

EFFICACY AND SAFETY OF β -ARTEETHER AND α/β -ARTEETHER FOR TREATMENT OF ACUTE *PLASMODIUM FALCIPARUM* MALARIA

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Abstract. One hundred thirty-eight adult patients with acute *Plasmodium falciparum* malaria were randomized to receive either β -arteether or α/β -arteether. The drugs were administered in the dose of 150 mg once a day intramuscularly for three consecutive days in hospitalized patients. After one week of hospitalization, patients were followed-up for three weeks after release from the hospital. There was no statistically significant difference between cure rates, mean fever clearance time (FCT), mean parasite clearance time (PCT), and occurrence of side effects in either group. The cure rate was 97.14% for β -arteether and 97.01 for α/β -arteether ($P = 0.9660$). The mean PCT was 38.49 hours for β -arteether and 36.90 hours for α/β -arteether ($P = 0.6054$), and the mean FCT was 37.27 hours for β -arteether and 37.9 hours for α/β -arteether ($P = 0.8718$). Both arteether formulations were safe and efficacious in reducing the clinical symptoms of acute falciparum malaria. There was also rapid clearance of parasitemia with both formulations. Thus, either β -arteether or α/β -arteether can be used in the treatment of acute falciparum malaria.

INTRODUCTION

Malaria causes major health and economic burdens in most tropical countries.¹ More than 40% of the world's population live in malaria-endemic areas. An estimated 300–500 million cases and 1.5–2.7 million deaths occur each year due to malaria.² In India, over the past two decades, malaria incidence has been fluctuating between two and three million cases each year.^{3,4} India has 40% of all malaria cases outside Africa.

Plasmodium falciparum most commonly causes severe (life-threatening) malaria if not treated timely. It affects all age groups, although the reported mortality varies considerably depending upon the age, immunity, clinical complications, and access to appropriate treatment.⁵ The situation has been further complicated by the spread of chloroquine-resistant malaria. Currently, chloroquine resistance is more prevalent in northeastern and southeastern India with high morbidity and mortality.

The widespread resistance of *P. falciparum* to chloroquine in India precludes the use of this drug in treatment of severe malaria. Pyrimethamine-sulfadoxine and mefloquine cannot be used as primary drugs for management of severe malaria because they are oral drugs (therapy in severe malaria should always be parenteral because of inability to take oral medication and the uncertain bioavailability of oral medication).⁶ Therefore, the essential choice is between quinine and artemisinin derivatives. It is important to note that as far back as in 1997 some pockets of quinine resistance were detected in northeastern states of India. Quinine also has undesirable side effects including hypoglycemia and cinchonism. It must be given three times a day as an intravenous infusion that requires close medical supervision.

Considerable impetus to the management of malaria has been given by the artemisinin (qinghaosu) derivatives, which were first isolated in 1971 by Chinese chemists. Artemisinin and its derivatives are known for their potent antimalarial activity, which is characterized by an almost immediate onset

and rapid reduction of parasitemia, with complete clearance in most cases within 48 hours.⁷ They are also preferred because of fewer side effects and ease of administration. Arteether is the ethyl ether derivative of dihydroartemisinin. In India, arteether is available as α/β -arteether developed by the Central Drug Research Institute (CDRI), Lucknow.⁸ Outside India, arteether is available as β -arteether developed by World Health Organization (WHO) Special Program for Research and Training in Tropical Diseases.⁹

The efficacy and safety of β -arteether and α/β -arteether have been established.^{10–13} However, no trial comparing the two drugs has been conducted. Tripathi and others have shown that both β -arteether and α/β -arteether have comparable activity and are curative at a dose of 5 mg/kg for three days against blood-induced *Plasmodium cynomolgi* B infection in the rhesus monkey; α -arteether alone is slightly less active, with a 50% cure rate at this dose.¹⁴ The purpose of this study was to assess efficacy and safety of β -arteether in comparison with α/β -arteether given as an injection for the treatment of acute *P. falciparum* malaria in Indian patients.

