RESEARCH ARTICLE

COMPARATIVE STUDY OF QUININE PLUS DOXYCYCLINE VERSUS ARTEMETHER PLUS DOXYCYCLINE IN UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA IN A TERTIARY CARE TEACHING HOSPITAL OF EASTERN INDIA

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ABSTRACT

Background: The treatment of falciparum malaria has changed over the past two decades in response to declining sensitivity of P. falciparum to conventional antimalarial drugs. The treatment depends on patient's age, the severity of infection, the likely pattern of susceptibility to antimalarial drugs, cost and availability of such drugs. For this reason recommendations vary according to geographic region and should be under constant review. In this perspective we conducted the present study in this part of the world, Burdwan Medical College, West Bengal, India, where no such study conducted before. **Objective:** The objective of our study was to evaluate the efficacy of Artemether and Doxycycline combination against Quinine and Doxycycline combination in acute uncomplicated falciparum malaria as the primary objective. Our secondary objective was to evaluate the safety profile of the two combination regimens in terms of the adverse event profiles. **Materials and Methods:** In this study total 84 patients were randomly recruited after fulfillment of the inclusion criteria, from the Medicine inpatients Department of Burdwan Medical College& Hospital, West Bengal, during the period of May 2007 to December 2010. All the eligible patients suffering from uncomplicated falciparum malaria were randomly allocated to two groups. The 1st group was receiving Quinine sulfate 10 mg salt per kg body weight 8 hourly for 7 days plus Doxycycline hyclate 100 mg 12 hourly for 7 days. And the 2nd group was receiving Artemether 80 mg every 24 hours for 5 days with an additional 80 mg dose 12 hours after the first dose, plus Doxycycline hyclate 100 mg (of Doxycycline) 12 hourly for 7 days. They were discharged after 7 days and advised for follow up on days 14 and 28. Efficacy was measured by the two variables: [1] Primary efficacy variables, included as (i) Fever Clearance Time and (ii) Parasite Clearance Time and the [2] Secondary efficacy variables, included as (i) Cure Rate and (ii) Relapse Rate. **Results:** In our study, cure rate was 84.21% and 100% of the 1st group & 2nd group respectively, with the later was significantly better than the 1st one (p= 0.014). Fever Clearance time of the 2nd group was significantly shorter (p= 0.001) than that of the 1st one and the Parasite Clearance Time of the 2nd group was also significantly shorter (p= 0.002) than that of the 1st one. Though the frequency of nausea and vomiting was slightly higher in the 2nd group, but not statistically significant (p= 0.11). **Conclusion:** In our study, in this institution combination of Artemether plus Doxycycline was highly effective than the combination of Quinine plus Doxycycline in the uncomplicated falciparum malaria and was well tolerated.

Key Words: Malaria, Plasmodium falciparum, Uncomplicated, Artemether, Doxycycline

INTRODUCTION

Malaria is the world's most important parasitic infection [1]. At present about 100 countries or territories in the world are considered malarious, almost half of which are in Africa, south of the Sahara [2]. The incidence of malaria worldwide is estimated to the 300-500 million clinical cases each year- majority caused by Plasmodium falciparum. Malaria is thought to kill between 1.1 & 2.7 million people worldwide each year [2] and kills a child somewhere in the world every 30 seconds [3].

The treatment of Plasmodium falciparum malaria has been changed over the past two decades in response to declining sensitivity of Plasmodium falciparum to conventional antimalarial drugs [1]. The parasite remains fully sensitive to chloroquine only in Central America, north of the Panama Canal, in Haiti, Egypt and in scattered pockets of Asia and South America [4]. Southeast Asia, including India, lie in the zone of chloroquine resistance [2, 4]. However, world maps that depict countries as having or not having drug resistant malaria are potentially misleading, as there is great heterogeneity within countries and across boundaries. Local knowledge is therefore of paramount importance [4].

