Original Article

TO COMPARE THE RELAPSE RATE OF ARTESUNATE WITH TETRACYCLINE AND QUININE WITH TETRACYCLINE IN UNCOMPLICATED FALCIPARUM MALARIA

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ABSTRACT

Objective: To determine the relapse rate of falciparum malaria treated with artesunate plus tetracycline (AT) versus quinine plus tetracycline (QT) in uncomplicated patients of malaria.

Methodology: A cross sectional comparative study was carried out at Combined Military Hospital, Quetta from 01 May to 30 November 2006. Ninety patients of age-sex matched group with uncomplicated falciparum malaria having parasitemia >1%, age between 14-65yrs, either sex and with no previous malaria treatment related to the present attack were recruited from emergency department, medical wards, included in the study. One group was given quinine along with tetracycline (QT) and the other group was given artemesinin and tetracycline (AT). The patient was discharged from the hospital when three negative blood smears were obtained. Thereafter, blood smears were taken at days 7, 14, 21 & 28 after the start of the treatment, as outdoor patients. Parasitological response was regarded as radical cure with parasite clearance by day 7 without recrudescence up to day 28. Fever and parasite clearance times were noted as the time from the initiation of treatment to the first of three consecutive normal axillary temperature readings (<37^0 C) or negative blood peripheral film slides, respectively.

Results: Out of 90 patients of falciparum malaria, treatment was completed in 85 patients. The cure rates using treatment with AT was effective in 35 of 45 (77.7%) while QT was effective in 34 of 45 (75.5%) of the patients without any statistically significant difference (p = 0.68). Poor compliance with the treatment schedule was observed in 2 of 45 (4.4%) in the AT group and 4 of 45 (8.8%) QT group of patients. Cure rates of 95.5% and 91.1% would have been obtained in the AT and QT groups if only compliant patients (n = 69) were considered. Parasitemia at day two cleared faster in the AT group than the QT group (91.1% versus 44.4%, respectively; p-value <0.001).

Conclusion: Combination of artesunate plus tetracycline is effective in the treatment of uncomplicated falciparum malaria and may provide a useful alternative to other treatment regimens.

KEY WORDS: Malaria, Plasmodium falciparum, Quinine, Drug resistance, Artesunate.

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INTRODUCTION

Malaria ranks among the major health problems in Pakistan. Endemic in ninety-one countries, which consist of forty percent of the world population, malaria affects an estimated

300 million people per year worldwide causing 1.5-3 million deaths per year.[1] Pregnant women and non-immune people are at particular risk. Problem has further compounded by the emergence of drug resistant strains of Plasmodia and insecticide resistance in anopheline mosquito, which is the causative vector.[2]

Pakistan is a tropical country having a vast system of irrigation and a lot of stagnant water after heavy rainfall in monsoon season providing an ideal environment for mosquito breeding. Transmission of malaria remains throughout the year but becomes more intense after the rains in the months from July to November.[3]

Falciparum malaria is a febrile illness, which presents after about 7–14 days of incubation period. Patients usually presents with moderate intermittent fever and headache. Typical tertian fever may not always be present. Patient is usually pale, icteric, may have spleenomegaly and herpes labialis. It can result into severe anemia, jaundice, cerebral malaria, pulmonary edema, algid malaria, acute renal failure, black water fever and hypoglycemia. [4]

Plasmodium falciparum infection is more dangerous and responsible for most of the deaths, which occur due to malaria.[5] Parasite induces knob formation at the surface of infected RBCs resulting into cyto-adhereance (adhesion of infected RBCs to capillary endothelium) and rosetting (adherence of uninfected RBCs to infected RBCs forming aggregates) thus, causing micro-vascular obstruction and impaired delivery of oxygen to the tissues.[6] P.falciparum is common in Africa, Haiti, New Guinea, South America, and Eastern Asia.[7] In Pakistan Southern Punjab, Baluchistan and Sindh are the areas where falciparum malaria is common and a rapid increase in falciparum malaria amongst children has been described in Sindh.[8]

Chloroquine remains the most widely used antimalarial drug in the world. However; falciparum malaria is rapidly becoming resistant to chloroquine. Chloroquine resistance was first encountered in Latin America in 1959 and reported from Thailand in 1962.[9] About 54% cases resistant to chloroquine have been reported from Indonesia and 67% Kenya.[10,11] Chloroquine resistance in falciparum malaria was first reported in Pakistan from Quetta in 1982. It also exists in Punjab and encountered in NWFP.[12]

