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Comparison of quinine and rabeprazole with quinine monotherapy in the treatment of uncomplicated falciparum malaria

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Abstract

Objective: This study was conducted to assess the effect of combination treatment of quinine and rabeprazole in the treatment of uncomplicated *Plasmodium falciparum* malaria.

Methods: The study included 50 patients of uncomplicated *P. falciparum* malaria. Group 1 (25 patients) received quinine and placebo (Q+P) while Group 2 (25 patients) received quinine and rabeprazole (Q+R). Diagnosis was confirmed by peripheral blood film (PBF) and rapid diagnostic test (RDT). Temperature was recorded every 6 h. All patients were followed-up on Days 7, 14, 21, 28 for detailed clinical and parasitological examination.

Results: A total of 20 patients in each group completed the treatment and followed-up for 28 days. While two patients in Group 1 (Q+P) and one patient in Group 2 (Q+R) were lost in follow-up; and seven (Q+P = 4, Q+R =3) patients were withdrawn from the study. Fever clearance time (FCT) of the two groups was also almost similar (Group 1 : 2 = 52.8 : 51.3 h). No statistically significant difference was observed in early treatment failure (ETF) either of the groups. None of the patients in both the groups showed late clinical failure (LCF) or late parasitological failure (LPF). However, there was a significant difference in the parasite clearance rates of the two groups ($p<0.05$).

Conclusion: The study results suggest that addition of rabeprazole to quinine regimen resulted in an increase in the parasite elimination rate, which may be helpful in reducing the duration of treatment and increasing patient compliance.

Key words Falciparum malaria; quinine; rabeprazole; India

Introduction

Malaria is a protozoan disease caused by infection with parasites of genus *Plasmodium*[1]. Five species responsible for human infection are *P. falciparum*, *P. vivax*, *P. malariae, P. ovale* and *P. knowlesi* (recently reported in human infection). At present about 300–500 million new cases are detected each year and 1.1 to 2.7 million deaths are reported annually, mostly due to *P. falciparum* malaria[1].

Quinine is one of the oldest and very useful drug for the treatment of falciparum malaria and is effective in uncomplicated as well as severe cases. It acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development of circulating ring stages of *P. falciparum*. It also has effect on the pre-erythrocytic stages of malaria parasites[2]. To reduce the onset of resistance and increase the patient compliance, quinine is used in combination with an antibiotic, usually doxycycline, tetracycline, clindamycin or azithromycin[2]. Over dosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, which can also be fatal[3]. Multi drug resistant *P. falciparum* is an important

public health problem in many areas where malaria is endemic, and in last few years the declining efficacy of important antimalarial drugs has left us with an increasingly limited choice of effective antimalarial drugs[4,5].

Proton pump inhibitors (PPIs) have antiparasitic and antibacterial properties. Omeprazole inhibits the growth of *Leishmania donovani*[6] and is also effective against the bovine pathogen *Tritrichomonas foetus*. PPIs also have antibacterial activity against *Helicobacter pylori* and rabeprazole is the most effective amongst different PPIs.

Earlier study on the efficacy of four PPIs, viz. omeprazole, lansoprazole, rabeprazole and pantoprazole against *P. falciparum in vitro* has shown definite action against three different isolates of *P. falciparum*[7]. Earlier an *in vitro* study also found combination of quinine and omeprazole to be significantly synergistic[8], similarly another *in vitro* study found rabeprazole and lansoprazole to be the most effective antimalarial agents amongst the available PPI[7]. Thus, we decided to study its synergistic efficacy in the treatment of uncomplicated falciparum malaria.

Material & Methods

This study was conducted between July and November 2007 on 50 adult hospitalized patients of uncomplicated *P. falciparum* malaria. The diagnosis was confirmed by microscopic examination of Giemsa stained peripheral blood smear. Patients of *P. falciparum* mono infection with density of 1000 – 100,000 asexual parasite/µl were included in the study. Other inclusion requirements were documented fever (axillary temperature >37.5^{o}C) in the past 48 h in absence of another obvious cause of fever, willing to participate in the study, willing to stay in hospital up to one week and to come for follow-up visits up to 28 days.