MATERIALS AND METHODS

Study area. This multicentric study evaluated the efficacy and safety of β -arteether and α/β -arteether injections in the treatment of acute *P. falciparum* malaria in a comparative, randomized, and double-blind trial. The trial was conducted at hospitals in Kolkata (West Bengal), Bikaner (Rajasthan), Baroda (Gujarat), Rourkela (Orissa), and Gwalior (Madhya Pradesh) because *P. falciparum* malaria is more prevalent in these regions and there is no significant variation in endemicity. The trial was initiated at all centers after obtaining the necessary clearance from the concerned ethics committees. Written informed consent was obtained from all patients prior to inclusion in the study.

Recruitment and treatment of patients. The sample size was calculated by taking the response rate of β -arteether at 1.00 and of α/β -arteether at 0.86. The power of the test was 80% with confidence interval of 95%. A total of 138 adult patients were enrolled in the trial. Patients in the study were adults of either sex with acute *P. falciparum* malaria diag-

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nosed by the presence of ring forms of *P. falciparum* in thick and thin peripheral blood smears (parasitemia > 5%). Patients were excluded from the trial if they had severe complications such as cerebral malaria or renal failure, were taking cardioactive drugs, had a history of adverse effects from arteether or its related qinghaosu compounds or any other antimalarial drugs, or had any other significant abnormality (clinical or laboratory) on pre-trial screening. Pregnant and lactating mothers were also excluded from the trial.

After confirmation of diagnosis, the patients were hospitalized for one week. A thorough clinical examination and necessary laboratory investigations (hemogram, blood platelet count, blood glucose, blood urea nitrogen, serum creatinine, liver function tests, electrocardiogram) were conducted. All laboratory investigations were repeated at the end of the study. A posterior-anterior chest radiograph was done if clinically indicated.

Patients were randomized to receive either α/β -arteether or β -arteether (coded as drug A and drug B, respectively). The codes were broken after analysis of results. The method used for randomization was permuted block randomization. Blocks having equal numbers of As and Bs (A = intervention and B = control) were used. A random number sequence is used to choose a particular block, which sets the allocation order. The randomization was center specific.

The principal investigator of each center was responsible for enrolling the participants and assigning participants to the groups. The formulations were packed in identical packs and coded drug A and drug B. To avoid patient selection bias, a double-blind design was used. Neither the investigator nor the patients knew which treatment was given. The injections were provided in ampules of similar shape and size. Arteether formulations were administered at a dose of 150 mg a day by intramuscular injection for three consecutive days.

Assessment and follow-up of patients. Patients were followed-up in the hospital for seven days. On day 7, they were discharged. Subsequent follow-up was done on days 14, 21, and 28. Clinical assessment was performed by observing the signs and symptoms of the patients. The primary outcome measure was cure rate and the secondary outcome measures were parasite clearance time (PCT), fever clearance time (FCT), safety, and occurrence of side effects. A patient both clinically and parasitologically negative after four weeks of therapy would be considered as cured. The PCT is the time between beginning of the antimalarial treatment and the first negative blood slide. Parasites count were made every six hours until the first negative blood slide was obtained. The FCT is the time from beginning antimalarial treatment until the patient is apyrexial. The approach used here involved recording the time when the temperature decreased below 37.5°C and remained below 37.5°C for 24 hours. Temperature was also recorded every six hours.

Side effects were closely monitored in all patients and noted if observed. No other antimalarial agents other than the coded samples were used. Drop out cases with various reasons (e.g., non-compliance, side effects) were noted. Any abnormal laboratory values were noted.

All the data was carefully entered in the case record form provided. The data were then analyzed statistically.

Statistical analysis. Statistical analysis were carried out for PCT, FCT, and cure rate. Null hypothesis were 1) the cure rate of both groups is the same, 2) the mean FCT of both

TABLE 1
Demographic characteristics of the patients

Drug	Total no. of patients (n = 138)	Sex	Age (in years), mean \pm SD	Weight (in kg), mean \pm SD
β -arteether	70	M = 47 F = 23	32.32 \pm 17.5	56.38 \pm 16.2
α/β -arteether	68	M = 52 F = 16	34.64 \pm 14.8	57.51 \pm 13.7

groups is the same, and 3) the PCT of both groups is the same. The hypothesis was tested by using the Students' *t*-test for equality of means and proportions. A 95% confidence interval was computed for each variable of interest.

RESULTS

Study population. One hundred and thirty-eight patients were enrolled in the trial. The trial was initiated in May 2002 and was completed at all centers by January 2003. There were 70 patients in the β -arteether group and 68 patients in the α/β -arteether group.