This has prompted the renewed use of quinine and its isomers quinidine and other drugs like Artemisinin its derivatives. Quinine is regarded as the drug of choice by most authorities in cases of severe falciparum malaria. It acts on the late stage parasites sequestered in the microcirculation, but it clears parasitemia less rapidly. Resistance to quinine has been observed in South East Asia[13], but not yet in Pakistan. Artemisinin, an active antimalarial compound extracted from Chinese plant qinghao (Artemisia anua L.), and its derivatives show high activity and low toxicity against P. falciparum. As with all other artemesinin derivatives, oral artesunate is highly efficacious in clearing parasites and fever, with virtually no side effects. However, treatment failures caused by an R1 type response has been a problem with recrudescence rates of up to 100% when it was used alone in short term (1-3 days) regimen.[14]

The objective of this study was to investigate the efficacy of artesunate (seven days) plus tetracycline (seven days) compared with quinine (three days) plus tetracycline (seven days) in the treatment of uncomplicated falciparum malaria in Baluchistan.

METHODOLOGY

This comparative prospective study was conducted at Combined Military Hospital Quetta, which is 800 bedded tertiary care hospital for Armed Forces personal, their families, parents and civilians from 01st May to 30th Nov. 2006.

Patients of Plasmodium falciparum malaria with parasitemia >1% confirmed by demonstration of asexual forms in standardized blood films (thick smears stained with Giemsa stain) and aged between 14- 65yrs of either sex were included from emergency department and

medical wards. Patients with mixed infection, inability to take oral medication, I/V drug user, pregnancy and lactation, impaired consciousness, convulsions, respiratory distress, substantial bleeding , anemia (Hb < 7.1 g/dl) and jaundice were excluded from the study.

After detailed history and clinical examination, the diagnosis was made on thick and thin peripheral blood smears and by counting the percentage of parasitized red cells. Symptoms and physical examination findings were recorded daily. Vital signs were recorded every eight-hour daily until at least three normal temperature readings were obtained. Parasitemia was also assessed every eight-hour until three negative slides were obtained. One group was given quinine along with tetracycline (QT) and the other group was given artemesinin and tetracycline (AT). Intake of medication was supervised. When three negative blood smears were obtained the patient was discharged from the hospital. Thereafter, blood smears were taken at days 7, 14, 21 & 28 after the start of the treatment, as outdoor patients.

Parasitological response was regarded as radical cure with parasite clearance by day 7 without recrudescence up to day 28. Fever and parasite clearance times were noted as the time from the initiation of treatment to the first of three consecutive normal axillary temperature readings (<37^0 C) or negative blood peripheral film slides, respectively.

Data was entered and analysed on SPSSv10.0. Chi square test was used and a *p*-value of <0.05 was taken as significant.

RESULTS

Out of 90 patients of falciparum malaria, treatment was completed in 85 patients. Treatment could not be completed in five patients either because of severe vomiting at the beginning of the treatment period (one from the AT group and two from the QT group) or they were lost to follow-up before the end of the treatment (one from the AT group and one from the QT group). Follow-up to day 28 was completed in 69 patients whereas 12 patients were lost to follow up after the end of the treatment period on day 7. There was no evidence of confounding or interaction regarding the age group, gender and weight. The two treatment groups were similar with regard to clinical and baseline laboratory findings at the time of admission.

The treatment of AT was effective in 35 of 45 (77.7%) while QT was effective in 34 of 45 (75.5%) of the patients without any statistically significant difference (p = 0.68). For the 12 patients who completed the treatment schedule and cleared parasitemia before they were lost to follow up, it was not possible to distinguish between an S and an RI type response. Poor compliance with the treatment schedule was observed in 2 of 45 (4.4%) in the AT group and 4 of 45 (8.8%) QT group of patients. Therefore, failure rates of 22.2% in the AT group and 24.4% in the QT group were obtained, including three RI recrudescence (two in the AT group and one in the QT group), undefined treatment response (S/RI), and poor compliance to the treatment schedules, which were considered as treatment failures.

Cure rates of 95.5% and 91.1% would have been obtained in the AT and QT groups if only compliant patients (n = 69) were considered in the analysis as only three recrudescences occurred (all type RI), two in the AT group and one in the QT group. The proportion of patients clearing their infection determined by blood examination on day 2 was much higher in the AT group (91.1%) than in the QT group (44.4%) with a significant p-value of <0.001.