The treatment of malaria depends on patient's age, the severity of infection, the likely pattern of susceptibility to antimalarial drugs, cost and availability of such drugs. For this reason recommendations vary according to geographic region and should be under constant review [1]. Though chloroquine is still the mainstay of antimalarial treatment, the emergence of Plasmodium falciparum resistant to this drug has challenged control efforts and has been linked to increased mortality [5]. Krishna [6], stated that "assume that Plasmodium falciparum is chloroquine resistant unless in an area with known chloroquine sensitivity". White and Breman [7], have opined "in areas where Plasmodium falciparum is still sensitive, chloroquine is used as the second drug". Todd et al. [8], also agreed with this view and recommended that "Plasmodium falciparum is now resistant to chloroquine almost worldwide, notable in Asia and Africa, so quinine is the drug of choice as dihydrochloride or sulfate".

Quinine is a good alternative to chloroquine but it has several limitations [9]. It is used in combination with tetracyclines, such as doxycycline, in areas where quine resistance is also documented or possible. The artemisinin derivatives are better tolerated alternatives to quinine. Artemisinin and its derivatives are sesquiterpene lactone peroxides derived from the leaves the sweet wormwood (Artemisia annua) and related plants [4]. It has been used

traditionally in Chinese medicine as 'qinghaosu'- pronounced 'ching-how-soo' [10]. Three derivatives are currently available- Artesunate, a water soluble form, and the lipid soluble Artemether and Arteether [11]. Artemisinin derivatives kill all stages of malaria parasites, including 'young rings' by interacting with heme to produce carbon-centered free radicals that alkylate proteins and membranes [11]. They have potent antimalarial activity, attractive safety profiles and are yet to be associated with significant resistance [5]. Qinghaosu and its derivatives have been studied extensively in China and Southeast Asia during the last 10 years. The effectiveness of these drugs in clearing parasites has been thoroughly documented [12].

The essence of our study is to search for a better combination regimen in comparison to the older quinine-doxycycline duo. There is growing belief among malariologists that to prevent resistance, falciparum malaria should no longer be treated with single drugs in endemic areas, the same strategy that has been applied to the treatment of other infectious diseases of major global public health significance such as tuberculosis and HIV/AIDS. This strategy is based upon simultaneous use of two or more drugs with different modes of action [7]. The basic tenet is that the probability of resistance developing simultaneously to two chemotherapeutic agents with independent mechanism of action is extremely low, of the order of once in 10^{12} treatments. This frequency is the product of the probabilities of the acquisition of a resistant mutation to each drug multiplied by the number of parasites in a typical infection [3]. Combinations also prevent recrudescence or relapse of symptoms.

Combination of quinine with doxycycline is time-tested and retains at least 85% effectiveness nearly everywhere [1]. As quinine has limitations and artemisinin compounds are good alternatives, several drug combinations with artemisinin have been and are being evaluated till date. For example, artesunate plus amodiaquine, artemisinin derivative with mefloquine, artemether with lumefantrine and so on. Assessment of these and other effective and well-tolerated combination regimens containing artemisinin compounds is needed in other geographical areas [5]. In this scenario we conducted our study in this geographical area, Burdwan Medical College& Hospital, West Bengal, India. For our study we had chosen artemether in combination with doxycycline and compared to the standard quinine plus doxycycline regimens. All drugs were administered by the oral route.

MATERIALS AND METHODS

Study duration: For the individual patients, the study duration was 28 days including follow-up study visits. The entire study was completed from May 2007 to December 2010.

Ethical consideration: This study was conducted in accordance with the principles enunciated in the Declaration of Helsinki for Biomedical Research involving Human Subjects. Also every effort was made to adhere to the spirit of the Good Clinical Practice guidelines of the Government of India [13]. Written informed consent was taken from each of the individuals. The protocol and the patients' informed consent form was approved by the Institutional Ethics Committee.

Sample size: Total 84 patients, suffering from uncomplicated falciparum malaria, were recruited from the Medicine inpatients Department of Burdwan Medical College,West Bengal, after fulfillment of the inclusion& exclusion criteria.

