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Original Article

Comparison of the efficacy of artesunate-amodiaquine with quinine-clindamycin for treatment of uncomplicated falciparum malaria in children

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Abstract

Background Drug-resistant *Plasmodium falciparum* malaria is a major contributor to increasing malaria-related morbidity and mortality. Artesunate-amodiaquine is a potential combination therapy that shows improved treatment efficacy. Clindamycin in combination with quinine is also a safe and effective treatment for multidrug-resistant *P. falciparum* malaria.

Objectives To compare the efficacy of artesunate-amodiaquine and quinine-clindamycin combination therapies for the treatment of uncomplicated falciparum malaria.

Methods This randomized open label trial in 232 children aged between one month and 18 years old took place in Mandailing Natal, North Sumatra, from August to September 2006. The AA group received a 3-day oral course of artesunate (4 mg/kg BW once a day) plus amodiaquine (10 mg/kg BW once a day). The QC group received a 3-day course of clindamycin (5 mg of base/kg BW twice a day) plus a 7-day course of quinine (10 mg of salt/kg BW orally for the first four days, then 5 mg of quinine salt/kg BW for the next three days). We performed thin and thick peripheral blood smears on days 0, 2, 7, and 28.

Results A total of 232 eligible children were enrolled but only 227 completed the study (114 in group AA, 113 in group QC). The cure rates were 100% in both groups by the second day, and there was no recrudescence in either group. We found more side effects in AA group compared with in QC group, i.e., headache and vomiting.

Conclusion Artesunate-amodiaquine and quinine-clindamycin combinations showed similar efficacy for the treatment of uncomplicated *P. falciparum.* **[Paediatr Indones. 2009;49:91-6]**.

Keywords: *artesunate-amodiaquine, quinine-clindamycin, uncomplicated falciparum malaria*

Malaria has been a scourge of mankind for centuries.[1] Malaria (*mala* means bad and *aria* means air)[2] is an acute and chronic protozoan illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly.[3] Malaria is a major communicable disease of the tropics and subtropics, killing more than one million people each year,[4] and is undergoing a resurgence in areas where it was previously controlled.[5] This disease is distributed throughout tropical countries but its incidence is lower in dry climates and at high altitudes.[6] Results from malariometric survey showed high parasite rates (parasite rates of more than 2%) in endemic malaria in Sumatra Utara Province from 1989 until 1993.[8]

Chloroquine-resistant strains of *P. falciparum* have been reported from many areas of the world, i.e., Indian subcontinent, Southeast Asia, Oceania, Panama, and South America and from extensive areas of East Africa. If chloroquine-resistance is

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suspected, quinine should be used for treatment instead. However, quinine should not be used alone because it is associated with a significant recrudescence rate.[9]

In Southeast Asia, tetracycline is commonly combined with quinine for treating falciparum malaria; however this combination cannot be used for children under eight years old and pregnant women. Use of clindamycin in combination with quinine for treating human volunteers with chloroquine-resistant malaria was first described two decades ago.[10] Since then, interest in clindamycin as an antimalarial has renewed and a number of recent clinical trials have evaluated clindamycin as a partner in a combination for treatment of malaria.[11]

Artemisinin or qinghousu is extracted from the leaves of the shrub *Artemesia anua*. Artemether and artesunate are available derivatives. Artemisinine acts rapidly, is safer,[1] and is effective as blood schizonticides against all types of malaria.[12] It is now recommended that antimalarial agents should be combined with artemisinin or its derivatives to protect against development of multidrug resistance strains.[2] We aimed to compare the efficacy of artesunate-amodiaquine and quinine-clindamycin combinations for the treatment of uncomplicated falciparum malaria in children.

Methods

The study was conducted in Mandailing Natal regency in August and September 2006. The protocol has been approved by local ethics committee. We included patients living in the study area presenting with uncomplicated *P. falciparum* malaria, aged between one month and 18 years, positive blood smears for *P. falciparum*; had not taken antimalarial drugs for the last month. We excluded patients with severe malaria or who refused the drugs or took alternative drugs.

