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Original Article

# Artesunate-amodiaquine versus artesunate-sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in children

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## Abstract

***Background*** Malaria is a major cause of morbidity and mortality in children, especially in developing countries. Artemisinin combination therapy (ACT) has higher rates of parasite clearance and inhibition of anti-malarial drugs resistance than non-ACT. Hence, we compared the efficacies of artesunate-amodiaquine (AS-AQ) versus artesunate-sulfadoxine pyrimethamine (AS-SP) combination therapies in children with uncomplicated falciparum malaria.

***Objective*** To compare the fever clearance time, parasite clearance time, and length of hospital stay in uncomplicated falciparum malaria patients treated with AS-AQ and AS-SP.

***Methods*** We reviewed the medical records of children aged 1-14 years with uncomplicated falciparum malaria admitted to Prof. Dr. R. D. Kandou Hospital between January 2002 – June 2010. Treatment efficacy was evaluated by fever clearance time, parasite clearance time, and length of hospital stay. The differences of treatment efficacy between the two groups of therapy were analyzed by independent T-test.

***Results*** We identified 185 children with uncomplicated falciparum malaria, 104 cases were treated with AS-AQ while the other 81 received AS-SP. Parasite clearance time was shorter in AS-AQ group than in AS-SP group at 1.38 (SD 0.69) versus 1.91 (SD 0.93) days, respectively (95%CI of differences 0.30 to 0.76, $P<0.05$). The length of hospital stay was shorter in AS-AQ group than in the AS-SP group, at 5.01 (SD 1.22) versus 6.04 (SD 0.98) days, respectively (95%CI of differences 0.71 to 1.35, $P<0.05$). However, there was no statistically significant difference in fever clearance time between the groups.

***Conclusion*** AS-AQ combination therapy reduces parasite clearance time and length of hospital stay compared to AS-SP combination therapy in children with uncomplicated falciparum malaria. **[Paediatr Indones. 2014;54:46-51.]**

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

Malaria is a major cause of morbidity and mortality in children, especially in developing countries.[1] This disease poses a major health challenges since 3 billions people are at risk of malaria infections, with 250 millions cases of infection and 1 million deaths annually. Africa has the world's highest burden of disease,[2-4] while Indonesia has about 60% of its population living in areas of various endemicities.[1,5] Five species of plasmodium are known to infect humans; those are *P. falciparum, P. vivax, P. malariae,*

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*P. ovale,* and *P. knowlesi.*[6,7] *Plasmodium falciparum* is associated with high morbidity and mortality.[8] Limited facilities for malaria blood smear examination and irrational anti-malarial therapies has contributed to anti-malarial drug resistance and increased mortality in the last decades.[1,2]

Antimalarial drug resistance, especially to chloroquine, was first reported in Indonesia in East Kalimantan in 1973.[9] Since that time, *P. falciparum* chloroquine resistance has widely spread in Indonesia. In 1990, chloroquine resistance was reported to occur in all Indonesian provinces. In addition to chloroquine resistance, sulfadoxine-pyrimethamine (SP) resistance was also reported in some areas of Indonesia. Anti-malarial drug resistance increases the morbidity and mortality of malaria. The World Health Organization (WHO) has recommended combination therapy malarial drugs (artemisinin combination therapy/ ACT) for countries with monotherapy anti-malarial drug resistance problems.[10] Artemisinin based combination therapy deliverers more rapid cure than non-ACT in terms of parasite clearance, reducing gametocyte carriage and delaying the development of anti-malarial drugs resistance,[3,10] thereby preventing resistance problems. The Indonesia Ministry of Health guideline recommends malaria drug of choice includes combination of amodiaquine (AQ) to replace chloroquine and SP in *P. falciparum* malaria.[8] The objective of this study was to compare the efficacy between artesunate-amodiaquine (AS-AQ) to that artesunate-sulfadoxine/pyrimethamine (AS-SP) combination therapies in children with uncomplicated falciparum malaria.

