

Treatment of Uncomplicated *In Vitro* Chloroquine Resistant Falciparum Malaria with Artemether in Irian Jaya*

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Abstrak

Malaria falsiparum resisten klorokuin merupakan masalah penanggulangan malaria yang sulit di Indonesia terutama di Irian Jaya. Artemeter adalah obat antimalaria baru yang dilaporkan sangat efektif dan aman pada uji klinik. Obat ini belum tersedia di Indonesia. Dalam rangka mendapatkan obat antimalaria alternatif untuk pengobatan malaria falsiparum resisten klorokuin, telah dilakukan uji pengobatan artemeter pada penderita malaria falsiparum tanpa komplikasi di RS Freeport, Tembagapura, Irian Jaya, Indonesia pada bulan April - November 1994. Uji pengobatan ini bertujuan untuk menilai efikasi dan keamanan artemeter. Sebanyak 66 dari 307 kasus malaria falsiparum tanpa komplikasi memenuhi syarat untuk dilakukan tes sensitivitas *in vitro*. Hanya 44 dari 54 penderita malaria falsiparum tanpa komplikasi yang *in vitro* resisten klorokuin dapat dianalisis. Penderita diobati dengan artemeter oral 1.6 mg/kg b.i.d pada hari 0 dan dosis tunggal pada hari 1-4. Semua penderita dirawat di rumah sakit sampai sembuh secara klinis dan parasitologis. Gejala dan tanda klinis utama yang ditemukan adalah sakit kepala (82 %), pucat (55 %), mual (55 %), demam (41 %) dan menggigil (39 %). Angka kesembuhan artemeter adalah 100 % (38/38, 38/38, 31/31) pada hari 7, hari 14, dan hari 21. Angka kesembuhan ini menurun menjadi 90.3 % (28/31) pada hari 28 karena adanya 3 (9.7 %) kasus rekrudesen. Angka rata-rata waktu bebas panas dan waktu bebas parasit adalah : 9 ± 10 jam dan 31 ± 10 jam (hari 7, hari 14), 8 ± 10 jam dan 30 ± 9 jam (hari 21), 8 ± 10 jam dan 29 ± 9 jam (hari 28). Sakit perut (7.9 %) dan diare (5.3 %) tercatat sebagai efek samping dari artemeter yang bersifat ringan dan sembuh tanpa pengobatan. Artemeter efektif dan aman untuk pengobatan malaria falsiparum tanpa komplikasi yang *in vitro* resisten klorokuin sampai dengan hari 21 di Timika, Irian Jaya. Modifikasi dosis dan jadwal pemberian artemeter atau kombinasi artemeter dengan obat antimalaria lain perlu diteliti untuk mendapatkan kesembuhan radikal.

Abstract

Chloroquine resistant malaria is a serious problem in Indonesia especially in Irian Jaya. Artemether is a new antimalarial drug, reported to be very effective and safe in clinical studies. This drug is not yet available in Indonesia. To obtain an alternative antimalarial drug for the treatment of chloroquine resistant falciparum malaria cases, a trial of artemether treatment for uncomplicated falciparum malaria was conducted at Freeport Hospital, Tembagapura, Irian Jaya, Indonesia in April - November 1994. The objective of the study was to assess the efficacy and tolerance of artemether. Sixty-six out of 307 uncomplicated falciparum malaria cases were eligible for *in vitro* sensitivity tests. Only 44 of the 54 uncomplicated *in vitro* chloroquine resistant falciparum malaria patients could be recruited in this study. They were treated orally with 1.6 mg/kg b.i.d on day 0 and followed by a daily dose on day 1-4. All patients were hospitalized until clinically and parasitologically cured. The most frequent symptoms and signs of these patients were headache (82 %), pallor (55 %), nausea (55 %), fever (41 %) and chills (39 %). The parasite clearance rate of artemether was 100 % (38/38, 38/38, 31/31) on day 7, day 14, and day 21. However this was reduced to 90.3 % (28/31) on day 28 because of the presence of 3 (9.7 %) recrudescence cases. The mean fever clearance times and parasite clearance times were as follow : 9 ± 10 hours and 31 ± 10 hours (day 7, day 14), 8 ± 10 hours and 30 ± 9 hours (day 21), 8 ± 10 hours and 29 ± 9 hours (day 28) respectively. Abdominal pain (7.9 %) and diarrhoea (5.3 %) were noted as the side effects of artemether, both mild and self-limiting. Artemether is effective and well tolerated for the treatment of uncomplicated *in vitro* chloroquine resistant falciparum malaria until day 21 in Timika, Irian Jaya. Modification of artemether dosage and schedule or combination of artemether with other antimalarial drugs should be studied to achieve a radical cure.

