

The effectiveness of chloroquine compared to Fansidar in treating falciparum malaria

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ABSTRACT

Background The most difficult problem in eradicating malaria is the resistance of *P. falciparum* to drugs. Mandailing Natal has the highest malaria incidence in North Sumatera.

Objective This study aimed to investigate the efficacy of chloroquine and Fansidar in treating falciparum malaria.

Methods A randomized double-blind study was done from April to May 2001. Eighty-three patients with acute uncomplicated *P. falciparum* malaria infection were randomized into two groups. Group I (35 patients) received chloroquine and group II (48 patients) received Fansidar. Blood examinations were performed on the 1st, 2nd, 7th, and 28th days.

Results The resistance of *P. falciparum* to drugs in the chloroquine group were found in 10 patients with R II and 1 patients with R III, while in the Fansidar group, there were 14 patients with R II.

Conclusion The efficacy of chloroquine and Fansidar in treating falciparum malaria was not significantly different [**Paediatr Indones 2004;44:17-20**].

Keywords: chloroquine, Fansidar, Plasmodium falciparum, drug resistance

Malaria is the world's most important parasitic infection and ranks among the major health and developmental challenges facing a large part of the world. Malaria is endemic in 91 countries, affecting 40% of the world population. The worldwide prevalence of the disease is estimated to be 300 to 500 million clinical cases each year and the annual mortality was 0.5 to 2.5 million people.¹ In Indonesia, malaria is one of the reemerging diseases; about 35% of its population live in endemic areas. The morbidity and mortality of malaria have slightly increased over the last 4 years. The Indonesian

Family Health Survey in 1995 estimated that 15 million people suffered from malaria resulting in 30,000 deaths.²

The use of chemotherapy is very important to reduce the morbidity and mortality of malaria. Unfortunately, the most difficult problem is the resistance of *P. falciparum* to antimalarial chemotherapy. In general, resistance appears to occur through spontaneous mutations that could reduce sensitivity to drugs. The resistance is also the result of unwise use of chemotherapeutic agents, migration of populations, and the wide use of sulfonamides derivatives.^{3,4} In 1991, the resistance of falciparum malaria to chloroquine had spread to all endemic areas in Indonesia with RI–RIII gradation. The resistance to sulfadoxine-pyrimethamine was found in 10 provinces of Indonesia with RI–RII gradation.^{5,6} Mandailing Natal was a district area with the highest malaria incidence in North Sumatera, with a parasite rate (PR) of 10.65%.⁷ To our knowledge, there had been no clinical study of antimalarial drugs in this area.

The aim of this study was to know the effectiveness of chloroquine and Fansidar in the treatment of falciparum malaria in the district of Mandailing Natal.

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Methods

This randomized trial was done on 83 patients with uncomplicated malaria at 3 public health services in Mandailing Natal i.e., Panyabungan Jae, Mompang, and Siabu, from April until May 2001. The age ranged from 6 months to 80 years old.

Subjects were randomly divided into two groups. The first group (35 patients) was treated with chloroquine with an initial dose of 10 mg/kg body weight followed by 5 mg/kg body weight at 6, 24, and 48 hours. The second group (48 patients) was treated with a single dose of Fansidar (sulfa-doxine-pyrimethamine) consisting of 25 mg/kg bodyweight of sulfadoxine and 1.25 mg/kg body weight of pyrimethamine.⁸

The diagnosis was based on clinical symptoms and microscopic parasitological examination of thick and thin blood films stained with Giemsa. The resistance test was based on the criteria of resistance established by WHO i.e., *extended standard field in-vivo test*. The blood film of falciparum malaria was examined on the 1st, 2nd, 7th, and 28th day of treatment with guidelines of interpretation as follow:⁹

- 1) Sensitive (S): Clearance of asexual parasitemia within 7 days of the initiation of treatment without subsequent recrudescence within 28 days.
- 2) Resistant I (RI): Clearance of asexual parasitemia as in sensitive (S) followed by recrudescence within 28 days.
- 3) Resistant II (RII): Marked reduction (a decrease to 25% or less of pre-treatment level) of asexual parasitemia, but no clearance within 7 days.
- 4) Resistant (RIII): No marked reduction of asexual parasitemia in 48 hours.

