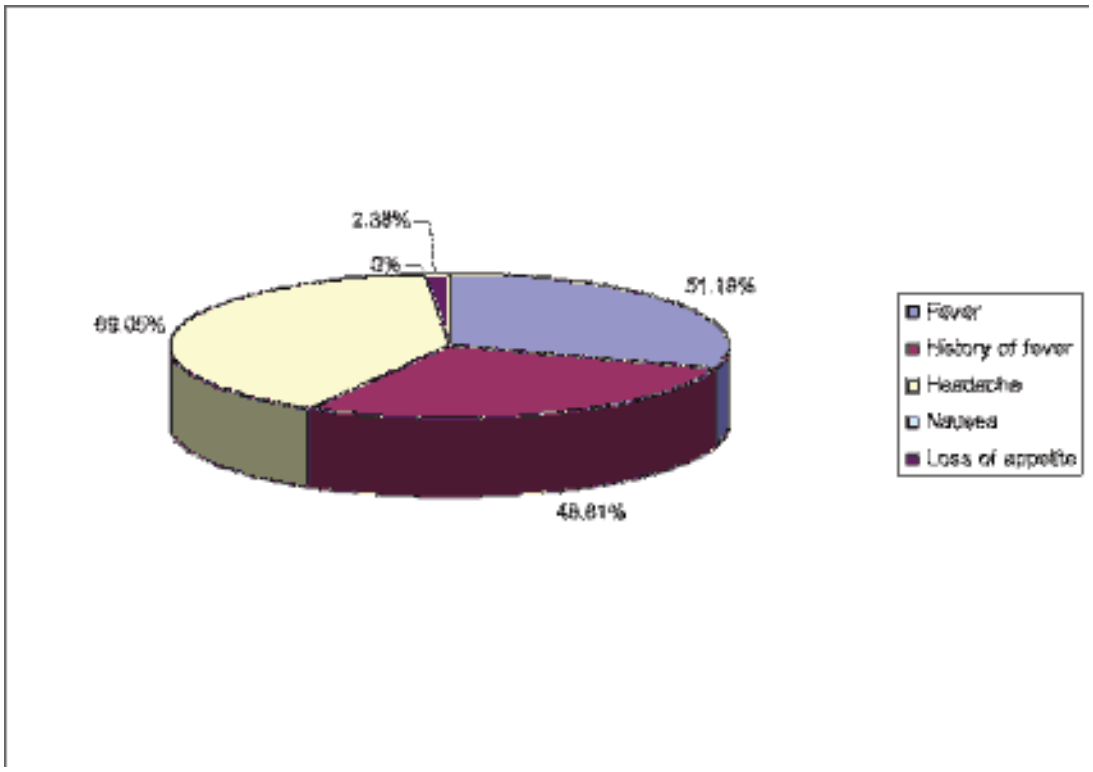

Table 3: Vivax malaria response to chloroquine

Age Group	Gender		TS		EIF		LTF		Total		Remarks
	Male	Female	n	%	n	%	n	%	n	%	
<10 years	11	5	16	(100)	0	(0)	0	(0)	16	(100)	
10-20 year	14	12	26	(100)	0	(0)	0	(0)	26	(100)	
>21	20	22	42	(100)	0	(0)	0	(0)	42	(100)	
Total	45	39	84	(100)	0	(0)	0	(0)	84	(100)	

Note: Ts: Treatment Success ETF: Early Treatment Failure LTF: Late Treatment Failure

Discussion

In vivo testing is generally considered the method of choice for assessing the efficacy of antimalarial drugs against *Plasmodium spp*. because it most closely parallels the response of individual patients to those drugs. WHO guidelines for such trails are increasingly being used by investigators and public health workers to assess drug efficacy and have proven extremely useful in obtaining the information necessary to develop or modify national malaria treatment policies[7]. The result of present study showed a high slide positivity rate in Jhalari (36.13%) and in Krishnapur (50%). Both selected sites are highly endemic area of malaria and reported more than 50 percent of the total malarial cases of whole district[2]. No Pf cases were encountered during the study period. The factors might be due to spraying insecticides in the identified area, distributing antimalarial drugs in the peripheral level by public health system and technical man power and highly equipped laboratory in the endemic area.