## Methods

We reviewed medical records of children admitted to Prof. Dr. R. D. Kandou Hospital Manado between January 2002 – June 2010 with uncomplicated falciparum malaria who received AS-AQ and AS-SP treatment. The inclusion criteria were children aged one year–14 years with uncomplicated falciparum malaria, not previously treated with any anti-malarial drugs, and without other diseases. Uncomplicated falciparum malaria was defined as a symptomatic falciparum malaria parasitemia < 5% without evidence of vital organ dysfunction, and be able to take oral therapy. We excluded children with mixed malaria, tertiana malaria, severe malaria, or incomplete data. The malaria treatment was in accordance with the protocols from the WHO and Ministry Of Health Indonesia.

The data collected were age, gender, clinical and laboratory characteristics. Children were treated with a combination of the following doses: AS 4 mg/kg/d for 3 days, AQ 10 mg base/kg/d on 1st and 2nd day and 5 mg base/kg/d on 3rd day, as well as a single dose of SP 1-1.5 mg/kg pyrimethamine on 1st day. All children received a single dose of 0.75 mg/kg primaquine.

Treatment efficacy was evaluated by fever clearance time, parasite clearance time, and length of hospital stay. Parasite clearance time was defined as the time between onset of anti-malarial drugs administrations and the disappearance of asexual *P. falciparum* from the patient's blood. Results were considered to be negative for parasites if no asexual *P. falciparum* was observed on thick blood smear evaluations performed once every 24 hours for 3 consecutive days. We used semi-quantitative methods of thick blood smears for parasite counts with the following interpretations: + (1-10 asexual parasites per 100 thick film fields), ++ (11-100 asexual parasites per 100 thick film fields), +++ (1-10 asexual parasites per single thick film field), and ++++ (more than 10 asexual parasites per single thick film field). Fever clearance time was defined as the time between the anti-malarial drug administrations and the start of the period in which the body temperature remained below 37.5 °C for 72 hours. The hospital length of stay was defined as the duration between hospital admission and discharge as an ambulatory patients.

We also evaluated adverse events by reviewing the daily complaints during treatment. The comparison of combination treatment efficacies was analyzed by independent t-test. All data were analyzed with SPSS 17.00 software.

## Results

During the study period there were 682 cases of malaria, 185 patients met the eligible criteria. From these 185 patients, 104 cases were treated with combination AS-AQ and 81 cases with combination

AS-SP. Subject's mean age was 6.85 (SD 3.36) years. Patients' baseline characteristics of age, gender, clinical manifestations, and laboratory findings are shown in **Table 1**.

Following initiation of treatment, we found that patients in the AS-AQ groups had a shorter mean parasite clearance time compared to those in AS-SP group [1.38 (SD 0.69) days vs. 1.91 (SD 0.93) days, respectively; 95%CI of differences 0.30 to 0.76]. The AS-AQ group also had a shorter length of hospital stay than the AS-SP group [5.01 (SD 1.22) days vs. 6.04 (SD 0.98) days; 95%CI of differences 0.71 to 1.35]. There was no statistically significant difference in fever clearance time between the groups [1.40 (SD 0.97) days vs. 1.54 (SD 0.84) days; 95%Cl -0.13 to 0.41] (**Table 2**). No adverse event was observed in both groups of treatment.

**Table 1.** Characteristics of children with uncomplicated falciparum malaria

| Characteristics | AS-AQ group (n=104) | AS-SP group (n=81) |
|---|---|---|
| Mean age years (SD) | 6.53 (3.13) | 7.23 (3.61) |
| Gender | | |
| Males, n (%) | 61 (58.7) | 55 (67.9) |
| Females, n (%) | 43 (41.3) | 26 (32.1) |
| Clinical manifestations | | |
| Fever, n (%) | 104 (100) | 81 (100) |
| Shivering, n (%) | 53 (65.4) | 34 (42) |
| Simple febrile seizure, n (%) | 3 (3) | - |
| Laboratory findings | | |
| Mean hemoglobin (SD), g/dL | 10.30 (2.37) | 10.65 (1.77) |
| Mean WBC (SD), /mm$^3$ | 6,830 (7,800) | 5,472 (2,084) |
| Mean platelets (SD), /mm$^3$ | 135,863 (89,534) | 128,443 (91,037) |

