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Original Article

Comparative efficacy of artesunate and sulphadoxine-pyrimethamine combination with artesunate and amodiaquine combination in uncomplicated falciparum malaria in children

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Abstract

Background Malaria is still an important cause of mortality and morbidity in children and adults in tropical countries. Multidrug resistance againts chloroquine and sulphadoxine-pyrimethamine had brought to an introduction of artemisinin-based combination.

Objective To assess the alternative treatment of uncomplicated *falciparum* malaria in children using artesunate and sulphadoxine-pyrimethamine combination comparing to artesunate and amodiaquine combination.

Methods This is a single-blind randomized trial. Sixty-seven children aged six months to 13 years, were recruited. Thirty-three children were treated with artesunate 4 mg/kgbw/day for three days with an additional sulphadoxine-pyrimethamine (pyrimethamine 1-1.5 mg/kgbw) single dose on the first day, while 34 children were treated with artesunate and amodiaquine base 10 mg/kgbw/day for the first two days, then 5 mg/kgbw/day on the third day. Body temperature and parasite count were recorded everyday for at least seven days. The outcomes were fever clearance time, parasite clearance time, cure rate and side effects. Statistical analysis was performed using the student t-test.

Results The statistical analysis showed that there were no difference between these two groups either in fever clearance time ($P>0.05$), or in parasite clearance time ($P>0.05$). The cure rate was 100% in both groups. Vomiting was found in one patient treated with artesunate and amodiaquine combination.

Conclusion The combination of artesunate and sulphadoxine-pyrimethamine and combination of artesunate and amodiaquine were found to be equally effective in the treatment of uncomplicated *falciparum* malaria in children **[Paediatr Indones 2008;48:240-5]**.

Keywords: *uncomplicated falciparum malaria, artesunate, sulphadoxine-pyrimethamine, amodiaquine.*

Malaria is an important cause of mortality and morbidity in children and adults in tropical countries.[1] An estimated of 300-500 million individuals are infected with malaria every year, where 23 million of them lived in highly endemic area in Africa. Infection due

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to malaria causes an estimation of one to 2.7 million morbidity worldwide each year, mainly in tropical developing countries.[2,3] In Indonesia, 15 million malaria cases were reported with annual death of 38,000. It is estimated that 35% of the Indonesia population live in a high risk area to be infected with malaria.[2]

Most malaria-associated deaths are due to *Plasmodium falciparum*; children under the age of five and non-immune travelers are especially vulnerable to severe infection.[3] Falciparum malaria is an acute or chronic infection caused by *Plasmodium falciparum,* characterized by recurrent fever, anemia and hepatosplenomegaly.[4,5] The diagnosis of malaria is established by clinical manifestations and identification of parasites on peripheral blood patients.[6-8]

Malaria infection rate had been increasing in recent years and its treatment has been hampered by the increasingly resistance of the parasites to antimalarial drugs. Chloroquine and sulphadoxine-pyrimethamine resistance in *falciparum* malaria is well advanced, many patients treated with these will not benefits from the treatment and sometimes even die.[9] According to *Pedoman Penatalaksanaan Kasus Malaria di Indonesia* in year of 2006, the first line treatment of uncomplicated falciparum malaria is artesunate and amodiaquine combination plus primaquine.[2] In Indonesia, the first report of chloroquine resistance in falciparum malaria was from East Kalimantan in 1974. Until 1977, chloroquine resistance was only in East Kalimantan and Irian Jaya. Since that, many provinces in Indonesia reported chloroquine resistance.[10] The first report sulphadoxine-pyrimethamine resistance in *falciparum* malaria was from Irian Jaya. Study in Manado (January 1983 – December 1985) found resistance II (R II) to sulphadoxine-pyrimethamine (Fansidar^{R}) in five patients (13.5%) from 37 patients.[11] Rampengan *et al*[12] from their study, found resistance II (R II) to quinine sulphate (8.6%).

Started from all the facts mentioned, an alternative antimalarial drugs to treat and prevent resistance to *Plasmodium falciparum* is needed. *Plasmodium falciparum* resistance had reported from almost all antimalarial, except artemisinin and its derivates.[1] Recently WHO formulated a policy that elevates combination antimalarial therapy to preferred first therapy for all malaria infections in areas where *Plasmodium falciparum* is the predominant infecting species of malaria.[10]

This study assessed the alternative treatment for uncomplicated *falciparum* malaria in children using artesunate and sulphadoxine-pyrimethamine combination compared with artesunate and amodiaquine combination.