The inclusion criteria were patients with positive falciparum malaria with a parasite density of $\geq 1000/\mu\text{l}$, had not taken any antimalarial drugs during the last 2 months, no history of antimalarial drugs hypersensitivity, and did not suffer from any other diseases.

The exclusion criteria were patients with severe illness, vomiting, infection of other kinds of malaria parasite, and pregnant woman.⁹

Only patients who continued to have examination of their blood until the 28th day were included in the analysis. Cure rate (radical clearance of parasitemia within the 28-day follow up period) was used as a primary parameter in the evaluation of drugs' effectiveness. Geometric means of variables were calculated with

non-parametric Kolmogorov-Smirnov test. Chi-square test was used to compare the 28-day cure rate; p value of <0.05 was considered significant.¹⁰

Results

During the study period, 255 patients were examined for thin and thick blood films stained with Giemsa method. Of these, 104 patients were infected by *P. falciparum* and divided into two groups i.e., the chloroquine and Fansidar group. In the Fansidar group, 4 patients were excluded because they rejected to continue blood examination. In the chloroquine group, 14 patients were also excluded for the same reason and 3 patients were excluded because of adverse effects of chloroquine. Finally, there were 48 and 35 patients in the Fansidar and chloroquine groups respectively.

Table 1 shows the characteristics of the two groups. Females were more than males. The mean of age showed that adult patients were dominant in this study. In overall, the characteristics of the two groups were not statistically different.

Physical examination showed that the most frequent symptoms and signs in uncomplicated falciparum malaria were fever, pallor, splenomegaly, hepatomegaly, and jaundice (**Table 1**).

The results of routine hematological examinations were generally within lower values except for the mean of platelet count, which was in normal values (**Table 2**). The results of hemoglobin, erythrocyte, hematocrit, and platelet count examinations on admission showed no significant difference ($p=0.979$, 0.846, 0.172, and 0.659 respectively) between the two

TABLE 1. CHARACTERISTICS OF SUBJECTS

	Chloroquine (Group 1)	Fansidar (Group 2)	p
Number of patients	35	48	
Sex			
Male	17	22	
Female	18	26	0.490
Age (years)	25.8 (21.9)*	18.9 (21.9)*	0.725
Body weight (kg)	32.2 (15.9)*	25.5 (17.7)*	0.698
Fever	33	46	0.565
Pallor	19	31	0.238
Icterus	2	3	-
Hepatomegaly	3	6	0.368
Splenomegaly	11	18	0.075

* Mean (Standard Deviation)

TABLE 2. LABORATORY RESULTS ON ADMISSION

	Chloroquine (Group 1)		Fansidar (Group 2)		p
Hemoglobin (g/dL)	10.7 (0.396)*	n=15	10.3 (0.286)*	n=32	0.979
Erythrocyte (10 ⁶ /μl)	3.77 (0.125)*	n=15	3.41 (0.105)*	n=26	0.846
Hematocrit (%)	34.9 (1.81)*	n=15	30.2 (0.91)*	n=26	0.172
Platelets (10 ³ /μl)	221 (11.51)*	n=31	227 (8.31)*	n=43	0.659
Parasite count (/μl)	3309 (1449)*	n=35	2920 (835)*	n=48	0.014

*Mean (Standard Error)

groups, but the parasite count showed significant difference ($p=0.014$).

The results of parasite count examination showed that 24 patients in the chloroquine group and 34 patients (71%) in the Fansidar group remained sensitive to the treatment. In the chloroquine group, resistance developed in 11 patients, 10 patients with RII and 1 patient with RIII. In the Fansidar group, resistance was found in 14 patients, all with RII. The difference in resistance between the two study groups was not statistically significant ($p=0.494$) as shown in Table 3.