WBC=white blood cells

**Table 2.** Efficacies of AS-AQ and AS-SP in uncomplicated falciparum malaria

| Variables | AS-AQ group | AS-SP group | 95%CI of differences | P value |
|---|---|---|---|---|
| Mean parasite clearance time, days (SD) | 1.38 (0.69) | 1.91 (0.93) | 0.30 to 0.76 | 0.042 |
| Mean fever clearance time, days (SD) | 1.40 (0.97) | 1.54 (0.84) | -0.13 to 0.41 | 0.056 |
| Mean length of hospital stay, days (SD) | 5.01 (1.22) | 6.04 (0.98) | 0.71 to 1.35 | 0.023 |

## Discussion

Our results show that the combination therapies of AS-AQ and AS-SP were efficacious against uncomplicated falciparum malaria. Amodiaquine and SP were appropriate compounds to be combined with AS. The efficacy of SP alone was certainly less than ideal (<80%).[11] A study in Manado, Indonesia found the efficacy of SP to be less than 80%, while 13.5% of subjects developed RII resistance.[12] Similary, a Kenyan study found the efficacy of SP to be only 62.7%, with 17.8% developing R I resistance, 9.3% R II resistance and 10.3% R III resistance.[13] Grade III resistance (R III) was a parasitemia on day 2 of 25% of the initial (day 0) value. If no data for day 2 were available, data for day 3 were used instead. Grade II resistance (R II) was a parasitemia on day 7 in patients without grade III resistance. Grade I resistance (R I) was a parasitemia on day 14 in patients without grade II or III resistance. However, SP is typically given as a single dose, making it a potential partner drug for AS.[14] Combination therapy of AS-AQ and AS-SP were found to be efficacious options for uncomplicated malaria in Nuba Mountain, Sudan, providing rapid and sustained fever and parasite clearance, as well as gametocyte suppression.[15] Another study also reported that oral artesunate was well tolerated when administered with AQ or SP.[16]

The WHO strategy to lower mortality associated with malaria is early diagnosis and effective treatment with the recommended therapy (ACTs).[17,18] The principle of combination therapy is using 2 or more blood schizontocidal drugs simultaneously, where each drug acting independently of the other and having different biochemical targets in the parasite.[1] In the last decade, ACTs were widely accepted as malaria therapy.[19] Artemisin combination therapy (ACT) may

resolve the therapeutic efficacy and prevent drug resistance to *P. falciparum*.[20] The ACTs now widely used are the artemisinin group (artemether combined with lumefantrine, artesunate combined with amodiaquine, artesunate combined with sulfadoxine/pyrimethamine and artesunate combined with mefloquine).[21] The efficacy of AS-AQ and AS-SP was found to be 100% and recrudescence was less than 5%.[16]

The rationale for ACTs rests on three main arguments: 1) that drugs with independent modes of action might improve efficacy, 2) that high efficacy and gametocyte reduction might reduce malaria transmission, and 3) that resistance might be retarded because the probability of parasite resistance to both drugs is low, and because artesunate rapidly reduces the biomass of multidrug-resistant parasites, leaving few parasites to be killed by high concentrations of the companion drug.[22]

Artemisinin is a sesquiterpene lactone antimalarial drugs from qinhaosu herbs (*Artemisia annua*), now widely used to treat malaria and other parasitic diseases.[1,21,23-25] Artemisinin derivatives are the partner of choice for combined drugs because they are absorbed well, safe, quickly metabolized to an active form, have shorter half-lives (1-3 hours), strong activity,[1,21,25] and achieved peak levels in 1-2 hours.[23] Sodium artesunate is effective because it clears parasites faster ($10^4$ fold in 48 hours single erythrocytes cycle).[24] Since artemisinin derivatives haved shorter half lives, treatment failure may occur if it is used as a mono therapy.[21] The artesunate-amodiaquine combination was reported as tolerable, able to prevent gametocyte formation, have faster effects, effective in multidrug-resistant parasites,[23] and inexpensive. Side effects are gastrointestinal complaints (nausea and vomiting), neurotoxicity, and in an animal study, a reported embryotoxin effect. However, to date there has been no increase in cases of congenital anomalies or developmental abnormalities in humans.[1, 25]