These patients were randomly divided into two groups. They were allocated in accordance with a randomization chart. Group 1 (25 patients) received quinine with placebo [Q+P; Quinine (10 mg/kg bw) 8 h orally + Placebo (BD) orally for 7 days] and the Group 2 (25 patients) received quinine with rabeprazole [Q+R; Quinine (10 mg/kg bw) 8 hourly orally + Rabeprazole (20 mg BD) orally] for 7 days. Identical appearing capsule filled with inert substances were used as placebo. Patients of both the groups received 45 mg of primaquine in a single dose on 3rd day. Temperature was recorded every 6 h. Laboratory investigations were performed on all patients in the beginning, and later if considered necessary. Blood smears were taken six hourly till it became negative for two consecutive times. Since all patients were hospitalized, compliance was ensured. All patients were followed on Day 7, 14, 21, 28. On every visit a complete physical examination was done and peripheral blood smear was studied for the evidence of parasite. Patients who withdrew before receiving at least one dose of the study drugs and patients lost to follow-up after randomization, were excluded and their records were deleted from the database. All the end points and adverse effects were recorded before the randomization. SPSS 12.0 software and strata 9.0 were used for data management and statistical analysis. For all statistical analysis $p<0.05$ was considered to be statistically significant.

Results

Out of 50 patients enrolled only 40 could complete the study. The demographic profile and symptomatology of two groups were almost similar and described in Table 1. Therapeutic response to drug regimen was classified as per WHO criteria. Early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical response (ACR) were taken as primary outcome measures. Fever clearance time (FCT) and parasite clearance time (PCT) were taken as secondary outcome measures. The details of response in two groups are shown in Table 2. The FCT of both the groups was almost same having 52.8 and 51.3 h and was not statistically significant. The mean PCT of Group 1 and Group 2 were 60.30 and 51.9 h respectively

Table 1. Clinical characteristics of patients with *P. falciparum* malaria

Characteristics	Group 1 (Q+P) (n=20)	Group 2 (Q+R) (n=20)	Total patients (n=40)
Age			
Mean	26.05	35.1	30.575
SD	10.555	18.352	15.471
Sex			
Male	10	16	24 (60)
Female	10	4	16 (40)
Clinical symptoms			
Fever	20	20	40 (100)
Chills and Rigors	13	14	27 (67.5)
Nausea and Vomiting	14	16	30 (75)
Abdominal pain	2	4	6 (15)
Dizziness	2	3	5 (12.5)
Diarrhea	1	2	3 (7.5)
Headache	13	12	25 (62.5)
Bodyache	11	10	21 (52.5)
Parasite density in the beginning			
≤20,000	8	10	18 (45)
20,001 – 40,000	9	10	19 (47.5)
40,001 – 60,000	1	0	1 (2.5)
60,001 – 80,000	1	1	2 (5)

Figures in parentheses indicate percentage.

Table 2. Details of primary efficacy variables

Parameters	Group 1 (Q+P) (n=20) No. (%)	Group 2 (Q+R) (n=20) No. (%)	Total patients (n=40) No. (%)	χ^2	*p*-value
ETF	3 (15)	0 (0)	3 (7.5)	3.243	>0.05
LCF	0 (0)	0 (0)	0 (0)		
LPF	0 (0)	0 (0)	0 (0)		
ACR	17 (85)	20 (100)	37 (92.5)	3.243	>0.05

ETF – Early treatment failure; LCF – Late clinical failure; LPF – Late parasitological failure; ACR – Adequate clinical response.

which was statistically significant (p <0.05) (Table 3). These were secondary outcome measures.

Discussion

Quinine is an important drug for the treatment of *P. falciparum* malaria, however, the mono therapy decrease the selection pressure and ultimately leads to development of resistance. Thus, quinine is used with antibiotic like doxycycline, tetracycline or azithromycin to overcome this phenomenon[5]. PPI is another group of drugs with well-proved anti-malarial activity and also helpful in overcoming commonly observed gastrointestinal side-effects like nausea and vomiting. Rabeprazole is considered to be the most potent PPI amongst the other commonly available drugs[9] and based on these observations we planned this observational study to see the synergistic effect of these two drugs.

The important clinical observation of this study was evidence of ETF in three out of the 20 patients receiving Q+P, 2 out of these 3 patients had parasitaemia on Day 2 higher than Day 0 count, irrespective of axillary temperature and one patient had parasitaemia on Day 3 with axillary temperature ≥37.5. ETF was not observed in any patient of Q+R group. However, the difference was not statistically significant. None of the patients in either group experienced LCF or LPF. The Q+P group showed 85% ACR while the Q+R group showed 100%. However, the difference was not statistically significant (p >0.05), which may be because of less number of cases.

