

## IN VIVO EFFICACY AND SAFETY OF QUININE-DOXYCYCLINE COMBINATION IN ACUTE PLASMODIUM FALCIPARUM MALARIA

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### ABSTRACT

**Objective:** To find out the in vivo efficacy and adverse effects of quinine doxycycline combination in malaria caused by Plasmodium (P.) falciparum.

**Methodology:** It is a prospective, observational study conducted at Department of Medicine, Combined Military Hospital, Quetta, Balochistan, Pakistan, from September 2006 to December 2006. Three hundred thirty seven subjects with positive P.falciparum rings on malaria slide fulfilled the selection criteria and were included in the study. Mean, minimum and maximum values along with standard deviation of age, malarial parasite index fever clearance time and parasite clearance time were calculated. Frequencies of various adverse events and deaths observed during this study were also calculated.

**Results:** Of 337 subjects, 256 had P.falciparum while 81 had mixed infection involving both P.falciparum and P.vivax. Mean fever clearance times in P.falciparum infected subjects and mixed infection were 46.3 hours and 44.16 hours respectively. The mean parasite clearance times in P.falciparum infected subjects and mixed infection were 70.32 hours and 68 hours respectively. About 3.3% of the subjects developed mild to moderate side effects including tinnitus, prolongation of QT interval and vomiting. Mortality rate observed in this study was about 0.6%.

**Conclusion:** Quinine doxycycline combination therapy may be used safely and effectively in the management of P.falciparum malaria.

**KEY WORDS:** Quinine doxycycline combination, Malaria, Plasmodium falciparum, Mixed infection.

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## INTRODUCTION

Malaria is the world's most important parasitic infection and one of the major causes of morbidity and mortality. Despite years of continual efforts, it is still a threat to over two billion people and one to three million people die worldwide every year.<sup>1</sup> Among the four species of malarial parasite, the protozoan plasmodium (P.) falciparum accounts for the majority of instances of morbidity and mortality. Mixed infections with more than one species of parasite commonly involve P.falciparum with the attendant risk of severe malaria. The increasing prevalence of multi-resistant

*P.falciparum* malaria is a serious public health threat to the global control of malaria, especially in poor countries like Pakistan.<sup>2</sup>

The artemisinin based combinations like artemether-lumefantrine (Coartem), Artesunate-modiaquine, piperaquinedihydroartemisinin-trimetoprim (Artecom) and Pyronaridine-artesunate etc. as well as the non-artemisinin-based combinations like Atovaquone-proguanil (Malarone), Mefloquine-sulfadoxinepyrimethamine (Fansimet), and Quinine-Doxycycline etc. have been proposed in various studies.<sup>3,4</sup>

With the emergence of sporadic resistance to conventional quinine monotherapy in Southeast Asia and Western Oceania, it is being used in combination with an antibiotic such as doxycycline or tetracycline as the treatment of choice even in severe or complicated falciparum malaria.<sup>5,6</sup> Several adverse reactions have been reported in literature with quinine based therapy including tinnitus, nausea, vomiting, dizziness, myocarditis, hypotension, hypoglycemia and occasionally acute renal failure.<sup>5,7-10</sup>

With the recent reports of slowly declining efficacy of quinine and *P.falciparum* being resistant to most of the available antimalarial drugs and recommendations to administer (almost 5-6 times more expensive) artemisinins based combinations,<sup>11</sup> utility of time tested quinine doxycycline combination has become doubtful despite being still considered as the treatment of choice in latest united kingdom malaria guidelines.<sup>6</sup>

Considering the facts that the Quetta is a highly endemic malarious area<sup>12</sup> and that a drug combination will not work everywhere due to difference in drug resistance between regions, this study was designed to determine the in vivo efficacy and adverse events of quinine doxycycline combination in Quetta Balochistan Pakistan.

## METHODOLOGY

This prospective observational study was conducted from September 2006 to December 2006 at Department of Medicine, Combined

Military Hospital Quetta, Balochistan a tertiary care hospital. All subjects fulfilling inclusion criteria (12 to 60 years age group, malarial parasite film showing *P.falciparum* rings) during the above mentioned period were enrolled in this study after taking informed consent. Subjects with pregnancy, history of antimalarial drug intake during current illness or other co morbid conditions were excluded.

