

## Comparison of quinine-doxycycline and quinine-clindamycin for falciparum malaria in children

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### Abstract

**Objective** To compare the efficacy of quinine-doxycycline to quinine-clindamycin combination, as treatment for uncomplicated falciparum malaria in children.

**Methods** This randomized open labelled controlled trial was conducted from July to August 2007 at Mandailing Natal, Sumatera Utara Province. The subjects were 8 – 18 year old children with positive *Plasmodium falciparum* from the peripheral blood smear. Simple randomization was performed to determine subject study into two groups of treatment, one group received quinine-clindamycin and the other received quinine-doxycycline treatment. The parasitemia was counted on day 0, 2, 7 and 28. We also observed the adverse effects of the antimalarial combination.

**Results** Two hundred and forty six children who fulfilled the inclusion criteria were divided into two groups. All subjects completed the study. Cure rate achieved 100% from peripheral blood smear examination at the second day observation and showed no recrudescence at day 28<sup>th</sup>. ( $P=0.0001$ ). During 28 days follow up, there were 21 (17.6%) patients suffered from headache, 18 (14.6%) vomit and 40 children (32.5%) suffered from tinnitus in quinine-doxycycline combination, compared to quinine-clindamycin combination group only 4 (3.3%) suffered from headache, 1 (0.8%) suffered from tinnitus and there was no vomiting experience in any patient ( $P < 0.0001$ ).

**Conclusion** Combination of quinine with either clindamycin or doxycycline are effective as an alternative antimalarial treatment. The combination of quinine-clindamycin is well tolerated than the combination of quinine-doxycycline, and this combination may be particular value for young children and pregnant women, as these two groups cannot receive doxycycline. [Paediatr Indones. 2011;51:187-91].

**Keywords.** quinine-doxycycline, quinine-clindamycin, falciparum malaria, parasitemia

Malaria is still a major health problem in Indonesia with high morbidity, especially in area out of Java and Bali island, where there is a mixture of citizen from the endemic area and non endemic area.<sup>1-3</sup> There are many drugs use as antimalarial, however broadly used of malaria treatment without any basis of rationale treatment cause multidrugs resistant malaria is spreading.<sup>4</sup> Although cloroquine is still the basic therapy for falciparum malaria, the resistancy is high, now the multidrug antimalarial resistant in South East Asia, including in Indonesia become wider.<sup>5</sup> A clinical trial on several places in Indonesia showed high resistancy to cloroquine, about 75-95% in Irian Jaya and in Mandailing Natal, Sumatera Utara. Study from Emil Azlin et al (2001), showed resistancy to chloroquine and fansidar are about 32% and 29% respectively.<sup>6</sup>

Antimalarial drugs combination therapy, usually consist of rapid acting, short half-life antimalarial drug and drug with more slowly acting agent and longer

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half-time, has been considered for the treatment of falciparum malaria.<sup>7,8</sup> There are many study on combination of antimalaria drugs as alternative therapy for preventing resistant of *Plasmodium falciparum*. Combination of quinine-clindamycin in several pharmacokinetics study showed high efficacy for the treatment falciparum malaria in children.<sup>9</sup> Other alternative therapy is a combination of antimalarial drug with doxycycline.<sup>10,11</sup> But there is limited study on pharmacokinetics of this multidrugs regiment for children with uncomplicated falciparum malaria.<sup>11,12</sup>

In this study, we compared the efficacy of quinine-clindamycin with quinine-doxycycline combination as alternative treatment of uncomplicated falciparum malaria in children.

## Methods

This study was conducted from July to August 2007 at seven sub districts of Mandailing Natal, Sumatera Utara province. The subjects of this study were elementary to high school students age 8 – 18 years old with uncomplicated Falciparum malaria. The diagnosis based on the finding of *Plasmodium falciparum* on peripheral blood smear examination. A fully informed consent has been taken before the enrollment of subject. The inclusion criteria were age 8 – 18 years old, suffer from uncomplicated falciparum malaria, and never got any antimalarial drug at least for one month before this study. The exclusion criteria were severe malaria and considered as unable to participate the study completely.