Keywords: Falciparum malaria, uncomplicated, chloroquine resistance, artemether

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INTRODUCTION

In Indonesia, only four antimalarial drugs, are available and have been registered namely : chloroquine, sulfadoxine-pyrimethamine, quinine and primaquine. Cases of *Plasmodium falciparum* resistant to these drugs and new antimalarial drugs such as mefloquine and halofantrine have been reported. However, the proportion of resistant cases is still relatively low, except in Irian Jaya, East Timor, and East Kalimantan (Figure 1).¹⁻⁶

Timika is a subdistrict of Fak-fak district of Irian Jaya province. *In vitro* sensitivity tests on falciparum malaria cases showed 64.4% resistant to chloroquine while *in vivo* studies showed resistant to chloroquine at the level of S or RI (51.3%), RII (43.6%) and RIII (5.1%).⁷ Falciparum malaria resistant to chloroquine is a serious malaria control problem in that area.

Artemether is a derivate of artemisinin (qinghaosu), a new antimalarial which has been developed in China as an extract of the traditional medicinal herb Qinghao (*Artemisia annua L.*). Clinical trials of artemether have shown to have high efficacy against uncomplicated and complicated falciparum malaria, vivax malaria, chloroquine and multidrug resistant *P. falciparum*. Artemether has a rapid onset of action and destroys asexual parasites at an early stage of development. No resistance to this drug has yet been demonstrated and it has low toxicity.⁸⁻¹¹ This drug is not yet available commercially in Indonesia.

In the search for an alternative antimalarial drug for the treatment of chloroquine resistant falciparum malaria, a trial of artemether treatment for uncomplicated *in vitro* chloroquine resistant falciparum malaria cases was conducted in Timika, Irian Jaya. The objective of the study was to assess the efficacy and tolerance of artemether in Indonesian patients.

MATERIALS AND METHODS

This is a collaborative study between the Ministry of Health, Jakarta; the University of Indonesia, Jakarta; and Freeport Hospital, Tembagapura, Timika, Irian Jaya, Indonesia.

Study site and duration of study

The study was conducted in Timika Health Center for *in vitro* drug sensitivity test. The treatment trial was carried out at the Freeport Hospital in Tembagapura, Timika, Irian Jaya, Indonesia where there is no malaria

transmission (altitude around 2,000 m). This study was performed during April - November 1994.

Study design

The study was an open, selected trial of artemether treatment in uncomplicated falciparum malaria which was shown to be *in vitro* chloroquine resistant prior to initiation of therapy.

Patients

A total of 66 uncomplicated falciparum malaria patients were selected through Active Case Detection (ACD) and Passive Case Detection (PCD) according to WHO criteria for *in vitro* and *in vivo* antimalarial sensitivity tests.¹²

1. Age over 12 years old.
2. Positive blood smear of the asexual forms of *P. falciparum* with parasite density about 1,000 - 60,000/ μ l and 500 - 100,000 μ l for *in vitro* and *in vivo* sensitivity test.
3. Without complications or other diseases.
4. Non-pregnant or non-lactating females.
5. No exposure to antimalarials, as treatment or prophylaxis in the past 14 days, urine test negative on Dill-Glazko and Lignin test.
6. Able to swallow oral drug.
7. No history of hypersensitivity to antimalarial drugs.
8. Willingness to participate and sign the informed consent form.

Setting

The sixty-six consenting patients were hospitalized at Timika Health Center for two days for close observation, during which *in vitro* antimalarial drug sensitivity test was performed.

To assure patient's safety during the *in vitro* test, the patient should be in this following conditions :

1. No signs and/ or symptoms of severe and complicated malaria.
2. The parasite density not exceeding 100,000/ μ l.

Patients harboring parasites shown to be *in vitro* sensitive to chloroquine were discharged and treated with standard chloroquine regimen. Patients with parasites shown to be *in vitro* resistant to chloroquine were send to Freeport Hospital, treated with artemether, and observed clinically and parasitologically for at least 7 days or until clinically and parasitologically cured.

