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Original Article

Efficacy of artemether-lumefantrine and artesunate-amodiaquine for treating uncomplicated falciparum malaria in children

Tri Faranita, Ayodhia Pitaloka Pasaribu, Muhammad Ali, Munar Lubis, Syahril Pasaribu

Abstract

Background Artesunate-amodiaquine (ASAQ) has been used as a first-line treatment for uncomplicated falciparum malaria in Indonesia since 2004. Its efficacy depends on amodiaquine resistance of the infecting parasites. Artemether-lumefantrine (AL) has been shown to be highly efficacious in treating uncomplicated falciparum malaria in several countries. However, there have been few studies on these anti-malarial medications in Indonesia.

Objective To compare the efficacy of AL to ASAQ for treating uncomplicated falciparum malaria in children.

Methods An open, randomized, controlled trial was conducted in school-aged children in the Mandailing Natal Regency, North Sumatera Province, Indonesia, from October to December 2010. A total of 280 pediatric, uncomplicated falciparum malaria patients were randomly assigned to receive either AL or ASAQ for 3 days. Participants were followed-up on days 1, 2, 3, 7, 14, 28 and 42 following the first medication dose. The outcomes noted were adequate clinical and parasitological response (ACPR), parasite reduction, parasite clearance time, fever clearance time and adverse events. Analysis was based on intention-to-treat.

Results In this study, ACPRs on day 42 were 86.4% and 90.7% for the ASAQ and AL groups, respectively (P=0.260). On days 7 and 14, the AL group had higher cure rates than that of the ASAQ group (P<0.05). Early treatment failure, late treatment failure and parasitological failure for both groups were similar. We also found faster parasite clearance time and higher parasite reduction in the AL group than in the ASAQ group. However, fever clearance time was shorter in the ASAQ group. The incidence of adverse events such as nausea, vomiting, malaise, and pruritus were similar between the two groups (P=0.441).

Conclusion AL had higher efficacy than ASAQ for the treatment of uncomplicated falciparum malaria in children.

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Keywords: *artemether-lumefantrine, artesunate-amodiaquine, uncomplicated falciparum malaria*

Malaria remains a major health problem for children and adults in tropical areas of the world.[1,2] In Indonesia, 411,000 malarial cases were reported in 2008, with 788 deaths in that year. *Plasmodium falciparum* infection caused 46% of these deaths.[3]

Most of the severe morbidity and mortality in malaria is caused by *Plasmodium falciparum*.[4] To prevent the progression to severe disease and

From the Department of Child Health, University of Sumatera Utara Medical School, H. Adam Malik Hospital, Medan, Indonesia.

Reprint requests to: Tri Faranita, University of Sumatera Utara Medical School, H. Adam Malik Hospital, **Jl. Bunga Lau No. 17, Medan 20136, In**donesia. Tel. +62-61-8361721, +62–61-8365663, Fax. +62-61-8361721. E-mail: *faranita.md@gmail.com*

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additional morbidities associated with malaria, it is necessary to determine an effective therapy for uncomplicated falciparum malaria.[5]

In 2004, Indonesia implemented the use of artesunate and amodiaquine (ASAQ) in combination as the national, first-line treatment for uncomplicated falciparum malaria, after a data review on chloroquine efficacy revealed widespread chloroquine resistance throughout the country.[6] Resistance to amodiaquine has been reported in Africa and Papua New Guinea.[7,8]

The combination of artemether and lumefantrine (AL) has been reported to be highly effective and well-tolerated in several African studies.[9,10] However, there has been limited information on the efficacy of these drugs in Indonesia. A previous study of this combination for treating falciparum malaria, vivax malaria and mixed infection malaria in Papua, Indonesia suggested that it was highly effective in children and adults.[11] The aim of this study was to compare the efficacy of artemether-lumefantrine to artesunate-amodiaquine for treating uncomplicated falciparum malaria in children.

Methods

This randomized, open-label, controlled trial was conducted between October to December 2010 with subjects 12 elementary schools, the Panyabungan Malaria Centre and the outpatient clinic at the Panyabungan District Hospital, North Sumatera, Indonesia.