After enrollment, all participants were hospitalized for seven days quinine doxycycline combination therapy (quinine 30mg/kg in three divided doses, Doxycycline 200 mg daily in two divided doses), Paracetamol and dimenhydrinate were provided, as needed, for symptoms of fever/headache/myalgias and nausea/dizziness, respectively. Other medications or intravenous fluids were provided only as prescribed by treating physician.

Their signs & symptoms, medication history, and adverse events were recorded daily. Routine physical examinations and laboratory tests were performed on a periodic schedule until 7<sup>th</sup> day. Blood smears were obtained twice a day until the malaria cleared followed by once daily for a week or as clinically warranted.

The efficacy of therapy in every subject was determined by fever clearance time and parasite clearance time. Fever clearance time was defined as the time until temperature was  $\leq 37.4^{\circ}\text{C}$  and remained there for at least an additional 48 hours. Parasite clearance time was defined as time from the start of treatment until the first negative blood smear for asexual stages, which remained negative for an additional 24 hours. All information was recorded in a previously designed proforma. All patients were evaluated daily for the reporting of adverse events during treatment that were new in onset or aggravated in severity or frequency after administration of the study drugs. An adverse event was considered to be drug related if its relationship to treatment was rated definite or probable by a study clinician.

The data was entered and analyzed in the SPSS 11.0 software. Mean, minimum and maximum values along with standard deviation of fever clearance time and parasite clear-

ance time were calculated. Frequencies of various adverse events and deaths noted during this study were calculated.

## RESULTS

In all, three hundred thirty seven subjects fulfilled the selection criteria and were included in the study. Out of these 337, 256 were having *P.falciparum* infection while remaining 81 had mixed infection (*P.falciparum* and *P.vivax* combination).

The mean age of participants was 27.9 years with range of 12-51 years. All subjects were exclusively male in this study as it was carried out in a military hospital, which mainly looks after soldiers. The mean malarial parasite index was 1.1 in *P.falciparum* while 1.2 in mixed infection. The mean fever clearance times in subjects with *P.falciparum* infection and mixed infection were 46.3 hours and 44.16 hours respectively. The mean parasite clearance times in subjects with *P.falciparum* infection and mixed infection were 70.32 hours and 68 hours respectively. About 96.7% individuals in this study tolerated seven day quinine doxycycline combination therapy without any adverse effects. Only 3.3% (11/337) subjects developed mild to moderate side effects including tinnitus, prolongation of QT interval and vomiting. About 0.78% (2/256) patients with *P.falciparum* infection died whereas none of

the patients with mixed infection died during this study. The overall mortality rate was about 0.6% (2/337).

## DISCUSSION

This study has demonstrated in vivo efficacy and safety of quinine doxycycline combination therapy in malaria caused by *P.falciparum* in this part of the world in the background of reports showing progressively increasing resistance and severe adverse effects.

This study reported mean fever clearance time in *P.falciparum* infected subjects to be 46.3 hours and this duration is much less than that observed in some of the international studies assessing quinine efficacy reported as 55 to 107 hours.<sup>5,7,13</sup> However few quinine efficacy determining trials showed almost similar duration<sup>14,15</sup> or even less in couple of studies.<sup>8,16</sup> This significant disparity in mean fever clearance time in existing documented data may be due to the difference in sample size as most of the studies enrolled smaller number of participants<sup>5,7,8,14</sup> and their fever was not monitored in hospital. Mean fever clearance time reported in this study is less than some of the previous trials<sup>7,13</sup> assessing the efficacy of artemisinin based combination reporting it to be 80 to 108 hours. In mixed infection involving both *P.falciparum* and *P.vivax*, mean fever clearance time was almost unchanged i.e. 44.16

Table-I: Main parasite clearance time in *P. falciparum* was 70.32 hours

Parameters	<i>P.falciparum</i> n = 256	Mixed infection n = 81
Age (years)	Mean 28.3 Range 12-51 Standard deviation 6.96	Mean 26.62 Range 14-43 Standard deviation 5.7
Malarial parasite index	Mean 1.1 Range Upto 20 Standard deviation 1.1	Mean 1.2 Range Upto 18 Standard deviation 1.21
Fever clearance time (hours)	Mean 46.3 Range 12-86 Standard deviation 1.2	Mean 44.16 Range 12-104 Standard deviation 1.41
Parasite clearance time (hours)	Mean 70.12 Range 24-136 Standard deviation 1.3	Mean 68 Range 24-130 Standard deviation 1.48
Adverse effects (n)	Tinnitus 4 ECG changes 2 Vomiting 2	Tinnitus 2 ECG changes 1 Vomiting none

hours. None of the studies in literature assessed the impact of mixed infection over the mean fever clearance time.