Amodiaquine, like chloroquine, is a 4-aminoquinoline. It is generally effective against chloroquine-resistant strains of *P. falciparum*, although there is some cross-resistance. Amodiaquine is fairly well tolerated and slightly more palatable than chloroquine.[26] Amodiaquine is structurally closely related to chloroquine and might also prevent heme detoxification.[21] The toxicity of AQ is agranulocytosis and hepatitis from bio activation of AQ into protein-reactive quinoneimin metabolites.[21,23,26] In vivo, AQ is rapidly converted by hepatic P450 enzymes into monodesethyl-AQ. This metabolite, which retains substantial antimalarial activity, has a half-life in blood plasma of 9–18 days and reaches a peak concentration of ~500 nM in 2 hours after oral administration. But, AQ has a half-life of ~3 hours, attaining a peak concentration of ~25 nM within 30 minutes of oral administration.[21] Artesunate-amodiaquine has proved to be an efficacious combination in areas where 28-day cure rates with amodiaquine monotherapy exceed 80%.[26] The Amodiaquine chemoprophylaxis should be avoided because of its potential toxicity in long term use.[23]

Sulfadoxine-pyrimethamine (SP) is a fixed combination of a long-acting sulfonamide and the antifolate pyrimethamine.[26] Sulafadoxine-pyrimethamine usually is also inexpensive, single dose drug, and usually used in chloroquine resistant areas.[27] A pyrimethamine component couples plasma protein and accumulates in kidney, lung, liver, and spleen. The pyrimethamine half-life is about 80-95 hours. Genetically, resistance to pyrimethamine occurs in the dihydrofolate reductase (DHFR) gene with a mutation in codons 16,50,51,59, 108, and 164.[28] Sulfadoxine-pyrimethamine toxicity is usually associated with serum sickness, urticaria, exfoliative dermatitis, and hepatitis.[25] Sulfadoxine-pyrimethamine is not recommended as prophylaxis because of adverse reactions of the skin,[27] and it is contraindicated for infants less than 2 months of age, those at risk of kernicterus, sulfonamide sensitivity, and breastfeeding mothers.[25] The combination of AS-SP has been evaluated extensively in children and adults with uncomplicated falcifarum malaria and sufficiently efficacious in area where 28-day cure rate with recurrence rates with SP alone exceed 80%.[26]
No significant difference in fever clearance time is observed between the AS-AQ and AS-SP groups in our study. Van den Broek *et al*[29] reported that fever disappeared ($<37.5^{O}$C) in the first day for about 86% of the subjects and in the second day for about 97%, respectively, in the AS-AQ group. Dorsey *et al*[30] reported that fever disappeared quickly and significantly with AQ-SP or AS-SP, when compared to SP alone. Koram *et al*[31] found that AS-AQ and a lumefantrine-artemether combination shortened the fever clearance times compared to chloroquine alone. Our study shows that an ACT combination therapy has fever clearance time on the second day

in uncomplicated falciparum malaria cases.

Parasite clearance time is widely use as a marker of efficacy for anti-malarial drugs. In our study, the AS-AQ combination had shorter parasite clearance time and duration of hospitalization than the combination AS-SP group. Tambajong *et al*[32] found that parasite clearance time was shorter in the artemether group than in the non-artemisinin group. Van den Broek *et al*[29] used the same combination medications as our study and had similar results, especially in parasite clearance time. However, Zwang *et al*[33] reported that there was no significant difference in fever and parasite clearance times in the AS-AQ group compared to AS-SP combinations.

In conclusion, AS-AQ combination therapy is more effective than the AS-SP combination in treating uncomplicated falciparum malaria. Combination of AS-AQ has been used as a first-line drug of therapy in our institution. The AS-SP combination can also be used as an alternative to ACTs, if the AS-AQ combination is unavailable.

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