Inclusion criteria:

a) Subject aged between 15 to 65 years.

b) Subject weighing at least 45 kg.

c) History of fever (≥ 100 ^{0}F) within the past 48 hours.

d) Screening of peripheral blood smears showing presence of Plasmodium falciparum.

e) Willing to provide written informed consent.

Exclusion criteria:

a) Female subject who is pregnant or breast feeding.
b) Estimated extent of parasitaemia > 10^5 /μL.
c) Screening of peripheral blood smears showing presence of mixed malarial infection i.e. Plasmodium vivax + Plasmodium falciparum.
d) Subject having evidence of
- Impaired consciousness.
- Severe anemia (Hb < 5 g/ dL).
- Jaundice or compromised liver function (ALT or AST > 3 times upper limit of normal.
- Respiratory distress.
- Hamaturia.
- Hypoglycemia (Blood glucose < 70 mg/ dL).

e) Subject having history of
- Optic neuritis.
- Significant tinnitus.
- Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Severe cardiac dysrhythmias.

f) History of use of any antimalarial for the current febrile episode or within the past 1 month.
g) History of use of any medication that may influence the activity of antimalarial drugs, e.g. folate, azithromycin, dapsone, etc. , within the past 7 days or longer depending upon the nature of the drug.
h) History of Blood transfusion within the past 1 month.
i) History of allergy (hypersensitivity) to artemether, quinine, doxycycline or closely related drugs.
j) Any concomitant serious disorder of the kidney, heart, lungs or other vital organs.
k) Unwilling to remain hospitalized for at least 7 days or to return for follow up at the stipulated days on 14th day and 28th days.
l) History of alcohol or substance abuse.

Study Methodology:

a) **Study design:** Our study was post registration (Phase IV), prospective, open, randomized, controlled study with the two parallel treatment groups.
b) **Study time schedule:** All the recruited subjects were admitted to the medicine inpatients departments and was studied as in-patient for 7 days. Thereafter they were discharged & was advised to come on the day 14 and 28th days for follow up study.

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c) Baseline assessment: At presentation every patient was screened for presence of a history of fever within the past 48 hours and the presence of Plasmodium falciparum in the peripheral blood smear. A serological test for Plasmodium falciparum HRP-2 antigen was also carried out. Blood was also collected for baseline laboratory test including complete hemogram & blood biochemistry.

d) Study evaluation: Plasmodium falciparum infection was diagnosed first. Then the response to study drugs was evaluated by Primary & secondary efficacy variables. Diagnosis of falciparum malaria was based on blood smear test [5, 12] and detection of Plasmodium falciparum HRP-2 antigen with a rapid dipstick antigen capture assay [14].

Blood Smear Test: Both thick & thin films were prepared from finger prick blood samples and stained with 2% Giemsa stain for 30 minutes. All smears being examined at the magnification of 1000. Blood smear was collected every 12 hours interval after commencement of treatment until two consecutive examinations were negative. From blood smear quantization of the parasitemia was done as follows. Total RBC or WBC was counted first. Then the number of asexual parasites per 1000 RBC in a thin film or parasites per 200 WBC in a thick film counted. Parasite density was calculated by multiplying both the numbers and expressed as parasites per µL. Blood film considered as negative when no parasites were seen in 200 oil-immersion fields in a thick blood film [5, 12].

Detection of Plasmodium falciparum HRP-2 antigen by rapid dipstick antigen capture assay: Antibody capture of circulating plasmodium specific antigens –a technique proposed for rapid diagnosis of malaria [14]. The Plasmodium falciparum histidine rich protein-2 (PfHRP-2)- a water soluble antigen released by blood stages of the parasite- a target for antigen capture assay. Fifty µL blood placed in a labeled polypropylene tube and three drops (about 100 µL) of a RBC lysing agent added. After gently agitating the tubes, specimens were ready for testing by the antigen capture assay. Assay test sticks were made of cellulose fiber and contain an immobilized IgG_1 monoclonal antibody directed against the synthetic peptide (AHH [AHHAAD] $_2$) from PfHRP2. Test sticks were packaged with desiccant in foil pouches and kept unrefrigerated. One drop of a lysed blood specimen dispensed into one well of a ten-specimen test-stick holder platform. The end of a test-stick was placed in the drop of lysed blood. The drop of blood was absorbed by the test-stick along its entire length, a process required 2- 10 minutes depending on the specimen.PfHRP2 antigen detector reagent (containing polyclonal antibodies against PfHRP2 that conjugated to liposomes containing pink dye) was then added to every specimen well. After the antigen detector reagent was absorbed by the test-stick, a wash reagent was added and absorbed. The result was read immediately. A positive test result (PfHRP2) showed as a thin, solid, pink band that appeared on the dipstick.

