Paediatrica Indonesiana

VOLUME 50 March • 2010 NUMBER 2

Original Article

Comparison of the efficacy of artemether-lumefantrine vs. artesunate plus sulfadoxine-pyrimethamine in children with uncomplicated falciparum malaria

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Abstract

Background World Health Organization (WHO) has recommended that countries with drug resistant malaria problem use combination therapies, especially artemisinin-based combination therapy (ACT). However, there is limited information on the efficacy of ACT in North Sulawesi.

Objective To compare the efficacy of artemether-lumefantrine and artesunate plus sulfadoxine-pyrimethamine (SP).

Methods This was a randomized experimental study, conducted in Prof. Dr. R. D. Kandou General Hospital, Manado from January until July 2009. There were 42 patients aged less than 13 years treated with artemether-lumefantrine and artesunate plus SP. Body temperature, parasite and gametocyte count were recorded every day until day 7 and follow-up reviews were done on day 14 and 28.

Results Fever clearance time showed a significant difference between artemether-lumefantrine group (median 27 hours) and artesunate plus SP group (median 18 hours), $P<0.05$). There was no significant difference in parasite clearance time ($P>0.05$) and gametocyte clearance time ($P>0.05$). The 28 day cure rate were 100% in the two groups. No side effect was found.

Conclusion Both artemether-lumefantrine and artesunate plus SP combination are effective and safe for the treatment of falciparum malaria in children. **[Paediatr Indones. 2010;50:112-7]**.

Keywords: *artesunate , sulfadoxine-pyrimethamine, artemether, lumefantrine*

Malaria has been one of the most serious health problems in the world. It is an acute or chronic disease which is caused by plasmodium and transmitted by anopheles mosquitoes. In Indonesia, there are 15 million cases of malaria with 38,000 deaths every year. In North Sulawesi malaria has been one of the most frequent diseases.[1] Among types of malaria, falciparum malaria is the most frequently found infection and can cause death. Efforts to reduce the morbidity and mortality rate are done by early diagnosis, prompt treatment, surveillance and vector control with aim to disrupt the malaria transmission. Resistance to antimalarial drugs has caused treatment failure which is a big challenge. In 1973, the first case of resistance to chloroquine was reported in East Kalimantan and in 1990 such resistance had been reported from all provinces of Indonesia.[2] In North Sulawesi, several studies were conducted by Rampengan et al[3-5] who reported 28.6% grade II resistance to chloroquine,

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13.5% to sulfadoxine-pyrimethamine and 8.6% to quinine. Kan et al[6] reported 19.6% grade II resistance and 7.5% grade III resistance to chloroquine.

World Health Organization (WHO) has recommended that countries with monotherapy drug resistance use the combination therapy, especially from artemisinin group or artemisinin-based combination therapy (ACT). Combination therapy can prevent drug resistance and increase efficacy without increasing drug toxicity.[7] In 2004, WHO recommended the combination of artemether-lumefantrine as an option in the treatment of falciparum malaria.[8]

There is still limited information on the efficacy of ACT in North Sulawesi. Based on drugs resistancy studies in North Sulawesi above we conducted a study to compare the efficacy of artemether-lumefantrine and artesunate plus SP in order to find an alternative antimalarial drugs which has high efficacy, safe, well tolerated and not expensive. Our hypotheses were that fever clearance time (FCT), parasite clearance time (PCT) and gametocyte clearance time (GCT) were faster in artemether-lumefantrine group compared to artesunate plus SP group and the 7, 14 and 28 day cure rate were greater in artemether-lumefantrine group compared to artesunate plus SP group.

Methods

A randomized experimental study was performed from January to July 2009 on 42 patients with uncomplicated falciparum malaria. They were randomly assigned to receive either artemether-lumefantrine or artesunate plus SP group. The study was conducted in Prof. Dr. R. D. Kandou General Hospital Manado. We included infants or children ≤ 13 years old with body weight more than 5 kg and diagnosed as uncomplicated falciparum malaria who did not take any malaria medicine in the last 14 days, and excluded patients presenting with one or more signs of severe or complicated malaria, severe malnutrition, allergy to sulfa or history of G6PD deficiency, or those with co-morbidity (e.g., dengue fever, pneumonia, typhoid fever and urinary tract infection).

Patients in the artemether-lumefantrine group were given tablets containing 20 mg of artemether and 120 mg of lumefantrine. Doses were given according to the body weight: 5-<15 kg 1 tablet, 15-<25 kg 2 tablets, 25-<35 kg 3 tablets and > 35 kg 4 tablets using 6 dose regimen, given at 0, 8, 24, 36, 48 and 60 hours (six doses). Patients with artesunate and SP group took artesunate with dose of 4 mg/kgBW once a day for three days. The dose of SP was based on pyrimethamine 1-1.5 mg/kgBW single dose on the first day. All were taken after meal.

