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STUDY TO KNOW THE IN VIVO SAFETY AND EFFICACY OF QUININE-DOXYCYCLINE GIVEN IN COMBINATION FOR THE TREATMENT OF ACUTE PLASMODIUM FALCIPARUM MALARIA

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Abstract:

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

Study Design: *A prospective observational study.*

Place and Duration: *In the medicine department of Allied Hospital, Faisalabad for one year duration from September 2018 to September 2019.*

Methodology: *Three hundred and thirty-seven patients with positive P. falciparum in the malaria test met the selection criteria and were included in the study. The mean, minimum and maximum values were calculated with the standard age deviation, the time to remove the fever from the malaria parasite index and the duration of the parasites. In addition, the frequency of various side effects and deaths observed during this study was also calculated.*

Results: *Of the 337 subjects, 256 had P. falciparum and 81 had mixed infections involving both P. falciparum and P. vivax. The mean time to remove fever in cases infected with P. falciparum and mixed infection was 46.3 hours and 44.16 hours, respectively. The mean elimination times of parasites in subjects infected with P. falciparum and mixed infection were 70.32 hours and 68 hours, respectively. Approximately 3.3% of subjects had mild to moderate side effects such as tinnitus, prolongation of QT interval and vomiting. The mortality rate observed in this study was around 0.6%.*

Conclusion: *Combination therapy with doxycycline can be used safely and effectively in the treatment of P. falciparum malaria.*

Keywords: *doxycycline quinine combination, malaria, Plasmodium falciparum, mixed infection.*

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INTRODUCTION:

Malaria is the most important parasitic infection in the world and is one of the main causes of morbidity and mortality. Despite years of continuous efforts, more than two billion people continue to be a threat and one to three million people die each year [1-3]. Among the four types of malaria parasites, protozoan plasmodium (P.) falciparum represents most cases of morbidity and mortality. Combined infections with more than one parasite species usually involve P. falciparum with a severe risk of malaria [4-6]. The increased prevalence of multidrug-resistant P. falciparum malaria is a serious threat to public health, especially from the global control of malaria in poor countries such as malaria. The artemisinin based combinations like Artesuna- teamodiaquine, artemether-lumefantrine (Coartem), Pyronaridine-artesunate and piperaquinedihydroartemis-inintrimetoprim (Artecom) etc. as well as the non-artemisinin- based combinations like Mefloq-uine-sulfadoxinepyri- methamine (Fansimet), Quinine-Doxycycline and Atovaquone-proguanil (Malarone) etc. have been suggested in different studies [7]. It has been used in combination with an antibiotic such as doxycycline or tetracycline as a preferred treatment in severe or complicated flasiparum malaria, with the emergence of sporadic resistance to traditional quinine monotherapy in Southeast Asia and Western Oceania. Adverse reactions such as tinnitus therapy, tinnitus, nausea, vomiting, dizziness, myocarditis, hypotension, hypoglycemia and sometimes acute renal failure have been reported in the literature. Because the recent reports on the gradual decline in the activity of quinine and P. falciparum are resistant to recommendations for most combinations of antimalarial drug and artemisinin based (about 5 to 6 times more expensive) combinations [8-9]. The use of a combination of the quinoline octanol line tested over time became questionable. It is still accepted as the treatment of choice in the latest malaria models in the UK.

MATERIALS AND METHODS:

This prospective observational study was held in the medicine department of Allied Hospital, Faisalabad for one year duration from September 2018 to September 2019. The criteria included (12-60 age group, malaria parasite film showing P. falciparum) in this study after informed consent was obtained. The history of swallowing of anti-marital medications during pregnancy or during other illnesses has been excluded. After enrollment, all participants were hospitalized for seven days with combination therapy with quinine doxycycline (three doses of quinine 30 mg / kg, 200 mg doxycycline twice daily in two divided doses), paracetamol and dimenhydrinate, respectively, for symptoms of fever / headache, Nausea / dizziness respectively. The drugs or intravenous fluids were given only as prescribed by the treating physician. Signs and symptoms, drug history and side effects were recorded daily. Routine physical examinations and laboratory tests were performed periodically until the seventh day. Blood stains were taken twice daily until malaria disappeared, followed once a week or clinically justified once a day. The efficacy of therapy in each subject was determined by the elimination of fever and elimination of the parasite. The duration of the clearance was defined as the time until the temperature was <37.4 ° C and remained there for at least 48 hours. The duration of the elimination of the parasite was defined as the time from the beginning of treatment to the first negative blood contamination for asexual stages, which remained negative for an additional 24 hours. All information was recorded in a pre-designed Performa. All patients were evaluated on a daily basis to report adverse events that were initially new during treatment or that were severely violated after administration of study drugs. Considering that the relationship with treatment was definite or probable by a study physician, an adverse event was thought to be drug dependent. Data were entered and analyzed in SPSS 18.0 software. The mean, minimum and maximum values were calculated with the standard deviation of time of extinction of fever and time of disappearance of parasites. The frequency of various side effects and deaths observed during this study was calculated.