Subjects were children aged 6–18 years with uncomplicated falciparum malaria. Informed consent was obtained from their parents or guardians. Exclusion criteria were as follows: symptoms and/or signs of severe malaria, severe malnutrition, mixed malarial infections, known allergies to the study medications, vomiting after two dosing attempts, intake of any prior anti-malarial drug or withdrawal of consent.

Potential participants were medically screened. After obtaining capillary blood samples, thick and thin blood films were microscopically examined for the presence of malaria parasites. Body weight and body height were recorded. Nutritional status was assessed using weight-for-height chart CDC 2000.[12]

After enrollment, patients were randomly assigned to receive either artemether-lumefantrine or artesunate-amodiaquine. Medications were administered according to weight-based guidelines. The ASAQ group received a 3-day regimen of artesunate at 4 mg/kg orally combined with amodiaquine at 10mg/kg once daily. Artemether-lumefantrine was administered twice daily as a three-day, six-dose regimen according to body weight [5 – <15 kg (1 tablet), 15 – <25 kg (2 tablets), 25 – <35 kg (3 tablets), ≥35 kg (4 tablets)] in the AL group. All drug doses were administered in front of physicians or guardians. Full drug doses were readministered if the patient either spat out or vomited the medications within 30 minutes. Vomiting of readministered medications resulted in withdrawal of the participant from the study. All excluded participants were given quinine for 7 days as well as doxycycline for children older than 7 years of age.

Clinical and laboratory assessments were made on days 0, 1, 2, 3, 7, 14, 28 and 42. Parents/guardians were encouraged to come to the clinic if their child felt sick. Study participants were visited at home by members of the study team if a subject was absent on a scheduled visit day.

Giemsa-stained blood films were read by experienced microscopists. Parasitaemia was quantified per 200 leukocytes on the thick film. Slide quality control was done by masked re-reading of 10% of the slides selected randomly.

Treatment outcomes were defined as adequate clinical and parasitological response (ACPR) on day 42, reduction in parasite counts, parasite clearance time and fever clearance time. Drug tolerability and safety were assessed clinically. An adverse event was defined as any undesirable medical occurrence in a patient during the study regardless of its relation to the treatment.

According to the WHO, ACPR is the absence of parasitaemia on day 28, without previously meeting criteria for early treatment failure (ETF), late treatment failure (LTF) or parasitological failure (PF). These criteria are defined as follows: ETF involves the presence of danger signs or complicated malaria or failure to adequately respond to therapy on days 0-3; LTF involves danger signs or complicated malaria or fever/history of fever in the previous 24 hours

and parasitaemia on days 4-28 without previously meeting the criteria for ETF; and PF is asymptomatic parasitaemia on days 4-28 without previously meeting criteria for ETF or LTF.

Sample size was calculated by a non-inferiority study formula, resulting in 140 subjects per group. Data was analyzed using SPSS version 18.0 and Microsoft Excel 2003. The significance level was accepted as $P < 0.05$ with 95% confidence intervals (95% CI).

Categorical variables were compared using the Chi square test. Independent t-test was used to compare reduction in parasite counts, parasite clearance time and fever clearance time. This study was an intention-to-treat analysis.

Results

Of 963 children screened for malarial infections, 482 children were infected and 202 children did not meet the criteria for enrollment. Of the 202 children, 200 had taken other anti-malarial drugs and 2 had mixed malarial infections. Of the 280 subjects enrolled, 140 received AL and the other 140 received ASAQ (**Table 1**).

In the AL group, 1 subject stopped taking medications without clear explanation and 1 subject moved away. In the ASAQ group, 2 subjects experienced adverse events causing them to prematurely withdraw from the study (one child experienced an allergic reaction with red skin and itching and the other child vomited after re-administration of the study drugs). These two children were excluded and treated with quinine.

Of the 276 children who completed the study, only 128 children in the AL group and 126 children in the ASAQ group completed the full 42 days of the study as others were lost to follow-up (**Figure 1**).