Methods

This study was a single-blind randomized trial. Subjects were uncomplicated *falciparum* malaria patients admitted to Prof. R. D. Kandou General Hospital, Manado since November 2006 until March 2007. The study was approved by Ethics Committee of Prof. R.D. Kandou General Hospital, Manado.

The inclusion criteria were uncomplicated falciparum malaria patients aged six months to 13 years old with history of fever ($\geq$7.5^{o}C) in more than 48 hours, *P. falciparum* monoinfection on thick blood film, no history of allergic reaction to the study drug, no history of treatment with artesunate, amodiaquine, sulphadoxine-pyrimethamine or other antibiotics act as antimalarial within the past 14 days and whose parents or guardian had given a written informed consent. We excluded severely sick patients with (not able to drink, severe vomiting more than twice within previous 24 hours, repeated generalized convulsion, lethargy or unconscious state), severe malnutrition, and any evidence of chronic disease or other acute infection.

Drop out was defined as termination from the study due to any reason such as repeated vomiting, unable to consume drug orally, hypersensitivity reaction, worsening of the condition, evidence of mixed infection on follow-up, or patient moved to other area. Patients who failed to respond the given treatment were treated with quinine with the dose of 10 mg/kgbw, three times daily.

Uncomplicated falciparum malaria was defined as patient with falciparum malaria without complication and do not fit the criteria of severe malaria from WHO.[2] Parasite count was measured as the number of parasites per 200 leukocytes on a thick blood film, assuming a total leukocytes count of 8000/μl. Only asexual parasites were measured (*schizon*, *trophozoid* or ring forms), while gametocytes were not measured. Fever clearance time was defined as the time taken for axillary's temperature to fell below 37.5^{o}C and remained for at least 72 hours. Parasite clearance

time was defined as the time taken for clearance of asexual parasites from peripheral blood film detectable by microscope and remained cleared during follow-up period. Resistance was defined as absence of asexual *parasitaemia* on day 7, reappearing on day 8-14 (early R I), or on day 15-28 (late R I); reduction in asexual *parasitaemia* below 25% of day 0 count on day 2, with asexual *parasitaemia* on day 7 (R II); parasites density on day 2 ≥ 25% of day 0 count (R III).

On admission, a standardized medical history was taken and clinical examination performed. The children were weighed, axillary temperatures taken, and capillary blood specimen was taken by venipuncture for malaria films, hemoglobin, leukocyte, hematocrit, platelet, and liver function test (ALT, AST). Enrolled patients were randomly assigned to either receive artesunate and sulphadoxine-pyrimethamine combination (group I) or artesunate and amodiaquine combination (group II). Doses were given according to body weight; artesunate 4 mg/kgbw/day for 3 days and sulphadoxine-pyrimethamine (pyrimethamine 1-1,5 mg/kgbw) single dose on the first day for group I and artesunate 4 mg/kgbw/day for 3 days and amodiaquine base 10 mg/kgbw/day for the first 2 days, then 5 mg/kgbw/day on the third day for group II. All doses were directly observed and repeated if vomiting occurred within 30 minutes. After treatment on day 0, children were assessed clinically and parasitologically on day 1 to 7. Body temperatures were measured on 00.00, 06.00, 12.00 and 18.00 each day. Parasite count was measured in the morning on day 0 to 7.

Data were analyzed using SPSS version 15. Statistical analysis was performed using the student t-test.

Results

Eighty-three *falciparum* malaria patients were admitted in Prof. R. D. Kandou General Hospital, Manado during study period. Seventy-one *falciparum* malaria patients were enrolled and randomly allocated into two groups, but 4 patients dropped out.

Thirty-three children were treated with artesunate and sulphadoxine-pyrimethamine combination and 34 children were treated with artesunate and amodiaquine. **Tables 1, 2,** and **3** show that the demographic, clinical, and laboratory data of the 2 groups were comparable.

Cure rate on the two groups was 100%. On day seven, there was no parasites found in these two groups. No serious side effects during seven days observation in the two groups. Only one child had repeated vomiting after consuming artesunate and amodiaquine combination.