All patients remained hospitalized during the treatment. Study assessments were scheduled daily from the start of treatment through day seven. At each assessment, patients were evaluated to medical history, physical examination, and thick blood smear for parasitemia. Thick blood smear was taken twice a day, stained with Giemsa stain and the parasite density was calculated by counting the number of asexual parasites per 200 white blood cells, based on the white blood cell count of each patient. The body temperature was assessed every six hours. Fever was defined if the body temperature was more than 37.5°C. The patients took antipyretic (paracetamol) if the fever occurred. We did home visit on day 14 and 28. The body temperature and thick blood smear were taken on each visiting. During the study, all patients were applied with mosquito repellent.

Primary outcome measures

Parasite clearance time (PCT) was defined as time (hour) from the first dose until first total and continued disappearance of asexual parasite forms that remained at least for an additional 48 hours. Fever clearance time (FCT) was defined as time (hour) from the first dose until the first time the body temperature decreased below and remained less than 37.5° C for at least a further 48 hours. We defined gametocyte clearance time as the time from the first dose until the first total and continued disappearance of gametocyte form that remained at least for an additional 48 hours. Day seven cure rate was the proportion of patients with clearance of asexual parasitemia within seven days of initiation of trial treatment, without subsequent recrudescence within these seven days. We called day 14 cure rate as the proportion of patients with clearance of asexual parasitemia within seven days of initiation of trial medication, without subsequent recrudescence within 14 days after study start. Day 28 cure rate was considered to be of greatest importance, and defined as the proportion

of patients with clearance of asexual parasitemia within seven days of initiation of trial drug, without subsequent recrudescence within 28 days after study start. Recrudescence was defined as the existence of positive blood smears after initial clearance of parasites from the peripheral blood.

Parasite clearance time, fever clearance time and gametocyte clearance time were analyzed using Mann-Whitney U test with P value < 0.05 was considered statistically significant. Characteristic of the subjects, cure rate, and side effects were presented descriptively. Data were analyzed using soft ware SPSS 15. We obtained informed consent from all parents of the subjects. The study was approved by the Committee for Medical Research Ethics of the Faculty Medicine, Sam Ratulangie University.

Results

A total of 47 patients were included in this study. There were 2 patients dropped out in this study because they refused to continue the medication and 3 patients were lost to follow-up on day 14. There were 21 patients in each group until the study was completed (**Figure 1**).