Baseline parameters. The two groups were similar with regards to the demographic data and baseline parameters. There was no statistically significant difference between the two groups. The demographic data of the patients at the time of admission is shown in Table 1. Figure 1 shows the progress of the patients throughout the trial. Table 2 shows the number of patients who completed the trial as well as dropouts. One

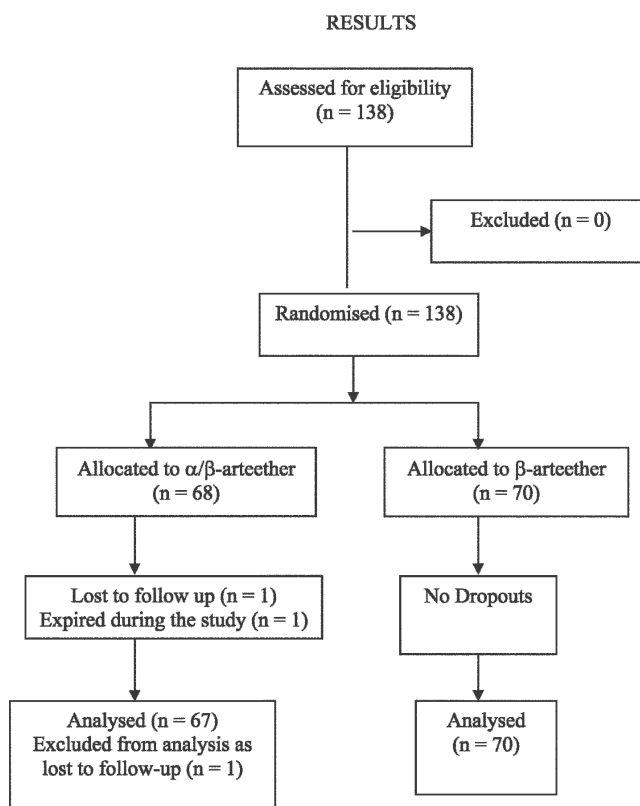


FIGURE 1. Flow diagram of the trial.

patient in the β-arteether group showed recurrence. Only one death (in the α/β-arteether group) occurred during the trial.

The primary analysis was intention-to-treat analysis and involved all patients who were randomly assigned a treatment. Statistical analysis was done for both primary outcome and secondary outcome and showed that at 5% level of significance, cure rates, mean PCT, and mean FCT for β-arteether and α/β-arteether were the same. Table 3 shows the trial outcome as observed from the pooled data.

Trial outcome. The cure rate was 97.14% for β-arteether and 97.01 for α/β-arteether ($P = 0.9660$). The mean PCT was 38.49 hours for β-arteether and 36.90 hours for α/β-arteether ($P = 0.6054$), and the mean FCT was 37.27 hours for β-arteether and 37.9 hours for α/β-arteether ($P = 0.8718$). The difference between the β-arteether and α/β-arteether groups was not statistically significant. No significant difference was found in the primary outcome measures and secondary outcome measures in both groups.

The most common adverse events observed were headache, nausea, cough, and dizziness. Less common adverse events were body ache, general weakness, vomiting, pain at injection site, abdominal pain, leg pain, chills and rigors, and watery diarrhea. Most of the adverse events appear to be due to malaria rather than the drug because the adverse events appeared on days 1–4. Adverse events observed in each group are shown in Table 4. No clinically significant biochemical changes were observed in any of the patients. There were no abnormal laboratory values post-treatment.

DISCUSSION

Artemisinin and its derivatives are known for their potent anti-malarial activity. Arteether is a useful treatment against chloroquine-resistant *P. falciparum* malaria. In addition, its efficacy, without an increased incidence of toxicity, is well suited for treatment of drug-resistant malaria. It has a longer $t_{1/2\beta}$ and more lipophilic properties than artemether, which favor its accumulation in brain tissue for the treatment of cerebral malaria. Other advantages of arteether are its stability, compared with sodium artesunate; its biochemical breakdown does not give methanol, as does artemether; and it is easily formulated in oil for parenteral administration.⁸ However, tolerability of arteether was similar to that of other artemisinin derivatives. Although neurotoxicity has been reported in experimental animals, there is no evidence of serious neurotoxicity due to any artemisinin derivative in humans in prospective studies of more than 10,000 patients. It also has the additional advantage of requiring only a three-day regimen compared with other artemisinin derivatives, which required a seven-day regimen as monotherapy.