DISCUSSION

Malaria, one of the world's oldest life-threatening diseases, remains the most serious infection in terms of human suffering and death. Malaria results in 300-500 million clinical cases each year, causes significant morbidity and mortality in Pakistan. Young pregnant females are the most vulnerable by malaria.[15]

More than half of the world population lives in areas where malaria continues to be a major threat to life. It is widely distributed in tropical and subtropical zones. Unfortunately, this problem is further compounded by increasing

prevalence of the most virulent species of malaria, Plasmodium falciparum, and due to the emergence and spread of resistance to antimalarial drugs. Strains of P.falciparum resistant to antimalarial drugs have generally arisen from areas with massive population movements, inadequate health services and improper use of antimalarial drugs, limited resources and operational difficulties in implementing malaria control activities. The prevalence of P.falciparum and emergence of resistance to antimalarial drugs is increasing. It needs multidimensional activities and measures.[16]

In our study effectiveness of AT compared with QT in the treatment of uncomplicated falciparum malaria has been assessed. Oral AT in this study population quickly cleared P.falciparum asexual parasitemia (98.5%) in two days and radically cured 80% of all patients and 97% in compliant patients. Only two RI resistance responses were observed. Moreover, the drug combination was very well tolerated with a low incidence of minor side effects.

These results concur with other similarly encouraging results regarding the use of oral artesunate alone or in combination with other drugs.[17] Cure rates between 72% and 92.5% and a parasite clearance in about two days with no important side effects was obtained when oral artesunate was used in Thai patients.[18] Oral artesunate followed by mefloquine achieved a cure rate of 100%, which was higher than that observed when artesunate or mefloquine were used alone in similar populations.[19]

In a study by Bhalli et al, 49% patients were put on quinine treatment and showed a good response with recovery. Resistance was seen in two cases which were treated with Fansemef (mefloquine + sulphadoxine + pyrimethamine) and responded well. Four patients were given quinine plus doxycycline and showed no resistance.[20]

In a study by Iqbal et al, 55% of the patients were put on quinine alone. One case was resistant to quinine and recovered on mefloquine and sulphadoxine plus pyrimethamine. Nine patients were put on quinine plus doxycycline to enhance the effects of quinine, all of them recovered. Quinine with three tablets of sulphadoxine plus pyrimethamine (Fansidar) was given to 15% of patients, fever subsided and parasitemia cleared much earlier than those patients who were given quinine only.[21]

A randomized trial using artesunate plus doxycycline and mefloquine plus doxycycline was conducted in Thailand with cure rates of 80% and 96%.[22] A cure rate of 90% was reported in Vietnamese patients when oral artesunate was administered together with tetracycline compared with a 50% cure rate when artemisinin was administered alone.[23]

In providing evidence of the effectiveness of the combination of oral artesunate and tetracycline, our study also corroborates the basis for combining artesunate, a fast acting drug with parasite clearance in two days and a shorter half-life, with tetracycline which is a slow–acting antibiotic with effect manifested in approximately 48 hrs but having schizonticidal activity.[24]

Quinine plus tetracycline has been used successfully as the standard treatment for falciparum malaria in our country and other regions with continued positive results. In our study the combination of quinine and tetracycline was found to be still highly effective, curing 75% of all patients and 98% of compliant patients.[25]

Despite the efficacy of the treatment using quinine plus tetracycline for seven days, in countries where this drug combination has been extensively used for more than 10 years, 24% resistance to short-term treatment with quinine plus tetracycline has been reported in Thai patients.[26] The artesunate and tetracycline regimen resulted in a shorter parasite clearance time. Consequently we may expect better compliance with artesunate in unsupervised treatment regimens because of lesser side effects, a decreased number of blood parasite cycles, as well as a reduced risk for developing severe disease.

The reasons for the occurrence of three RI type responses were not assessed. Problems related to drug absorption as well as real resis-

tance of the parasite to drug action could have explained these recrudescences. Therefore, further studies are needed to identify recrudescence-related problems as well as to optimize dosage and drug combinations for oral artesunate therapies. Information on the pharmacokinetics and toxicity is limited and further investigation is required before its widespread use can be recommended.

CONCLUSION

Further studies are needed before oral artesunate can be considered as an alternative treatment for P.falciparum malaria in this region as the results are promising. The present study shows that the treatment with oral artesunate plus tetracycline has an overall better performance than the standard treatment of oral quinine plus tetracycline for adults who have uncomplicated P. falciparum malaria. There was a lower incidence of side effects and a faster time to parasite clearance with an equally high cure rates, aspects that may contribute to improved effectiveness of malaria control programs.

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