The simple randomization using random table divided subject into two groups of treatment, group 1 received oral quinine for 7 days with the dosage of 10 mg/KgBW t.i.d for 4 days and continued with 5 mg/kgBW t.i.d for the next 3 days, combined with oral clindamycin with the dosage of 10mg/kgBW/d b.i.d for 3 days. Group 2 received oral quinine for 7 days with the dosage of 10mg/KgBW t.i.d for 4 days continued with 5 mg/kgBW t.i.d for the next 3 days, combined with oral doxycycline 2 mg/KgBW/d b.i.d for 7 days. All anti malaria drugs were taken after meal.

We repeated physical examination and peripheral blood smear on day 2, 7 and 28. Peripheral blood smear

was stained with giemsa according to the procedure and examined by trained laboratory analyst. Parasite was count in every 200 leucocytes. Patient was defined as cured if there is no parasite and no recrudescence in 28 days of observation. Body weight was measured with weight meter MIC (sensitivity 0.05 kg).

Data were exported to SPSS version 15.0 (SPSS Inc, Chicago) for statistical analysis. *Wilcoxon rank test* was used to analyze the data before and after therapy. Characteristic data and adverse effect was analyzed using *Pearson chi square* with 95% CI,  $p < 0.05$  was determined as significant.

This randomized open label controlled trial was approved by Ethics Committee of Sumatera Utara University.

## Results

A total of 300 children were screened and 246 were eligible to enroll in this study. These children were randomized into two groups; each group consist of 123 children, one group received quinine-clindamycin and the other group received quinine-doxycycline. All children in each group completed the study (**Figure 1**).

The characteristics of the subjects in each group are shown in **Table 1**. There were almost no significant differences between these groups. Most of the subjects were 8-15 years old, while subjects with age of >15 years old (10.6%) were most in quinine-doxycycline group.

Physical examination was performed to evaluate fever, pale, hepatomegaly, splenomegaly and parasitemia in both groups (**Table 2**). We found only 1 child (0.8%) with hepatomegaly at quinine-clindamycin group and 5 children (4.1%) have splenomegaly at quinine-doxycycline. Pale was found at two groups. And there were no different significant between two group in parasite count.

There were significant different of adverse effects in both groups ( $p < 0.05$ ), in quinine-doxycycline combination group, there were 17.1% of the subjects suffered from headache, 14.6% vomit and 32.5% suffered from tinnitus (**Table 3**).

There was no significant different on parasitemia. On day 2 of observation the parasitemia became negative, except on quinine-doxycycline group where

**Table 1.** Characteristic of sample

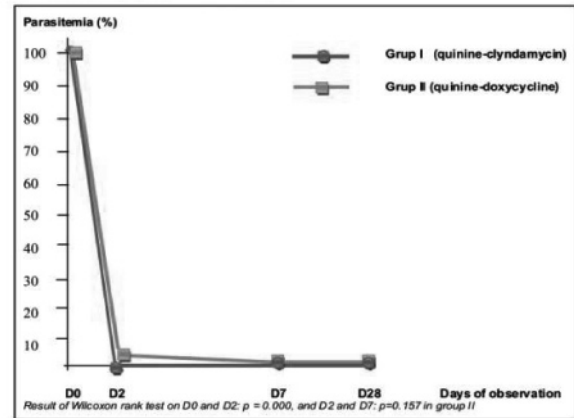
Characteristic	Quinine-clindamycin combination n (%)	Quinine-doxycycline combination n (%)
Age (years)		
8-15	120 (97.6)	111 (89.4)
>15	3 (2.4)	13 (10.6)
Sex		
Male	54 (43.9)	55 (44.7)
Female	69 (56.1)	68 (55.3)
Parent education		
Elementary school	88 (71.5)	80 (65.0)
Junior high school	18 (14.6)	12 (9.8)
Senior high school	15 (12.2)	28 (22.8)
University	2 (1.6)	3 (2.4)