Different field studies showed that when Plasmodium falciparum asexual parasitemia is greater than 60 parasites per µL, the dipstick test is 96.5- 100% sensitive [2]. At lower level of parasitemia the sensitivity decreases; however at 11-60 parasites per µL of blood, the assay still detects 70-80% of infection and at 10 parasites per µL of blood or less, the assay detects 11-67% of infection [13]. Since most individuals with symptomatic Plasmodium falciparum infection have greater than 60 parasites per µL of blood, the dipstick assay will be of particular use in rapid diagnosis of febrile patients and in epidemiologic field studies [12]. Furthermore because inexperienced microscopists often have difficulty in detecting less than 60 parasites per µL of blood, assessment of comparative sensitivity of blood films and dipstick assay among such technicians may indicate that dipstick has greater sensitivity than blood smear. Further the test is easy to perform, does not require electricity or elaborate equipment. Only a small amount of unprocessed whole blood is required. Analysis of a single specimen can be completed within 20 minutes. Usually PfHRP2 antigen is not detectable in blood 6 days after initiation of current chemotherapy suggesting that circulating antigen rarely lead to false positive test [14]. However, one problem with PfHRP-2 based tests is the persistence of HRP-2 antigen after effective treatment, possibly making these tests less suitable for identifying treatment failure [2]. Hence this test was not used during follow up period in this study.

Study treatment: All the eligible subjects were randomly allocated in to **two treatment groups**. **[A] 1st group total patients were 43**. **They received Quinine sulfate 10 mg (of the salt) per kg body weight 8 hourly for 7 days plus Doxycycline hyclate 100mg (of doxycycline) 12 hourly for 7 days.**

[B] In the 2nd group total patients were 41. They received Artemether 80 mg every 24 hours for 5 days with an additional 80 mg dose 12 hours after the first dose plus Doxycycline hyclate 100mg (of doxycycline) 12 hourly for 7 days.

All the drugs were administered by oral route. The following brands were used.

Artemether – Cap Larither [Manufacture: M/s IPCA Laboratories Ltd. Mumbai]. Each capsule contained 40 mg of artemether. Quinine was used as Tab Cinkona [Manufacture: M/s IPCA Laboratories Ltd. Mumbai]. Doxycycline was used as Cap Doxy-1 [Manufacture: M/s USV Limited, Mumbai].Each capsule containing 100 mg of doxycycline as hyclate.

Assessment of the Efficacy of the Study Drugs: By the two variables.

a) Primary Efficacy Variables: **(i) Fever Clearance Time** [14]: Defined as the time from the start of the treatment until the temperature measured in the mouth fall to < 99 ^{0}F (to the nearest 6 hours after start of treatment) and subsequent sublingual temperature remained < 100 ^{0}F for at least 24 hours. **(ii) Parasite Clearance Time** [14]: Defined as the time from the start of the treatment until the first time the slide became negative (to the nearest 12 hours after start of treatment), with subsequent blood smears remaining negative until the last study assessment on the day 28.

b) Secondary Efficacy Variables: **(i) Cure Rate:** Defined as the proportion of the patients who responded to treatment and remained symptomatically relieved (i.e. no fever) as well as free from parasitemia till the 28th day of follow up. **(ii) Relapse rate:** Defined as the proportion of

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the patients who responded to treatment (fever clearance and parasite clearance were achieved) but showed recurrence of symptoms (i.e. fever) and or parasitemia before the end-of-trial visit on day 28 following commencement of study medication.