The difference in ETF rate of the two groups can be due to the antimalarial activity of rabeprazole or the

Table 3. Changes in secondary efficacy variables

Parameter	Group 1 (n=20)			Group 2 (n=20)			*t*-value	*p*-value
	Mean	SD	SE	Mean	SD	SE		
FCT	52.8	20	4.47	51.3	16.68	3.73	–0.283	0.780
PCT	60.3	12.07	2.70	51.9	9.18	2.05	–2.424	0.026

FCT – Fever clearance time; PCT – Parasite clearance time.

increased susceptibility of the malarial parasites to quinine in the presence of rabeprazole. Nevertheless, the cure rate was 100% in both the groups, suggesting that even if it is due to declining susceptibility of *P. falciparum* to quinine, it is still a very effective antimalarial agent in this region, although the cure rate may be different at different places[10].

In spite of the observation of no significant difference in the cure rates of the two groups, the significant difference in the PCT of the two groups was evident (60.3 h *vs* 51.9 h, $p < 0.05$). A study from Thailand observed the mean PCT of patients treated with quinine mono therapy to be 82.1 h[11] whereas another study from Vietnam reported it to be 62 h[12]. This significant difference in the PCT of the two groups can certainly be attributed to the synergistic antimalarial activity of rabeprazole. This observation suggests that addition of rabeprazole to quinine facilitate the parasite elimination rate, and it may be helpful in reducing the duration of the quinine therapy, thereby decreasing the side-effects and increasing the patient compliance.

The PPIs are known to have antiparasitic and antibacterial activities. Omeprazole inhibits *Leishmania donovani* by inhibiting the P type K^+H^+ ATPase on its surface membrane[13]. An *in vitro* study demonstrated that omeprazole inhibits the growth of metronidazole resistant bovine pathogen *Tritrichomonas foetus* by inhibiting the enzyme *Pyruvate decarboxylase* of the parasite[14]. Certain *in vitro* studies have also shown a significant activity of PPIs against *P. falciparum*[7,15]. The precise mode of action of PPIs against *P. falciparum* is unknown, but they may have mechanisms distinct from those of the conventional drugs[7]. The PPIs are metabolized by hepatic CYPs and, therefore, may interfere with the metabolism of other drugs eliminated by this route. This effect may cause increase in the serum quinine concentration. PPIs may inhibit the growth of *P. falciparum* by inhibiting parasite ATPase activity, which in turn increases the pH of the acidic food vacuole. There is evidence that quinine also inhibits membrane ATPase in the same way as PPIs[16].

Another *in vitro* study reported the combination of omeprazole and quinine to be significantly synergistic against *P. falciparum*[8]. It was also having effective action against all of the *P. falciparum* clones tested at lower concentrations than omeprazole and pantoprazole. According to these studies for potent activity, the drug should have both hydrogen bond acceptor and hydrogen bond donor sites along with two aromatic hydrophobic sites. The hydrogen bond acceptor feature is totally absent in the mapping for pantoprazole. We used rabeprazole because of the fact that although all PPIs were found to be active against *H. pylori* in an *in vitro* study but rabeprazole had shown greater antibacterial properties against 8 strains of *H. pylori* than omeprazole and lansoprazole[17]. It was also better found than omeprazole and lansoprazole in inhibiting the urease activity of *H. pylori*[18] and suppressing the motility of *H. pylori*, *Campylobacter jejuni* and *C. coli*[19].

There was statistically significant difference in ETF or ACR in the two groups, which definitely indicates the antimalarial activity of rabeprazole. This observation is further supported by the significant difference in the PCT of the two groups. These results strongly suggest that addition of rabeprazole to quinine results in an increase in the parasite elimination rate and it may be helpful in reducing the duration of the quinine therapy, thereby decreasing the side-effects of quinine and increasing patient compliance. Our results showed that a rabeprazole-quinine combination could be a safe combination for *Pf* malaria. Moreover, a larger study or a randomized controlled trial can conclusively prove the antimalarial activity of rabeprazole and its use in management of malaria.

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