The study was a 28-day open randomized clinical trial. Eligible patients were randomly allocated to two treatment groups. One group (AA group) received artesunate (4 mg per kg of body weight) and amodiaquine (10 mg per kg of body weight) once a day for 3 days. The other group (QC group) received quinine (10 mg per kg of body weight for the first 4 days and then 5 mg per kg of body weight for the last 3 days) and clindamycin (5 mg per kg of body weight, twice a day. Thick and thin blood smears, and physical examinations were performed on days 0, 2, 7 and 28. For all patients, drugs were taken in front of the research team. If the patients vomited, the drugs were readministered. Fever was managed by giving paracetamol as appropriate. Data was analyzed using the chi-square test with SPSS software version 13.0.

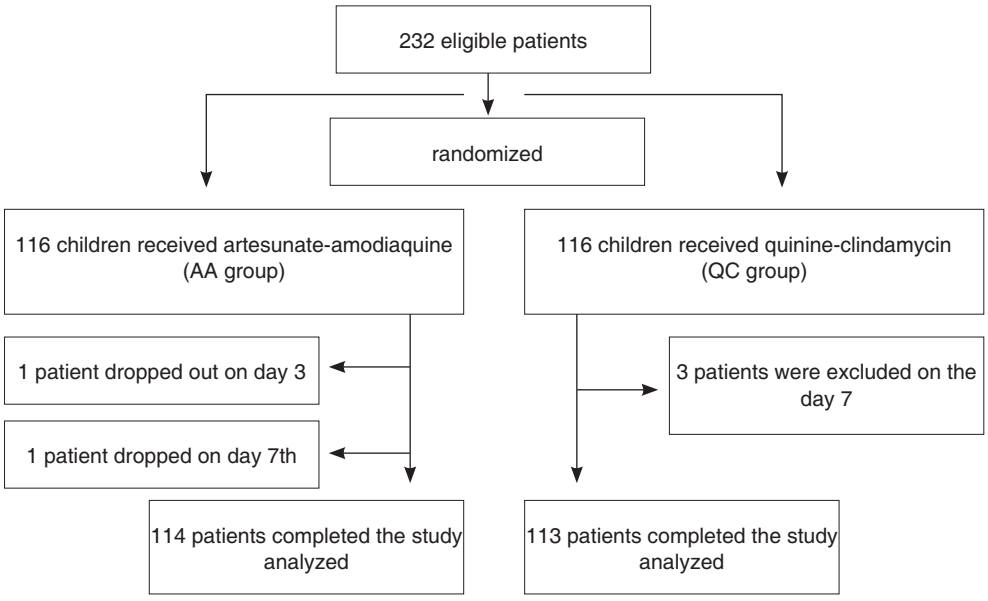

Figure 2. Trial profile

A P value of less than 0.05 was considered statistically significant.

Results

Of the 232 eligible patients, five patients (two patients in the AA group and three patients in the QC group) were excluded from analysis because they didn't complete the study (**Figure2**).

Table 1 shows the baseline characteristics of the patients in the two groups. In both groups, most patients aged under 12 years old (69.3% in the AA group and 96.5% in the QC group). Females outnumbered males in both groups. Regarding nutritional status, about half of the patients in the AA group were within the normal limits (51.8%), but we were also found patients who were overweight or with moderate malnutrition. In the QC group, most patients were within normal limits (78.8%) and there were no overweight or moderately malnourished patients. Parasitemia data indicated that in both groups the majority of patients fell into the < 200/μl or the 200-400/μl groups.

Physical examination before treatment revealed that in the AA group eight patients suffered from fever and eight were had a pale complexion, and in the QC group only one patient suffered from fever and two patients had a pale complexion. There was no hepatosplenomegaly in either group (data not shown).

In the AA group, we found significant side effects compared with QC group such as headache (n=17) and vomiting (n=8) (**Table 2**).

In both groups, parasitemia was negative by day 2 after treatment started. There was no recrudescence in either group; we conclude that cure rate in both groups was 100%.