Data Analysis: All the collected data were analyzed using the **S**tatistical **P**ackage for the **S**ocial **S**cience (SPSS**) ver-16** in Windows-7 and Microsoft Excel. Efficacy data evaluated by an intention-to-treat analysis for subjects who had taken study medication for at least 48 hours. Parametric data compared by the Student's t test, while non-parametric numerical data compared by the Mann-Whitney U test, with $p < 0.05$ was the cut-off level for statistical significance. Categorical data compared by χ^2 test and also by the Fisher's exact test.

RESULTS AND ANALYSIS

During the May 2007 to December 2010, total 84 patients were enrolled in this study. Out of that 43 patients were allocated randomly to the 1st group, i.e. quinine plus doxycycline group. In that group 90.697% & 9.303% of patients were male and female respectively. Age range of that group was 15 to 60 years. All the patients were suffering from fever. Duration of fever before admission was 4.3 ± 2.89 (Mean ± SD) days and highest fever before treatment was 38.7 ± 0.69 (Mean ± SD) ^{0}C. In the 2nd group 41 patients were allocated randomly i.e. they were belonged to artemether plus doxycycline group. In the 2nd group 87.804% & 12.195% of patients were male and female respectively. Average age was 23.6 ± 7.01 (Mean ± SD) years. All were suffering from fever. Average duration of fever was 4.5 ± 3.59 (Mean ± SD) and highest temperature before treatment was 38.8 ± 0.68 (Mean ± SD) ^{0}C. The details of the Clinical and Laboratory characteristic of the both two groups of patients, before treatment started, are shown in the **Table No. 1. & Table No. 2.**

Table No. 1: Showing the baseline Clinical Characteristics of both the two groups of the patients:

Table No. 1	1st Group: Quinine plus Doxycycline (n = 43)	2nd Group: Artemether plus Doxycycline (n= 41)
Sex: Male	39 (90.697%)	36 (87.804%)
Female	4 (9.303%)	5 (12.195%)
Age: Mean ± SD	23 ± 6.9 years	23.6 ± 7.01 years
Range	15-60 years	15-65 years
Weight: Mean ± SD	49.5 ± 5.60 kg	51 ± 5.89 kg
Fever: Duration before admission(Mean ± SD)	4.3 ± 2.89 days	4.5 ± 3.59 days
Highest temperature before treatment (Mean ± SD)	38.7 ± 0.69 ^{0}C	38.8 ± 0.68 ^{0}C
No. of Patients With Splenomegaly	14 (32.558%)	5 (12.195%)
With Hepatomegaly	8 (18.604%)	9 (21.951%)
With First Malarial Attack	8 (18.604%)	7 (17.073%)
Mean Parasite count	22860 per µL	25820 per µL
Range of Parasite count	412-151441 per µL	191-185410 per µL

Table No.2: Showing the baseline Laboratory Characteristics of both the two groups of the patients

Table No.2: Laboratory data (Mean ±SD)	1st Group: Quinine plus Doxycycline (n = 43)	2nd Group: Artemether plus Doxycycline(n= 41)
Packed Cell Volume (%)	34.9 ± 6.8	36.3 ± 6.2
WBC Count (per µL)	4853 ± 1419	5530 ± 4329
Platelet count (10^3/µL)	1661 ± 855	1593 ± 891
ESR (ml/hr)	42.1 ± 30.89	43.6 ± 24.53
Blood Urea (mmol/L)	6.12 ± 2.01	6.89 ± 4.13
Serum Creatinine (µmol/L)	102 ± 10	103 ± 17
Total Bilirubin(µmol/L)	22.1 ± 19.19	24.13 ± 21.3
Serum AST(µmol/L)	41.39 ± 22.5	51.1 ± 22.5
Serum ALT(µmol/L)	39.18 ± 22.5	41.13 ± 28.5
Serum Albumin (mg/L)	38 ± 3.8	38.5 ± 2.9