TABLE 2

Number of patients who completed and who dropped out of the trial

Center	No. of patients who completed the trial	No. of dropouts
Kolkata	26	0
Bikaner	26	0
Baroda	29	1*
Rourkela	30	0
Gwalior	26	0

* One patient in the α/β-arteether group was lost to follow-up during the study.

TABLE 3
Efficacy measures

Result	β-arteether group	α/β-arteether group
Cure rate ($P = 0.9660$)*	97.14%	97.01%
Parasite clearance time (in hours) ($P = 0.6054$)†	38.49	36.90
95% confidence interval	34.10 ± 42.90	32.85 ± 40.95
Standard deviation	18.653	16.782
Standard error	2.2455	2.0657
Fever clearance time (in hours) ($P = 0.8718$)‡	37.27	37.9
95% confidence interval	31.82 ± 42.78	32.66 ± 43.14
Standard deviation	22.64	20.71
Standard error	2.7868	2.6737

* Degrees of freedom = 135.

† Degrees of freedom = 124.

‡ Degrees of freedom = 133.

Arteether is available in India as α/β-arteether (Rapither AB; M/S Ipca Laboratories Ltd., Mumbai, India; Emal; M/S Themis Medicare Ltd., Vapi, Gujarat, India) and β-arteether (Betamolil) and outside this country as β-arteether (Artecef[®], Artecef BV, Maarsen, The Netherlands). Arteether as an anomeric mixture of α/β (30:70) was developed by Central Drug Research Institute in Lucknow and has been marketed in India since August 1997, well ahead of production by WHO. Outside India, arteether (β-anomer) has been developed by WHO and is marketed in The Netherlands (Artecef[®]).¹⁵

Pharmacodynamic studies have shown that both β-arteether and α/β-arteether have comparable activity and are curative at a dose of 5 mg/kg for 3 days against blood-induced *Plasmodium cynomolgi* B infection in the rhesus monkey; α-arteether alone is slightly less active, with a 50% cure rate at this dose.¹⁴ Since it is a 100% β anomer, it was assumed that β-arteether would be more effective than 30:70 α/β-arteether. However, there is no comparative clinical data on efficacy and safety of β-anomer of arteether and anomeric mixture. This is the first multicentric study that compared the efficacy and safety of both β-arteether and α/β-arteether for treatment of acute *P. falciparum* malaria and found them to be comparable in safety and efficacy. Both the drugs have significant benefits for all parameters of clinical assessment.

TABLE 4
Adverse events reported

Adverse events	No. of adverse events* (%)	
	β-arteether group n = 70	α/β-arteether group n = 68
Headache	4 (5.7)	3 (4.4)
Nausea	1 (1.4)	3 (4.4)
Cough	2 (2.9)	2 (2.9)
Dizziness	1 (1.4)	2 (2.9)
Body ache	1 (1.4)	1 (1.5)
General weakness	–	1 (1.5)
Vomiting	1 (1.4)	–
Pain at local injection site	–	1 (1.5)
Abdominal pain	1 (1.4)	–
Leg pain	1 (1.4)	–
Chills and rigors	1 (1.4)	–
Watery diarrhea	–	1 (1.5)
Total	13 (18.6)	14 (20.6)

* Some patients reported more than one adverse event.

The drugs were comparable in both primary outcome measures (cure rate) and secondary outcome measures (PCT and FCT). Both the drugs were well tolerated. There were no clinically significant side effects in either group, indicating that both the drugs are safe in the treatment of acute *P. falciparum* malaria.

The patient in the α/β -arteether group who died was a case of acute *P. falciparum* malaria. The patient did not have severe malaria with complications at the time of admission. However, symptoms of high-grade fever and dizziness persisted throughout his stay in the hospital. He died on the second day after receiving two doses of α/β -arteether. This death was not an unusual finding, if one considers the mortality associated with *P. falciparum* malaria. Death from acute *P. vivax*, *P. ovale*, and *P. malariae* malaria is rare.¹⁶ In contrast, *P. falciparum* malaria is a potentially lethal infection. The progression to severe disease can be rapid.