TABLE 3. SENSITIVITY OF *P. FALCIPARUM* TO THE TREATMENT

	Chloroquine (Group 1)	Fansidar (Group 2)	p
Sensitive (S)	24	34	0.494
Resistant I (RI)	0	0	
Resistant II (RII)	10	14	
Resistant III (RIII)	1	0	

The figure of parasite count after treatment also showed similar reduction of parasites on day 2, 7, and 28 in the two groups ($p>0.05$) (Figure 1).

In this study, the adverse effects of the drugs were also recorded. During the treatment, vomiting, diarrhea, abdominal pain, and dizziness were noted as the adverse effects of chloroquine. There was no complaint in the Fansidar group.

Discussion

This study was conducted in 3 public health centers in the district of Mandailing Natal, North Sumatera province. Eighty-three patients with uncomplicated falciparum malaria were treated by chloroquine and Fansidar. In the chloroquine group, we found 10 patients with RII and 1 with RIII; only 24 of 35 remained sensitive to the drug. In the Fansidar group, there were 14 RII patients (29%), while 34 (71%)

remained sensitive.

This result was different from a previous study conducted by Panjaitan *et al* in several subdistricts of North Sumatera in 1983-1986. They found falciparum malaria patients with RI-RIII to chloroquine in 4 subdistricts, but there was no resistant case to Fansidar.¹¹

Another study by the Department of Parasitology, Medical School, University of Indonesia in 1983 noted that *P. falciparum* was resistant to chloroquine in several endemic areas in Indonesia but remained sensitive to Fansidar. Only one case in East Timor was resistant to Fansidar, which was the first in Indonesia.¹²

Tuti *et al* in 1994 conducted *in vivo* tests on 17 patients with *P. falciparum* infection treated with chloroquine and Fansidar. They found one RIII and 3 RII cases in the chloroquine group while there was no resistant case to Fansidar.¹³ This result was different from a study in 1991 which found 2 (6%) RII cases that was resistant to Fansidar.¹⁴

Ompusunggu *et al* reported a higher resistant level from Sabang, Aceh in 1984-1985. *In vitro* test had been done for falciparum malaria. They found the resistant levels were 76.7% to chloroquine and 70% to Fansidar.¹⁵

Studies of *P. falciparum* resistance had been reported from several endemic areas in Indonesia. Although the district of Mandailing Natal is an endemic area with the highest incidence of malaria in North Sumatera,⁵ there had been no previous study of plasmodium resistance in this area. According to the Ministry of Health and Social Prosperity of Indonesia, an area with a resistance level above 25%-30% is categorized as malaria resistant area. These conditions had been found in Bukit Menoreh (Jawa Tengah and Yogyakarta), Timika, and Jayapura (Papua).¹⁶

Maybe this study did not accurately describe the condition of Mandailing Natal because of the field standard procedure that could cause bias and the small sample of this study. However, these findings suggested continuous studies in the future to

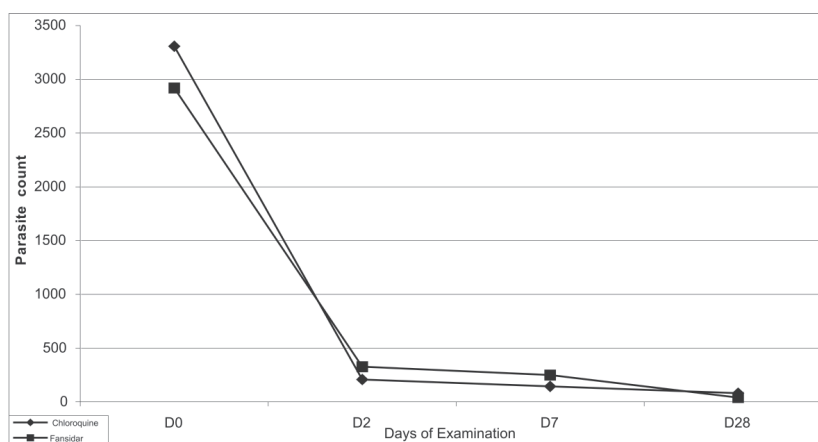


Figure 1. Parasite count after treatment

get successful malaria eradication, especially in Mandailing Natal.

We concluded that the effectiveness of chloroquine and Fansidar in the treatment of falciparum malaria was not significantly different.

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