**Table 2.** Signs and symptoms before treatment

Early sign and Symptoms	Quinine-clindamycin combination n (%)	Quinine-doxycycline combination n (%)
Fever	0 (0.0)	0 (0.0)
Pale	1 (0.8)	2 (1.6)
Hepatomegaly	1 (0.8)	3 (2.4)
Splenomegaly	0 (0.0)	5 (4.1)
Parasite count:		
< 200 / $\mu$ L	50 (40.7)	51 (41.5)
200 – 400 / $\mu$ L	54 (43.9)	40 (40.32)
400 – 600 / $\mu$ L	16 (13.0)	30 (24.4)
600 – 800 / $\mu$ L	3 (2.4)	2 (1.6)

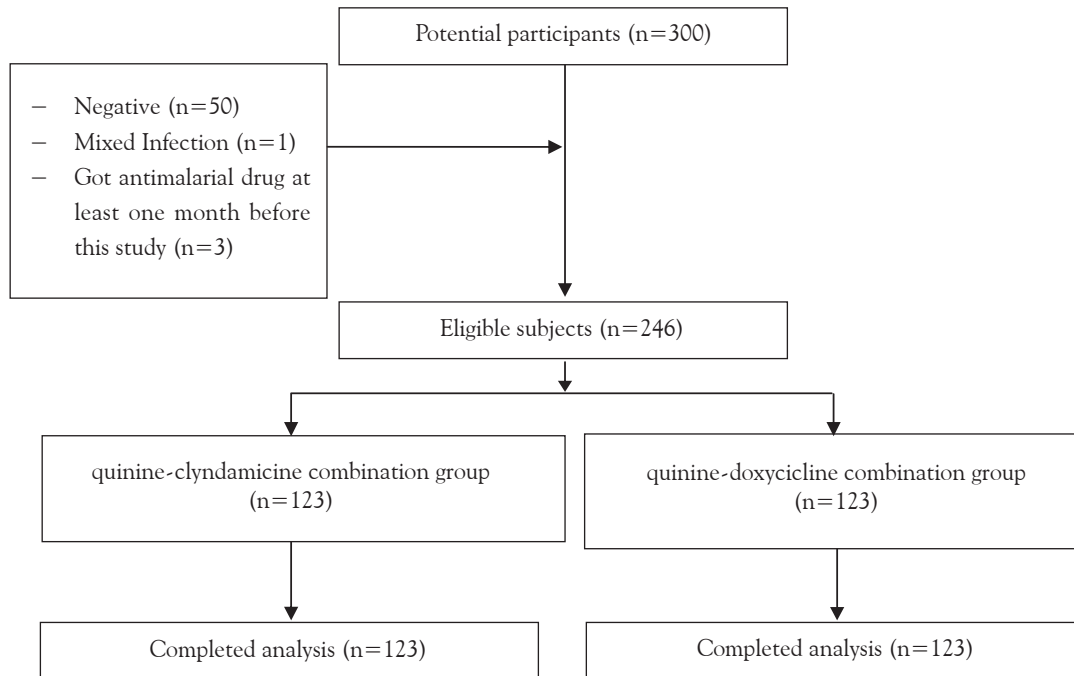
**Table 3.** Adverse effect of treatment

Side effect	Quinine-clindamycin combination n	Quinine-doxycycline combination n	P
Headache	4	21	<0.0001
Tinnitus	1	40	<0.0001
Vomit	0	18	<0.0001



**Figure 2 .** Parasitemia on day 2, 7 and 28

we found two subjects were still positive. While on day-7 and 28 observation, there was no parasitemia in both groups. (Figure 2)



**Figure 1.** Study algorithm

## Discussion

In this study we choose to use combination of quinine-clindamycin compared to quinine-doxycycline as a treatment of uncomplicated malaria in children. This therapy is rarely used for children in South East Asia particularly in Indonesia. Malaria treatment efficacy and drugs resistancy are still the major problems on malaria treatment. In South East Asia multidrugs resistant malaria is now so widespread that virtually no antimalarial can be used alone reliably.<sup>5</sup>

Quinine is the most frequent used drug and effective if there is resistance to chloroquine. Although this drug covers other antimalarial, following the development of widespread resistancy to chloroquine and other drugs, quinine is still important as antimalaria drug.<sup>5,11,14,15</sup> Quinine is effective to reduce parasitemia, but it need to combine with other drug because quinine monotherapy can not eliminate infection perfectly.<sup>16</sup>