This trial provides evidence that both β -arteether and α/β -arteether can be used for treatment of acute *P. falciparum* malaria. However, this study had some limitations. First, only 138 patients were studied. A larger number of patients should have been enrolled at each center to better identify the difference in efficacy between β -arteether and α/β -arteether. Second, more centers should have been studied, especially those in areas with chloroquine-resistant malaria. Third, the parasitic index and the gametocytocidal effect of arteether was also not evaluated.

Future research should address the duration of treatment with artemisinin. The present trial involved a three-day administration of both arteether formulations. Whether this three-day period is sufficient for the complete cure of malaria is not known because all artemisinin derivatives are recommended by the World Health Organization to be used for seven days as monotherapy. New trials should assess the justification for a three-day regimen of arteether.

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REFERENCES

1. Nosten F, Brasseur P, 2002. Combination therapy for malaria: the way forward? *Drugs* 62: 1315–1329.
2. Suh KN, Kain KC, Keystone JS, 2004. Malaria. *CMAJ* 170: 1693–1702.
3. World malaria situation in 1993. Part II, 1996. *Wkly Epidemiol Rec* 71: 25–29.
4. World malaria situation in 1994. Part III, 1997. *Wkly Epidemiol Rec* 72: 285–290.
5. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster, 2000. *Trans R Soc Trop Med Hyg* 94: S1–S90.
6. White NJ, 1996. The treatment of malaria. *N Engl J Med* 335: 800–806.
7. De Vries PJ, Dien TK, 1996. Clinical pharmacology and therapeutic potential of artemisinin and its derivatives in the treatment of malaria. *Drugs* 52: 818–836.
8. Valecha N, Gupta S, Usha D, Biswas S, Sharma A, Adak T, Asthana OP, Sharma VP, 1997. Efficacy of alpha,beta-arteether in acute uncomplicated *P. falciparum* malaria. *Int J Clin Pharmacol Res.* 17: 11–15.
9. Looareesuwan S, Oosterhuis B, Schilizzi BM, Sollie FA, Wilairatana P, Krudsood S, Lugt Ch B, Peeters PA, Peggins JO, 2002. Dose-finding and efficacy study for i.m. artemotil (beta-arteether) and comparison with i.m. artemether in acute uncomplicated *P. falciparum* malaria. *Br J Clin Pharmacol* 53: 492–500.
10. Asthana OP, Srivastava JS, Pandey TK, Vishwanathan KA, Dev V, Mahapatra KM, Nayak NC, Balsara AB, Mandal OP, Gupta N, Mishra SK, Mohanty S, Sathpathy S, Das BS, Patnaik JK, Sathpathy SK, Dash B, 2001. Multicentric clinical trials for safety and efficacy evaluation of alpha;beta arteether in complicated *P. falciparum* malaria. *J Assoc Physicians India* 49: 1155–1160.
11. Singh N, Shukla MM, Asthana OP, Sharma VP, 1998. Effectiveness of alpha-beta arteether in clearing *Plasmodium falciparum* parasitemia in central India (Madhya Pradesh). *South-east Asian J Trop Med Public Health* 29: 225–227.
12. Moyou-Somo R, Tietche F, Ondoa M, Kouemini LE, Ekoe T, Mbonda E, Nsangou C, Jemea B, Guemkam G, 2001. Clinical trial of beta-arteether versus quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. *Am J Trop Med Hyg* 64: 229–232.
13. Thuma PE, Bhat GJ, Mabeza GF, Osborne C, Biemba G, Shankankale GM, Peeters PA, Oosterhuis B, Lugt CB, Gordeuk VR, 2000. A randomized controlled trial of artemotil (beta-arteether) in Zambian children with cerebral malaria. *Am J Trop Med Hyg* 62: 524–529.
14. Tripathi R, Dutta GP, Vishwakarma RA, 1991. Comparison of antimalarial efficacy of alpha, beta, and alpha/beta arteether against *Plasmodium cynomolgi* B infection in monkeys. *Am J Trop Med Hyg.* 44: 560–563.
15. Kager PA, 2003. Three newly registered drugs in the Netherlands for the treatment and chemoprophylaxis of malaria: atovaquone-proguanil, artemether-lumefantrine and artemotil. *Ned Tijdschr Geneesk.* 147: 291–295.
16. White NJ, 2003 Malaria. Cook GC, Zumla A, eds. *Manson's Tropical Diseases*. 21st edition. Philadelphia: W. B. Saunders, 1205–1295.