The ACPRs on day 42 were 90.7% and 86.4% in the AL and ASAQ groups, respectively (P=0.260). Also, ETF, LTF and PF were similar in both groups. However, after the third day of observation, the mean reduction in parasite counts in the AL group (95.7%, SD 13.96) was significantly higher than that of the ASAQ group (74.8%, SD 21.25); (P=0.0001). Mean parasite clearance time was also significantly shorter

Table. 1. Baseline characteristics of subjects

Characteristics	AL n = 140	ASAQ n = 140
Sex, n (%)		
Male	77 (55.0)	63 (45.0)
Female	63 (45.0)	77 (55.0)
Mean age, years (SD)	7.9 (1.34)	8 (1.48)
Mean weight, kg (SD)	22.3 (4.41)	22.2 (3.91)
Mean height, cm (SD)	123.6 (6.84)	124.2 (8.39)
Nutritional status, n (%)		
Normoweight	60 (42.9)	75 (53.6)
Mild malnutrition	42 (30.0)	36 (25.7)
Moderate malnutrition	7 (5.0)	6 (4.3)
Overweight	31 (22.1)	23 (16.4)
Mean parasitaemia,/µl (SD)	1071.5 (294.89)	1105.2 (380.86)
Symptoms, n (%)		
History of fever	48 (34.3)	41 (29.3)
Fever	52 (37.1)	37 (26.4)
Pallor	44 (31.4)	45 (32.1)
Weakness	52 (37.1)	51 (36.4)
Headache	41 (29.3)	24 (17.1)
Cough	20 (14.3)	12 (8.6)
Vomiting	5 (3.6)	2 (1.4)
Diarrhea	20 (14.3)	22 (15.7)
Hepatomegaly	15 (10.7)	9 (6.4)
Splenomegaly	23 (16.4)	17 (12.1)

in the AL group [3.2 (SD 1.44) days] than in the ASAQ group [6.1 (SD 1.87) days]; (P=0.0001), but fever clearance time was significantly shorter in the ASAQ group (P=0.017) (**Table 2**).

During follow up (**Table 3**), cure rates on days 3, 28 and 42 were not significantly different between groups. However, on days 7 and 14, we found a significantly higher cure rate in the AL group than in ASAQ group (P<0.05).

During the study, we noted adverse events in both groups. In the AL group, 3 (2.1%) subjects had nausea, 2 (1.4%) had vomiting and 1 had (0.7%) malaise. In the ASAQ group, 5 (3.6%) had nausea, 6 (4.3%) had vomiting, 3 (2.1%) had malaise and 1 (0.7%) had pruritus. Adverse events in the two groups were not significantly different (P=0.441).