Table 1. Patients distribution according characteristics of subjects and groups

Characteristics	Group Artesunate & SP	Group Artesunate & Amodiaquine
Gender		
Boy	23	21
Girl	10	13
Age (year), mean (SD)	7.7±3.7	6.2±3.3
Body weight, (kg) mean (SD)	22.3±8.4	18.1±8.5

Table 2. Patients distribution based on clinic manifestations and physical examination

Characteristics	Group Artesunate & SP	Group Artesunate & Amodiaquine
Fever	100%	100%
Shivering	54.5%	38.2%
Headache	18.2%	5.9%
Anorexia	45.5%	32.4%
Myalgia	6.1%	5.9%
Nausea	45.5%	38.2%
Stomache	27.3%	17.6%
Diarrhea	6.1%	5.9%
Cough/cold	27.3%	29.4%
Hepatomegaly	69.7	61.8%
Splenomegaly	45.5%	32.4%
Body temperature on admission	38.3ºC	38.2ºC

Table 3. Laboratory findings on admission

Characteristics	Group Artesunate & SP	Group Artesunate & Amodiaquine
Hb (g/dl,mean (SD)	11.1±1.6	10.32±4
Leuco (mm3), mean (SD)	5,463.6+1,837.6	5,232.4+1,875.9
Platelet (mm3), mean (SD)	118,363.6+56,153.7	138,558.8+83,714.2
Parasit count (mm3), mean (SD)	6,381.8+17,614.4	11,207.1+24,537.8

Discussion

The characteristics of both groups in this study were in general similar. In general the clinical manifestations and laboratory findings were similar to that previously published.[13-21]

After treatment, in artesunate and sulphadoxine-pyrimethamine combination group had fever clearance time shorter than in artesunate and amodiaquine combination group. Although this study had a difference on fever clearance time, but there was no statistically difference between the two groups (P>0.05). This finding shows that both artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination had rapid elimination of fever in *falciparum* malaria patients. Van den Broek *et al*[21] found rapid elimination of fever (< 37.5°C) at day one and day two was 86% and 97% in the artesunate and amodiaquine combination group and 83% and 93% in the artesunate and sulphadoxine-pyrimethamine combination group, and on day three all but one (in artesunate and sulphadoxine-pyrimethamine combination group) were free from fever. Tambajong[23] in her study found that the fever had decreased rapidly in artemisinin group (artemeter). Dorsey *et al*[24] found significant decrease of fever in malaria patients which used artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination than using sulphadoxine-pyrimethamine alone. Koram *et al* [22] on their study in Ghana, found that artesunate and lumefantrin combination (Coartem) and artesunate and amodiaquine combination had rapid fever elimination than those using chloroquine alone or sulphadoxine-pyrimethamine alone.

Although there was difference in parasite clearance time in this study, but there was no statistically difference between this two groups (P>0.05). This result shows that therapy for the uncomplicated *falciparum* malaria patients used artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination were equally efficacious on parasite clearance time. Tambajong[23] found parasite clearance time were more rapid in artemisinin-based combination therapy than without using that combination. Van den Broek *et al* [21] in Sudan, who also used the same combination in his study, found rapid parasite clearance time. However, artesunate and sulphadoxine-pyrimethamine combination appeared slightly more efficacious than artesunate and amodiaquine combination. Koram *et al*[22] found that artesunate and lumefantrin combination (Coartem) and artesunate and amodiaquine combination had rapid parasite clearance time than using single antimalarial (chloroquine alone or sulphadoxine-pyrimethamine alone).

Cure rates on day seven in both artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination were equal (100%). Parasite sensitivity, clinical and parasitology responses were classified based on WHO.[25] From this classification, this study concluded that these two artemisinin-based combination therapies were equally efficacious in therapy uncomplicated *falciparum* malaria in children. Guthmann *et al*[26] found that the very low proportion of failures in both artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination than amodiaquine alone or sulphadoxine-pyrimethamine alone.

Side effects during seven days observation in the two groups occurred in one child, in artesunate and amodiaquine combination group. She had vomited 15 minutes after consuming these drugs and then the drugs were given again but then she vomited again. Those drugs were changed to other antimalarial (quinine sulphate) via nasogastric tube. This side effect maybe caused by amodiaquine which is in the combination of the drugs. Amodiaquine was an antimalarial 4-aminoquinolines group which its structure and activity is equal to chloroquine. This drug had equal side effect to chloroquine including nausea and vomiting.[27,28] Dorsey *et al*[24] on their study in Uganda on 183 children with uncomplicated *falciparum* malaria which treated with sulphadoxine-pyimrthamine alone, combination with artesunate or amodiaquine, found no patients had severe side effect and less than 1% vomited. The serum concentration of amodiaquine, artesunate or sulphadoxine-pyrimethamine was not measured in this study from the start, this was the limitation of this study.

We conclude that artesunate and sulphadoxine-pyrimethamine combination and artesunate and amodiaquine combination was found equally effective in treatment of uncomplicated *falciparum* malaria in children.

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