Table 1. Baseline characteristics of the patients

Characteristic	AA group n (%)	QC group n (%)
Age (years)		
< 12	79 (70)	109 (96)
12- 14	13 (11)	4 (4)
> 14-18	22 (19)	0
Sex		
female	46 (40)	54 (48)
male	68 (60)	59 (52)
Nutritional status		
moderate	7 (6)	0
mild	28 (25)	24 (21)
normal	58 (52)	89 (79)
overweight		0
Parasitemia		
< 200/μl	32 (28)	45 (40)
200 - 400/μl	67 (59)	50 (44)
> 400 - 600/μl	14 (12)	15 (13)
> 600 - 800/μl	1 (1)	3 (3)

Table 2. Side effects of the drugs

Characteristic	AA group n (%)	QC group n (%)	P
Headache			
headache	17 (15)	4 (4)	0.001*
no headache	97 (85)	109 (96)	
Tinnitus			
Tinnitus	1 (1)	1 (1)	0.321
No tinnitus	113 (99)	112 (99)	
Vomiting			
Vomiting	8 (7)	0	0.019*
No vomiting	106 (93)	113 (100)	

Discussion

The effectiveness of antimalarial agents varies between parasite species and between stages in their life cycles. In addition, parasite resistance to these drugs is an important therapeutic problem. Some major antimalarial drugs are classified by their chemical structure. Antimalarial drugs can also be classified by their selective actions on different phases of the parasite's life cycle.[12]

Quinine is a rapidly acting, effective blood schizonticide against the four malaria parasites. The drug is gametocidal for *P. vivax* and *P. ovale* but not very effective against *P. falciparum* gametocytes. Quinine sulphate is used with other drugs for the oral treatment of acute attacks of *P. falciparum* malaria that are resistant to chloroquine. Although chloroquine effectively reduces parasitemia, combination therapy with another drug is necessary because quinine alone fails to completely eliminate the infection.[12]

Clindamycin monotherapy for falciparum malaria is not recommended[11] because it could lead to the emergence of clindamycin-resistant *P. falciparum* strains.[13] The slow onset of action also makes it potentially dangerous in cases in which fast parasite

clearance is necessary such as in children and non-immune adults. Since clinical cure is also delayed, it should not be given to semi-immune individuals when other options are available.[11]

The combination of clindamycin with a fast-acting drug is necessary to take advantage of its full antimalarial potential. Quinine, with its fast action and short elimination half-life, makes an ideal partner for clindamycin.[11] Clindamycin in combination with quinine is a safe and effective treatment for multidrug-resistant *P. falciparum* malaria. This combination may be of particular value in children and pregnant women, in whom tetracyclines are contraindicated.[14] This combination was first evaluated clinically in small trials conducted in the United States and Thailand during the 1970s.[11]

In France, between June 1996 and December 1998, a three-day quinine-clindamycin regime for the treatment of imported uncomplicated *P. falciparum* malaria in returned travellers was well tolerated and compared favorably with a seven-day quinine regime, one of the standard regimes for the treatment of uncomplicated falciparum malaria in France. Benefits include reduction in the duration of the treatment and a trend toward a decrease in side effects. Therefore, shortening of the duration of quinine treatment to three days may be possible with the addition of clindamycin.[15]

In another study, carried out from February 1995 to March 1996, a three-day clindamycin-quinine regime to treat clinical malaria in 256 children from a primary school in Dienga, western Gabon was conducted. Treatment was well tolerated by all of the children and its efficacy was higher than 97% by day 20. Thus, this study also suggests that a three-day clindamycin-quinine regime might constitute a potential alternative to chloroquine for treating clinical malarial attacks in children.[16]

Pukrittayakamee also found that clindamycin is an effective and well tolerated alternative to tetracycline in combination malaria treatment. There were no treatment failures among the 60 patients treated with a seven-day course of quinine and clindamycin. Thus, estimated efficacy is 100%. The clindamycin was very well tolerated, and there were no adverse effects attributable to it. Unfortunately, clindamycin is significantly more expensive than tetracycline and, as cost is the major factor that determines the use of antimalarial drugs, this could be an issue. Nevertheless, clindamycin may be considered a safe and effective alternative to tetracycline in combination treatment of drug-resistant falciparum malaria.[14] In Indonesia, artesunate-amodiaquine are more expensive than quinine-clindamycin, hence the importance of quinine-clindamycin combination is considered as an alternative treatment for uncomplicated falciparum malaria.