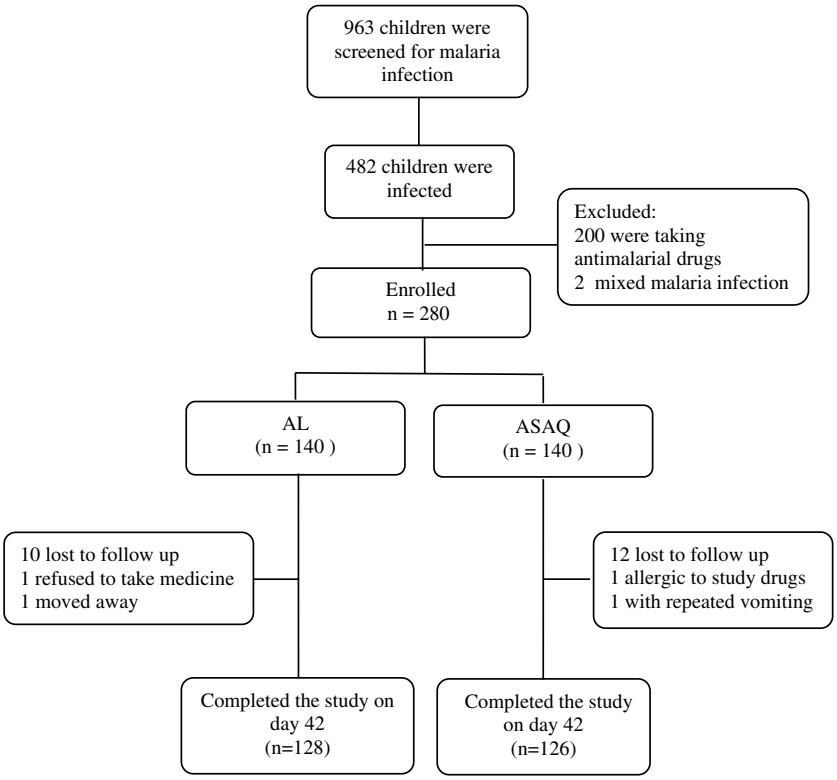

Figure 1. Study profile

Table 2. Treatment responses in both groups

Treatment responses	AL n = 140	ASAQ n = 140	P
Mean parasite clearance time, days (SD)	3.2 (1.44)	6.1 (1.87)	0.0001
Mean fever clearance time, days (SD)	1.0 (1.36)	0.7 (1.21)	0.017
ETF, n (%)	2 (1.4)	7 (5.0)	0.090
LTF, n (%)	10 (7.1)	12 (8.6)	0.657
PF, n (%)	1 (0.71)	0 (0)	0.316
ACPR at day 42, n (%)	127 (90.7)	121 (86.4)	0.260
Mean reduction in parasite count at day 3, % (SD)	95.7 (13.96)	74.8 (21.25)	0.0001

ETF: early treatment failure; LFT: late treatment failure; PF: parasitological failure; ACPR: adequate clinical and parasitological response

Table 3. Cure rate differences during follow-up

Cure rates n (%)	AL (n = 140)	ASAQ (n = 140)	P
Day 3	138 (98.57)	133 (95.0)	0.090
Day 7	136 (97.14)	127 (90.71)	0.024
Day 14	136 (97.14)	124 (88.57)	0.005
Day 28	127 (90.71)	121 (86.42)	0.260
Day 42	127 (90.71)	121 (86.42)	0.260

Discussion

In this open-label, randomized, controlled trial, AL had higher efficacy than ASAQ for treating children with uncomplicated malaria falciparum, similar to trials in Tanzania,[13] and Cameroon.[14]

We gave a six-dose regimen of AL to one group of subjects. Evidence from previous studies showed that AL had better efficacy in a six-dose regimen than a four-dose regimen.[15] Oral bioavailability of lumefantrine is highly dependent on its administration with fatty foods,[5] as was reported in several studies from Ghana.[16,17] We prepared fat-containing food or drink for participants before they took the medication.

ASAQ efficacy is influenced by amodiaquine-resistance status.[7,8] Several studies have suggested that resistance to amodiaquine occurs because of its structural similarity and mechanism of action to chloroquine.[7,8,18] Azlin *et al*. reported that 32% of subjects with uncomplicated falciparum malaria had chloroquine resistance in 2004 in Mandailing Natal, North Sumatera.[19] We found that the cure rate for the ASAQ group was 86.4%, a decrease from a previous study in 2006.[20]

Shorter parasite clearance time occurred in the AL group than in the ASAQ group, in contrast to a Nigerian study in which both groups had similar parasite clearance times.[21] We also noted a higher treatment failure in ASAQ group, but not significantly different from the AL group. Both of these findings suggest that longer parasite clearance times may have been associated with higher risk for treatment failure as seen as in Senegal.[22]

Rapid parasite clearance time has been associated with rapid fever clearance time.[22] However, we found that while the parasite clearance time in the AL group was shorter, the fever clearance time was longer than that of the ASAQ group. The ongoing fever following parasite clearance suggests that the fever may be an adverse event from the treatment.[23,24] Antipyretic use for fever treatment in malarial cases has been associated with longer parasite clearance time.[25] Several of our subjects used antipyretics, but we did not evaluate the correlation between antipyretic use and parasite clearance time.

Adverse events in the ASAQ group were nausea, vomiting, malaise and pruritus. Severe adverse events occurred in two subjects, one with recurrent vomiting and one with an allergic reaction. Both children received second-line treatment medications. Other common adverse events such as headache or tinnitus[25] from the drug combination were not observed in our subjects.

Adverse events in the AL group were nausea, vomiting and malaise. Studies in Uganda[27] and Senegal[23] reported temperature elevation, headache, stomachache and cough in patients taking AL. We did not observe these events in our subjects.

The objective of treating malaria with two or more blood schizontocidal drugs was to decelerate the development of resistance since the drugs have different mechanisms of action and parasitic biochemical targets.[5] Artemisinin and its derivates have gametocidal effects.[5,21] A limitation in our study was that we did not count the numbers of sexual parasites. Therefore, we could not determine the gametocyte clearance time in either group.

In conclusion, AL had higher efficacy than ASAQ for the treatment of uncomplicated falciparum malaria in children. We also found that both AL and ASAQ were safe for use in children.

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