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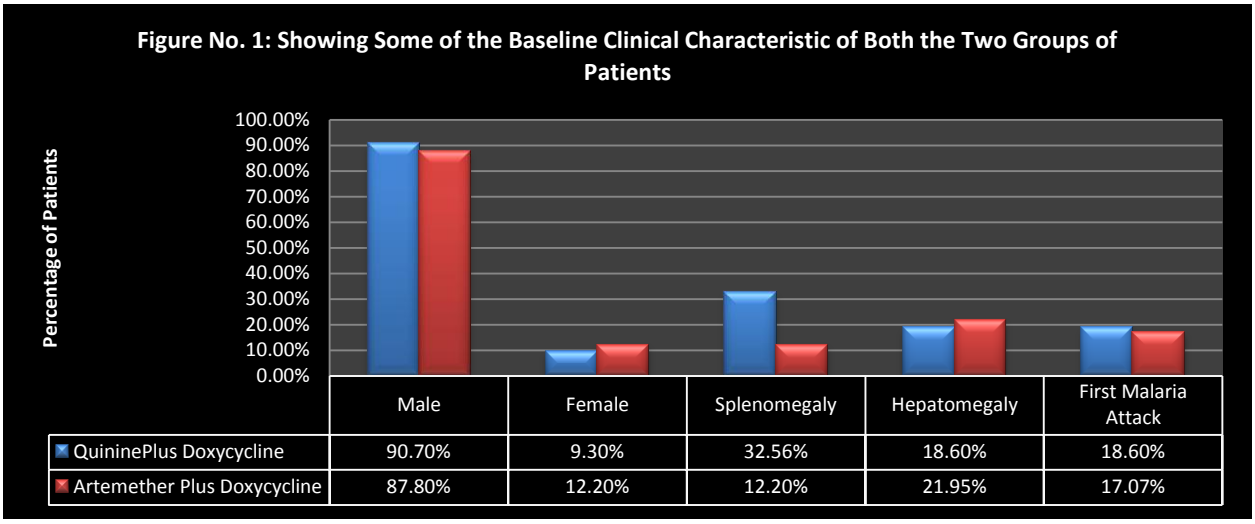

After treatment started, fever clearance time was significantly shorter in the 2nd group (artemether plus doxycycline) than that of the 1st group (p = 0.001). Similar significant faster response of parasite clearance time of the 2nd group (p= 0.002). Though in the two groups, the parasite count was reduced by 80% within the 60 hours, but the mean Parasite clearance time of the 1st group was 61.09 ± 28.06 hours (mean ±SD), while that of the 2nd group was 36.49 ± 28.19 hours (mean ±SD). Fever clearance time of the 1st group was 68.69 ± 38.06 hours (mean ± SD) and that of the 2nd group was 35.47 ± 22.19 hours (mean ± SD). In this study 38 patients of the 1st group completed the last 28th day follow-up study, while 39 patients of the 2nd group completed the same. Cure rate of the 1st group was 84.21%, while that of the 2nd group was 100%.

The details Therapeutic Responses of both the groups are shown in the Table No. 3.

Table No. 3: Therapeutic Efficacy Measurements:	1st Group: Quinine Plus Doxycycline (n= 43)	2nd Group: Artemether Plus Doxycycline (n=41)
No. of Patients with 28 days follow-up	38	39
No. (%) Cured in 28 days	32 (84.21%)	39 (100%)
Fever Clearance Time (hrs) Mean ± SD	68.69 ± 38.06	35.47 ± 22.19
Range (hrs)	6-149	4-129
ParasiteClearance Time(hrs) Mean± SD	61.09 ± 28.06	36.49 ± 28.19
Range (hrs)	18-90	16-69