Mean parasite clearance time in this study was 70.32 hours in *P.falciparum* infected subjects. This outcome was highly variable in different trials. Duration noted in this study is almost identical to one of the trial,<sup>5</sup> and less than the time noted in couple of other studies.<sup>7,13</sup> Some of the studies reported lesser mean parasite clearance time to be ranging from 22.4 to 51.9 hours.<sup>8,14,16</sup> These alterations in the outcome may be due to reasons already mentioned in fever clearance time or secondary to difference in parasite resistance between regions. Mean parasite clearance time in this study was almost similar to a trial<sup>7</sup> assessing the efficacy of artemisinin based combination. However it was lesser in some other studies.<sup>5,8,13,14</sup> Mean parasite clearance time in mixed infection caused by *P.falciparum* and *P.vivax* was almost similar i.e. 68 hours. None of the studies determined the effect of mixed infection over mean parasite clearance time.

No serious adverse reaction was observed with quinine-based combination in any of the enrolled subject in this study. Only mild to moderate side effects were seen in 3.3% individuals and these were much less than those noted in previous studies.<sup>5,7-10</sup> These adverse effects were successfully managed by decreasing the quinine dose without compromising the efficacy of therapy. About 1.8% subjects developed tinnitus in this study as compared to 89% in previous study.<sup>5</sup> QT interval prolongation was observed in only about 0.89% (3 / 337) of the subjects as compared to more frequent observation of this feature in another study.<sup>7</sup> About two subjects had excessive vomiting during this study and this adverse effect was seen even in upto 91% of subjects in previous trials.<sup>5,7</sup> None of the individuals in this study developed severe hypotension, hypoglycemia or acute renal failure which were observed in other studies.<sup>7-10</sup> This disparity in adverse reaction may be due to the fact that all antimalarial drugs were administered as per recommended protocols<sup>17</sup> under close

supervision of clinician in the hospital. This may also be due to younger age of enrolled subjects as their mean age was 27.9 years and majority of them were physically fit military soldiers.

The mortality rate of 0.6% (2 / 337) can be favourably compared to the mortality rates of 5% to 23.9% reported in existing documented studies of both quinine and artemisinin based combination therapies.<sup>7,8,10,14,15</sup>

*Clinical implication and limitations of the study:* This study highlighted the importance of seven day quinine doxycycline combination therapy in the management of *P.falciparum* malaria in this part of the world particularly in the backdrop of reports of slowly declining efficacy of this time tested therapy.

Although mean fever and parasite clearance times in this study were found longer in some instances as compared to previous studies but adverse events and mortality associated with quinine doxycycline combination therapy were much less as compared to all previous data assessing efficacy and adverse effects of both similar combination and artemisinin based combination.

Considering aforementioned advantages, almost 5-6 times cheaper price and low economic capacity of the people in the poor socio-economic communities like our region, quinine doxycycline combination may be used as the treatment of choice in the malaria caused by *P.falciparum*.

*Limitations of the study:* It consisted of exclusion of pregnant women, children of age less than 12 years and female gender. Although there is no difference in quinine metabolism between pregnant and non-pregnant women,<sup>18</sup> but Doxycycline is contraindicated in both pregnant women and children under 12 years.<sup>6,18</sup> Subjects were not followed up for 28 days for recrudescence due to financial constraints and limited hospital beds, as recrudescence was noted upto 6.6% of quinine treated cases in previous studies.<sup>8,13,15</sup> Limitations of this study need further attention from future researchers.

## CONCLUSION

Quinine doxycycline combination therapy may be used safely and effectively in the management of malaria caused by *P.falciparum* particularly in the low socioeconomic communities like majority of the population in this part of the world.

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