Ninety two cases (92) were enrolled in 14 days *in vivo* test of chloroquine. Eight cases (8.69%) dropped out and 84 cases completed the study. The age range of enrolled patients was 6-66 year, weight range (in kg) was 17-59 and parasite density was 1520-29600/ul. The observation of symptomatic pattern of representative showed 43 (41.19%) cases of fevers, 41 (48.80%) cases of history of fever, 58 (69.04%) cases of headache and 2 (2.38%) cases of loss of appetite were recorded.

Health workers in the developing countries often do not follow clinical Guide line. Twenty-eight health workers and 349 ill-child consultation were evaluated in Blantyre district, Malawi; 247 (70.8%) children were treated with an effective antimalarial, and 102 (29.2%) were subject to treatment error[8].

In the current *in vivo* study, the chloroquine at a dose 25mg/kg body weight was effective in all 84 cases. Clinical as well as parasitological response was best in each site with cure rate of 100 percent. Similar type of studies conducted in Kanchanpur and Dhanusha district showed no resistance in *Plasmodium vivax*[3]. But the preliminary study conducted in Bankey and Dhanusha district reported the presence of chloroquine resistance to *P. vivax*[10]. But studies conducted in Thailand and Philippines showed no resistance in *Plasmodium vivax*[11].

In Nepal, chloroquine is the drug used regularly for the treatment of uncomplicated *Plasmodium vivax* malaria by national malaria control program since the beginning. It is also used for the treatment of clinically suspected malaria. Early diagnosis and prompt treatment are fundamental for the control of malaria. They should be available where malaria occurs. Correct treatment of malaria shortens the duration of the disease and reduces the complication and deaths. However, in the endemic areas where the chloroquine is used in treatment of uncomplicated malaria but self medication and sub curative doses favors the selection of resistant parasite population. Wide spread of use and availability of the chloroquine in the community may lead to considerable drug pressure and development of resistance.

Conclusion

Chloroquine at a dose of 25 mg/kg body weight should be continuing to be the first choice of treatment of vivax malaria in Kanchanpur district. However, sentinel sites for monitoring *Plasmodium vivax* sensitivity to chloroquine should be established for regular assessment of malaria treatment policies in Kanchanpur district.

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Reference

1. WHO. World malaria report 2005. (from WHO website)
2. EDCD, Annual Report (2002 and 2003) His Majesty's Government, Ministry of Health and population, Kathmandu Nepal.

3. EDCD, Malaria Annual Report, 2002. The annual internal assessment of malaria and kalazaar control activities 2002. HMG Ministry of Health Department of Health Services, Epidemiology and Disease Control Division.
4. Sherchand JB, Shrestha MP, Shrestha BL, Banerjee MK, Shakya S. A preliminary Study on field trails with insecticide treated mosquito-nsets for malaria control in rural endemic communities for Nepal. *J Nep Med Assoc*; 1995; 33: 195 – 203.
5. WHO Monitoring Antimalarial Drug Resistant, Report of a WHO consultation Geneva, Switzerland, 3-5 December 2001.
6. WHO Assessment of therapeutic efficacy of antimalarial drug for uncomplicated falciparum malaria in areas with intense transmission WHO/ MAC/96.1077. Geneva, World Health Organization, 1996.
7. Barat LM, Himonga B and Inkuinita S. A systematic approach to the development of a rational malaria treatment policy in Zambia, 1998 Tropical Medicine and International Health 3, 535 -42.
8. Osterholt DM, Rowe AK, Hamel MJ, Flanders WD, Mkandala C, Marum LH and kaimlila N. Predictors of treatment error for children with uncomplicated malaria seen as out patients in Blantyre district, Malawi. Trop Med Int Health 2006. Aug; 11 (8): 1147-36.
9. Sherchand JB. The Value of malaria diagnosis: a preliminary study in the Terai district of Nepal, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR-RCS) CH-12211 Geneva 27-Switzerland 2002.
10. Sherchand JB. *In vivo* chloroquine test in two malaria endemic district of Nepal. *Journal of Nepal Association for Medical Laboratorsy Services*, 2003; 5: 1-3.
11. Baird JK, Conete-Miguel E, Bustos DG, Abrenica JA, Layawen AV, Calulut JM, Leksana B and Wignall FS. Survey of resistance to chloroquine by falciparum and vivax malaria of at Palawan, Philippines. 1996 Trans R Soc Trop Med Hyg 902: 413-4.