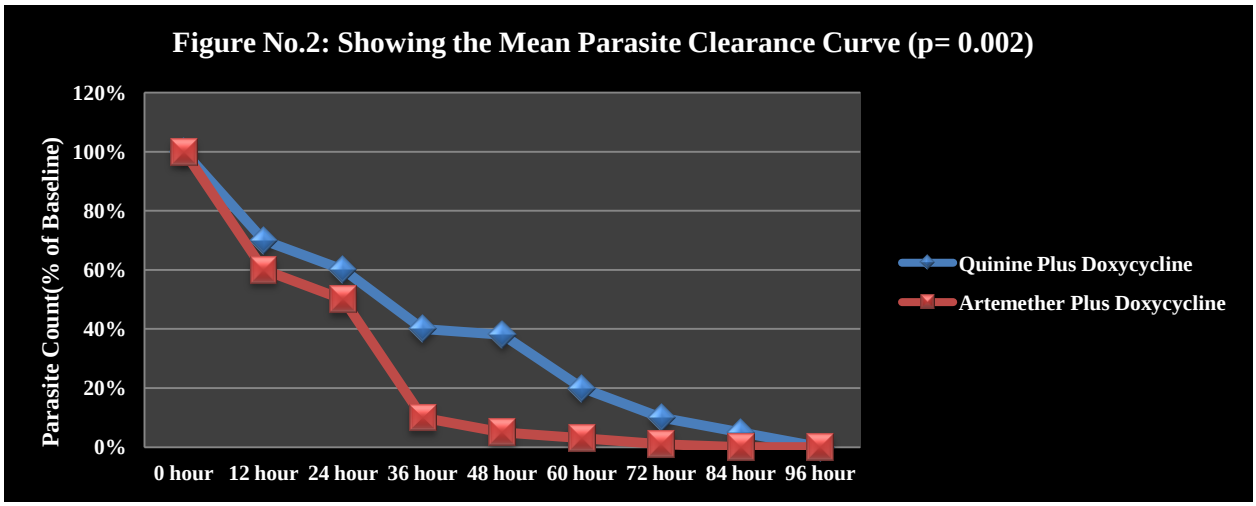

Figure 2: Time of the mean parasite clearance is distributed

The nature and the severity of the adverse drug reactions were not significantly different in both the two groups. Headache, dizziness had been noticed in only 13 & 8 patients of the 2nd group, while diarrhea was most common among the 44.186% of the patients of the 1st group. 7 artemether + doxycycline, treated patients reported nausea and 10 patients reported vomiting after 48 hours of treatment, but no additional treatment was required. No patients were discontinued from the study drug treatment due to adverse drug reaction.

Serial blood examination showed that packed cell volume gradually increased after treatment in both the groups. Absolute neutrophil counts were low before treatment in

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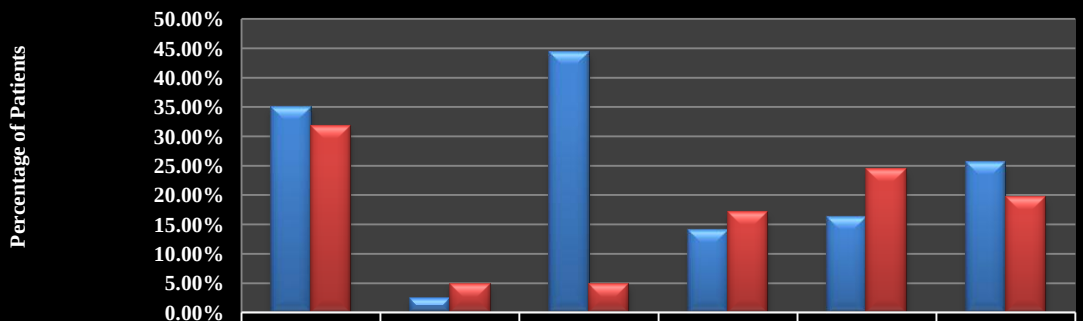
both groups, but gradually increased to normal values within 3-4 weeks of treatments.

The details adverse drug reaction profiles of the patients of both the two groups are shown in the Table No. 4.