RESULTS:

In total, three hundred and thirty-seven subjects met the selection criteria and were included in the study. Of these, 337,256 had P. falciparum infection, while 81 had mixed infection (P. falciparum and P. vivax combination). The mean age of the participants was 27.9 years between 12 and 51 years. In this study, all subjects were male only. The mean malaria parasite ratio was 1.1 in P. falciparum and 1.2 in mixed infection. The mean time to eliminate fever in individuals with P. falciparum infection and mixed infection was 46.3 hours and 44.16 hours, respectively.

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

Parameters	*P.falciparumn = 256*	*Mixed infectionn = 81*
Age (years)	Mean 28.3	Mean 26.62
	Range 12-51	Range 14-43
	Standard deviation 6.96	Standard deviation 5.7
Malarial parasite index	Mean 1.1	Mean1.2
	Range Upto 20	Range Upto 18
	Standard deviation 1.1	Standard deviation 1.21
Fever clearance time (hours)	Mean 46.3	Mean 44.16
	Range 12-86	Range 12-104
	Standard deviation 1.2	Standard deviation 1.41
Parasite clearance time (hours)	Mean 70.12	Mean 68
	Range 24-136	Range 24-130
	Standard deviation 1.3	Standard deviation 1.48
Adverse effects (n)	Tinnitus 4	Tinnitus 2
	ECG changes 2	ECG changes 1
	Vomiting 2	Vomiting none

The mean elimination time of the parasite in individuals with P. falciparum infection and mixed infection was 70.32 hours and 68 hours, respectively. Approximately 96.7% of the individuals in this study tolerated the combination therapy of quinine with doxycycline without any side effects of quinine. Only 3.3% (11/337) of the subjects developed mild to moderate side effects, such as tinnitus, prolongation of the QT interval, and vomiting. In this study, approximately 0.78% (2/256) of patients with P. falciparum infection died.

DISCUSSION:

This study demonstrated the in vivo efficacy and safety of combination therapy with Quinine doxycycline in malaria caused by P. falciparum in this part of the world in the background of reports showing an increase in resistance and severe adverse effects. This study reported that the mean elimination time of fever in subjects infected with P. falciparum was 46.3 hours and this time was much shorter than that observed in some of the international studies reporting that the reported quinine was between 55 and 107 hours, several studies have shown that there is almost a similar period or less [10]. This significant difference in mean fever removal time in the currently documented data may be due to the difference in sample size because most studies involve fewer participants and their fever is not under control. The mean elimination time of the reported fever in this study was slightly lower than the previous trials evaluating the effectiveness of the artemisinin-based combination, which is 80 to 108 hours [11-12]. In mixed infection involving both P. falciparum and P. vivax, the mean elimination time of the fever was almost unchanged, ie, 44.16 h. None of the studies in the literature evaluated the effect of mixed infection on the mean duration of clearance [13]. In this study, the mean elimination time for parasites was 70.32 hours in people infected with P. falciparum. This result was very variable in different trials. The time indicated in this study is almost identical to one of the trials and is shorter than the time specified in some other studies. Some of the studies reported that the mean elimination time of the average parasite was between 22.4 and 51.9 hours [14]. These resulting changes may occur in the elimination due to the reasons previously mentioned or the difference in the resistance between the regions. In this study, the mean elimination time of the parasite was almost similar to an assay that evaluated the efficacy of the artemisinin-based combination [15]. The mean elimination time of parasites in the mixed infection caused by P. falciparum and P. vivax was almost the same, ie 68 hours. None of the studies determined the effect of mixed infection on the elimination period of parasites. None of the subjects included in this study had a severe adverse reaction with quinine-based combination. Only mild to moderate side effects were observed in 3.3% of individuals and were much lower than those observed in previous studies. These side effects were successfully managed by reducing the dose of quinine without compromising the efficacy of the treatment. In these studies,

approximately 1.8% of the subjects developed tinnitus compared to 89% in previous studies.

CONCLUSION:

Combination therapy with Quinine doxycycline can be used safely and effectively in the treatment of malaria caused by P. falciparum, especially in low socioeconomic communities such as the majority of the population in this part of the world.

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