Clindamycine, a lincosamide antibiotic, was found to be highly effective when used for at least 5 days for the treatment of falciparum malaria in Brazil, Philippines, and Gabon. Because clindamycin is a slowly acting drug, clindamycin is a candidate for combination treatment with fast-acting drugs, such as quinine.<sup>12-17</sup> Clindamycin, usually combined with quinine, has been used extensively in South America and also proved effective in adults and children with acute malaria. The efficacy of clindamycin plus quinine for children has not been evaluated in the South East Asian region, where the most drug resistant *Plasmodium falciparum* strains are found.<sup>13</sup> Because of this reason, we used clindamycin 5 mg/KgBW two times daily combined with quinine for this study .

These dose are also used by the *Thai Government Pharmaceutical Organization*, either quinine used alone or combination with other drug such as clindamycin or tetracycline. Pukrittayakamee (1995) showed that clindamycin in combination with quinine was safe and effective treatment for multidrug-resistant *P. falciparum* malaria. There was no treatment failures among the 60 patients with 7 days course of quinine and clindamycin, thus estimated efficacy is 100%.<sup>13</sup> In our treatment, we found 100% cure level with combination of quinine-clindamycin, and there were no recrudence on the 28 days observation.

Other antibiotics such as tetracyclines are commonly combined with quinine for treating

*Plasmodium falciparum* malaria in South East Asia. However, because of the side effects, this combination usually avoided for children and pregnant women.<sup>18</sup> Tetracycline derivative like doxycyclin also may used as prophylaxis for malaria in areas with chloroquine and/or primethamine-sulfadoxine resistant to *Plasmodium falciparum*.<sup>19</sup> There is limited published information on pharmacokinetics of doxycyclin for children, because doxycycline is not suitable for children under 8 years old.<sup>20</sup> Combination with oral quinine for children age 8 years or more are alternative drug combination choice, in whom resistant with chloroquine.<sup>10,19</sup> The recommended dose for children is 2 to 4 mg/kgBW/day (up to 200 mg/day) divided and given every 12 hours.<sup>19,21</sup> We combined quinine with doxycycline 2 mg/KgBW/day for 7 days for our sample. We give minimal dose of doxycycline to minimize the adverse effect in children.

In United Kongdom, oral quinine plus doxycyclin are effective for treatment of uncomplicated falciparum malaria in adults, as one of 3 main therapeutic options for the malaria treatment, although doxycycline recommended give to children > 12 years old.<sup>21</sup> Wolfram et al compared efficacy of three drugs (quinine, quinine-clindamycin, quinine-doxycycline) for adult who suffer falciparum malaria in hiperendemic area shown cure rate up to 90% by combination drugs and just 38% by quinine monotherapy.<sup>12</sup> The cure level of combination quinine-doxycycline in our study is up to 100% and there were no recrudence on the 28 days observation.

From our analysis that combination quinine-clindamycine was more well tolerated than combination quinine-doxycycline.. During 28 days follow up, there were 21 (17.6%) patients suffered from headache, eighteen (14.6%) vomit and 40 children (32.5%) suffered from tinnitus in quinine-doxycycline combination, compared to quinine-clindamycin combination group only 4 (3.3%) suffered from headache, one (0.8%) suffered from tinnitus and there was no vomiting experience in any patient . These adverse effect were statistically significantly different. It is already known that administration of quinine regularly causes a complex of symptoms known as *cinchonism*, which characterized in its mild form by tinnitus, impaired high tone hearing, headache, nausea, headache include vomiting, diarrhea, abdominal pain and severe vertigo.<sup>11,13</sup>

As for doxycycline, gastrointestinal effects are fewer than tetracycline, although oesophageal ulceration can still be a problem if insufficient water is taken with tablet or capsules.<sup>11,19</sup> The principal adverse effect of clindamycin is diarrhoea, in extreme cases, pseudomembranous colitis caused by *Clostridium difficile*.<sup>11,13</sup> But did not occur in any of our sample in this study.

Combination of quinine with either clindamycin or doxycycline are effective as an alternative antimalarial treatment. The combination of quinine-clindamycin is well tolerated than the combination of quinine-doxycycline, and this combination may be particular value for young children and pregnant women, as these two groups cannot receive doxycycline.

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