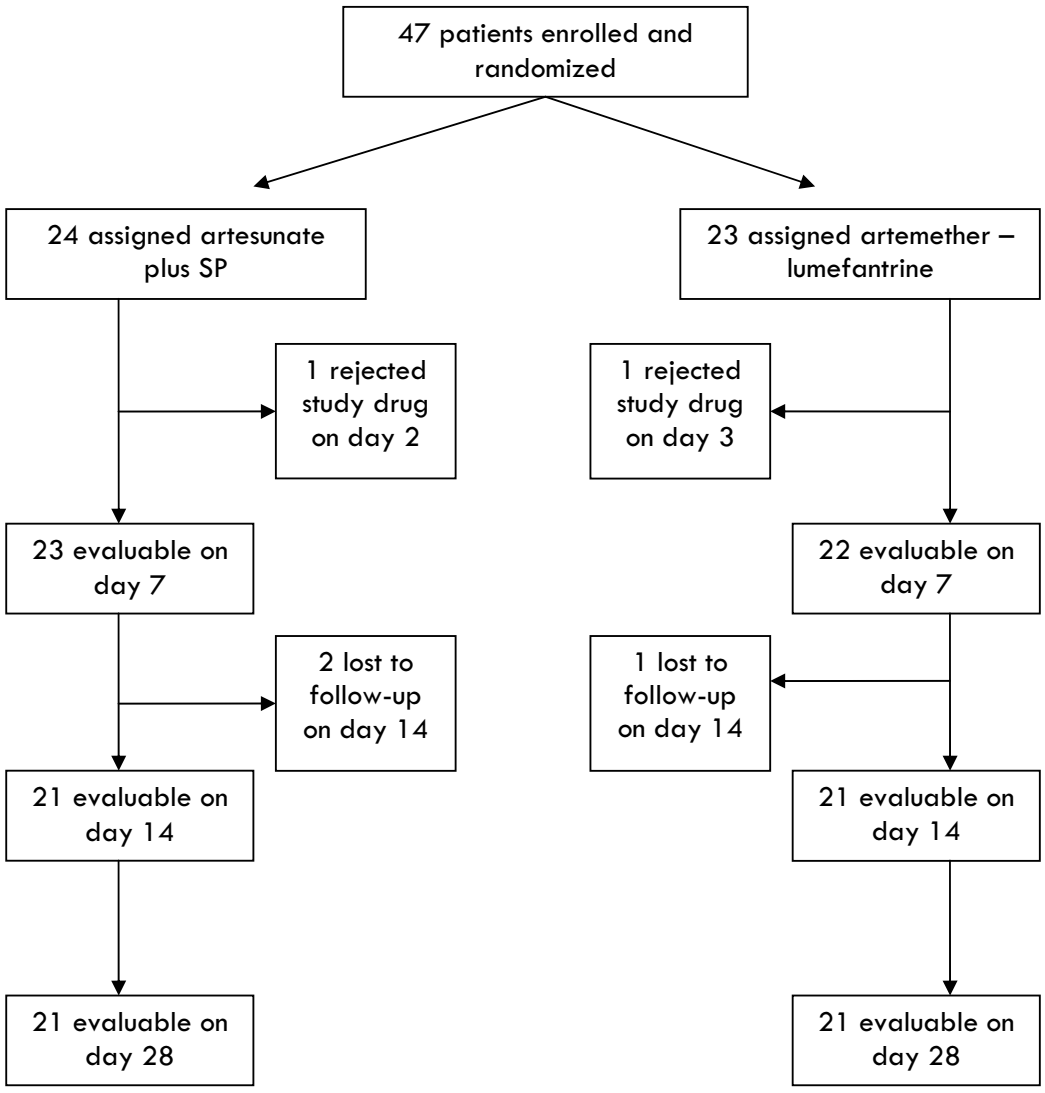

Figure 1. Trial profile

The baseline characteristics of the study subjects in both groups are depicted in Table 1. There were no apparent significant difference between both groups except that The mean parasite density was lower in the artemether-lumefantrine group compared to artesunate and SP group, P<0.05 (**Table 1**).

The median of PCT was same in both groups (12 hours in artemether-lumefantrine group and 12 hours in artesunate plus SP group. Analysis of FCT data suggested a more rapid resolution of fever with artesunate plus SP treatment than artemether-lumefantrine. For artesunate plus SP group, the median FCT was 18 hours and for the artemether-lumefantrine group was 27 hours, P<0.05. There was no significant difference in GCT between the two groups. The median GCT in artesunate plus SP group was 20 hours and for artemether-lumefantrine group was 22 hours, P>0.05. Day 7, 14 and 28 cure rates were 100% in both treatment groups (**Table 2**). No side effect was observed.

Table 1. Characteristic of subjects

	Artemether-lumefantrine N=21	Artesunate and SP N=21
Sex (male)	13	12
Age, mean (SD) yrs	5.85 (3.46)	7.43 (2.69)
Weight, mean (SD) kg	17.42 (6.99)	22.33 (8.39)
Fever	21	21
Chilled	9	11
Headache	4	7
Nausea/vomiting	15	15
Diarrhea	1	0
Convulsion	5	2
Hepatomegaly	13	10
Splenomegaly	7	5
Hb, mean (SD) g/dL	10.19 (1.84)	11.10 (1.38)
Platelets, mean (SD) /µL	149,619 (90,957)	126,523 (61,380)
WBC, mean (SD) /µL	4919 (1,768)	4848 (1,456)
Parasite count, median /µL	2880	6000

Table 2. Therapeutic responses

	Artemether-lumefantrine	Artesunate and SP	P
FCT, median, hr	27	18	0.003
PCT, median, hr	12	12	0.406
GTC, median, hr	22	20	0.273
The 7, 14 and 28 day cure rate (%)	100	100	

Discussion

We have shown that both treatment regimens for children with uncomplicated falciparum malaria were similar in terms of PCT, GCT and cure rate, but the FCT was more rapid in artesunate plus SP group. The median FCT in artesunate plus SP group was 18 hours and in artemether-lumefantrine group was 27 hours. Different results were reported by others, such as Mohamed *et al*[9] who found that in all patients treated with artesunate and SP or artemether-lumefantrine no fever on day 2. Broek *et al*[10] found the fever decreased on day 3 in both artesunate plus SP and Coartem group while other group[11] found fever clearance time faster in Coartem group (18 hours) than chloroquine group (27 hours), P=0.045.

Parasite clearance time is widely used as a efficacy marker of antimalarial drug; in our study both regimen gave 100% 28-day cure rate. Mohamed *et al*[9] found same parasite clearance time with artemether-lumefantrine and artesunate plus SP combination (on day 2). Broek et al[10] showed similar parasite clearance time with artemether-lumefantrine and artesunate plus SP (on day 3). In this study, the baseline characteristic of parasite density was significantly different in both group, artesunate plus SP group had higher parasite density than artemether-lumefantrine group, P<0.05. This could affect the result.

The eradication of gametocyte can lead to malaria elimination. Gametocyte is an important key in epidemiology because it has relation with the vector and host infection cycle. Both regimens were effective in gametocyte clearance. There was no significant difference in both groups. Guttmann et al[12] found one patient with positive gametocyte in artesunate and amodiaquine group and five patients in artemether-lumefantrine group.

Cure rate in malaria treatment is usually defined as 28 day cure rate. It shows the ability of antimalarial drug to eliminate the whole parasite during the infection.[13] Cure rate depends on several factor such as resistence, parasite burden, and immunity.[14] Both regimens in this study showed a very high cure rate (100%). Similar results reported a very high cure rate of artesunate and SP.[15,16] We found no side effect in both treatments.

In conclusion this study shows that both combinations (artesunate plus SP or artemether-lumefantrine) drugs are effective, safe and well tolerated for the treatment of uncomplicated malaria in children.

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