Table No. 4:Adverse Drug Reaction Profile	1st Group: Quinine Plus Doxycycline (n= 43)	2nd Group: Artemether Plus Doxycycline (n=41)
Headache	15 (34.88%)	13 (31.70%
Abdominal Pain	1 (2.32%)	2 (4.875%)
Diarrhea	19 (44.186%)	2 (4.875%)
Nausea	6 (13.953%)	7 (17.07%)
Vomiting	7 (16.27%)	10 (24.39%
Dizziness	11 (25.58%)	8 (19.51%)

Figure No. 3: Showing the distribution of Adverse Drug Reaction profile of the patients of both the two groups



	Headache	Abdominal Pain	Diarrhoea	Nausea	Vomiting	Dizziness
Quinine Plus Doxycycline	34.88%	2.32%	44.19%	13.95%	16.27%	25.58%
Artemether Plus Doxycycline	31.70%	4.88%	4.88%	17.07%	24.39%	19.51%

DISCUSSION

Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes. The most important of the parasitic diseases of humans, it is transmitted in 108 countries containing 3 billion people and causes nearly 1 million deaths each year [15]. Malaria has been eliminated from the United States, Canada, Europe, and Russia; in the late twentieth and early twenty-first centuries, however, its prevalence rose in many parts of the tropics [16]. Malaria can behave like an epidemic disease in some areas, particularly those with unstable malaria, such as northern India (the state of Rajasthan), Sri Lanka, Iraq, and Turkey, the horn of Africa, Rwanda, Burundi, southern Africa, Madagascar, and central Asia [17].

Malaria is a very common cause of fever in tropical countries. William Osler [7] stated that "Humanity has but three great enemies. Fever, famine and war, of these by far the greatest, by far the terrible, is fever". The treatment of falciparum malaria has changed radically in recent years. In all endemic areas, the World Health Organization (WHO) [18] now recommends artemisinin-based combinations as first-line treatment for uncomplicated falciparum malaria. These rapidly and reliably effective drugs are sometimes unavailable in temperate countries, where treatment recommendations are limited by the registered available drugs. Fake or substandard antimalarials are commonly sold in many Asian and African countries. Thus, careful attention is required at the time of purchase and later, especially when the patient fails to respond as expected [18]. Current Artemisinin based combination regimens that are well tolerated in adults and children >5 kg include artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulfoxadine-pyrimethamine, and dihydroartemisinin-piperaquine & pyronaridine [19].

But when we started our study, in the early 2007, we designed to use artemether plus doxycycline combination, by following the as usual strategy of the treatment of global public health importance, likes treatment of tuberculosis, HIV/AIDS, etc.

White NJ [20] stated that as a class, the artemisinins are very potent and fast-acting antimalarials, inducing more rapid parasite clearance and fever resolution than any other currently licensed antimalarial drug. They are particularly well suited for the treatment of P. falciparum malaria. . Artemisinins cause a significant reduction of the parasite burden, with a four-$\log_{10}$ reduction in the parasite population for each 48-hour cycle of intra erythrocytic invasion, replication, and regress. As such, only three to four cycles (6-8 days) of treatment are required to remove all the parasites from the blood. Additionally, artemisinins possess some gametocytocidal activity, leading to a decrease in malarial parasite transmission. Artemisinins act early in the asexual parasite development cycle, whereas

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quinine acts at the late stage [21]. Probably due to that reason in our study, artemether containing combination had shorter parasite clearance time & fever clearance time and no recrudescence among the patients of the 2nd group, it was 100% cure but in the 1st group it was at the rate of 84.21%.

In our comparative therapeutic trial of 43 months duration in total 84 patients with uncomplicated falciparum malaria, a combination of artemether plus doxycycline resulted in radical cures, with some self-limiting side effects in a few patients in comparison with quinine plus doxycycline group.

Different studies [22, 23, 24, 25] conducted in various parts of the world with the different combination of artemisinin based compound on the falciparum malaria producing varying results in their geographic area, but our study in this part of the world tally with some of the results.

CONCLUSION

Though there were limitations in this study especially involving small number of patients in only one institution, but the present study showed that artemether plus doxycycline combination was a safer and better alternative than the quinine plus doxycycline combination.

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