A regimen of 5 mg of clindamycin per kg of body weight plus 10 mg of quinine base per kg every 12 hours for three days may be an excellent option for the treatment of uncomplicated malaria in Africa and other areas with low-grade resistance to antimalarial drugs. A four-day treatment with a loading dose and subsequent administration every eight hour is appropriate for patients with very high initial levels of parasitemia and severe malaria. In areas with multiresistant parasites, the duration possibly needs to be prolonged to five or even seven days, however, further studies as needed to address this question.[11] In this study we used 5 mg of clindamycin per kg body weight every 12 hours, combined with 10 mg of quinine base per kg body weight for the first four days and then continued with 5 mg of quinine base per kg body weight for the last three days.

Clindamycin plus quinine is not an ideal antimalarial regime. The need for twice-daily dosing is an obstacle for its general use in areas where malaria is endemic. Given the short half-lives of both clindamycin and quinine, and the short treatment course, complete and accurate administration is essential. Assurance that the correct dose has been taken and that dosing has been for the correct duration is thus more important with clindamycin-quinine regimen.[11]

Sowunmi *et al* found that the combination of artesunate plus amodiaquine was therapeutically superior to a combination of chloroquine plus pyrimethamine-sulfadoxine, and significantly reduced gametocyte carriage following treatment.[17] Abacassamo *et al* conducted a study that assessed efficacy of chloroquine, sulphadoxine-pyrimethamine and amodiaquine towards *P. falciparum* and then tested the safety and efficacy of this combination in the treatment of uncomplicated malaria in three combinations: amodiaquine-sulphadoxine-pyrimethamine, artesunate-sulphadoxine and

amodiaquine-artesunate. The combination therapies gave rapid fever clearance time and reduced the incidence of gametocytemia during follow up.[18]

In another study, in Rwanda, Rwagacondo *et al* investigated the safety and efficacy of amodiaquine alone and compared this with amodiaquine-artesunate combination in 308 Rwandan children 6-59 months old with uncomplicated *P. falciparum*. The two regimes were well tolerated and no serious adverse events were recorded. Combining amodiaquine with artesunate increased the efficacy of the treatment.[19]

Meremikwu *et al* compared a three-day course of artesunate plus amodiaquine with a 6 dose course of artemether-lumefantrine over three days. From this study, artemether-lumefantrine and artesunate plus amodiaquine have high and comparable cure rates and tolerability among children under five.[20]

Adjuik *et al* performed trials in Kenya, Senegal and Gabon that compared artesunate-amodiaquine for three days with amodiaquine-placebo for three days. The combination of artesunate and amodiaquine improved treatment efficacy in Gabon and Kenya, and was equivalent in Senegal. Amodiaquine-artesunate is a potential combination therapy for use in Africa. Further investigation to assess the potential effect on the evolution of drug resistance, disease transmission, and safety of amodiaquine-artesunate are warranted. After treatment for one month, the cure rates for artesunate-amodiaquine compared with amodiaquine-placebo were 91% vs. 74% in Kenya, 93% vs. 94% in Senegal and 98% vs. 90% in Gabon.[21] In our study artesunate-amodiaquine combination therapy were effective and well tolerated when compared with quinine-clindamycin. There was no treatment failure in any patients (cure rate = 100%).

Amodiaquine may cause nausea, vomiting, abdominal pain and diarrhea.[4] In this study, in the AA group, we found significant adverse effects compared with QC group such as headache and vomiting.

Quinine-clindamycin combination therapy was compared with artesunate-amodiaquine therapy for the treatment of uncomplicated falciparum malaria in children. It was found that they have same efficacy, but because the quinine-clindamycin combination is cheaper than artesunate-amodiaquine it is preferable.

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