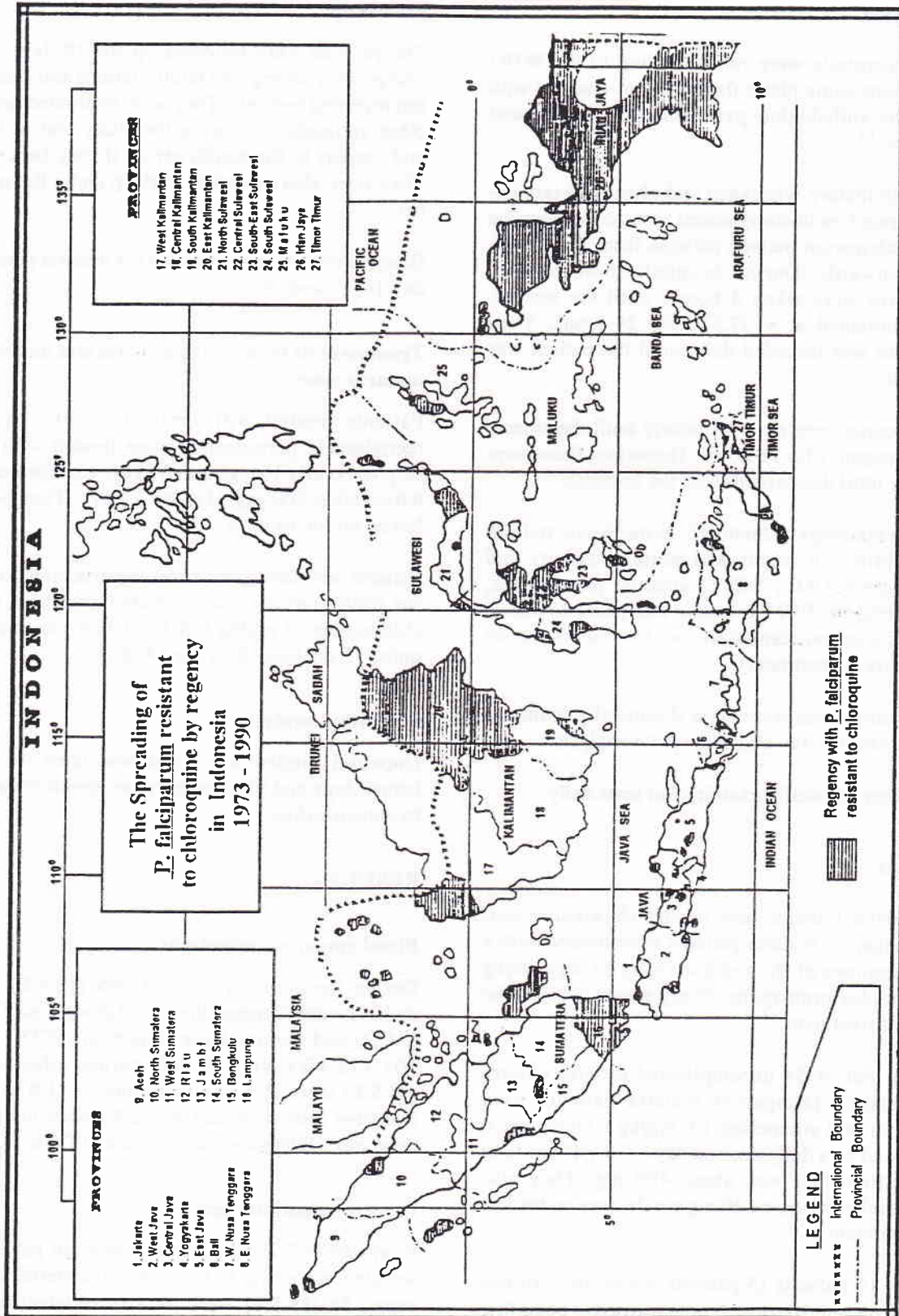


Figure 1.

Investigation

In vitro microtests were run according to the WHO specifications using plates that were pre-charged with chloroquine, sulfadoxine- pyrimethamine, quinine and mefloquine.¹³

A thorough history was taken and physical examination performed on uncomplicated *in vitro* chloroquine resistant falciparum malaria patients from time of admission onwards. During hospitalization, axillary temperatures were taken 4 hourly until the temperatures maintained at < 37.5°C for 24 hours. Then temperature was recorded daily until the patient was discharged.

Parasite counts were done 12 hourly until the smears remained negative for 36 hours. Thereafter, these were done daily until discharged from the hospital.

Routine hematology (hematocrit, hemoglobin, red cell count, white cell count and platelet count) and biochemistry (SGOT, SGPT, alkaline phosphatase, bilirubin, protein, BUN, creatinin and glucose) exams were conducted on admission (pre-treatment) and on discharge (post-treatment).

Other investigations were done if clinically indicated eg : ECG, chest X-ray and electrolyte analysis.

Patients were clinically examined at least daily.

Treatment

Seven patients found to have *in vitro* chloroquine sensitive falciparum malaria patients were treated with a standard regimen of chloroquine orally 25 mg base/kg for 3 days plus primaquine 30 mg single dose on the first day of treatment.¹⁴

Forty-four out of 54 uncomplicated *in vitro* chloroquine resistant falciparum malaria patients were treated with oral artemether 1.6 mg/kg b.i.d on day 0 and followed by a daily dose on day 1 - day 4. The total dose of artemether was about 480 mg. They also received oral primaquine 30 mg single dose on the last day of treatment.

The other 15 patients (5 patients whose *in vitro* test failed to grow and 10 patients who refused to be further hospitalized) were treated with oral quinine sulphate 10 mg/kg t.i.d for 7 days plus oral primaquine 30 mg, single dose.¹⁴

Follow up

The patients were followed up for 28 days. On discharge, they were given multivitamins and insecticide-impregnated bed nets. They were instructed not to take other antimalarials during the study and to immediately report to the health center if they become sick. They were also requested to sleep under the mosquito net.

Blood smears were rechecked for malaria parasites on day 14, 21 and 28.

Treatment of recurrent parasitaemia and vivax malaria cases

Patients treated with artemether who developed recrudescence parasitaemia were treated with quinine sulphate orally 10 mg/kg BW/dose, t.i.d for 7 days plus tetracycline 500 mg t.i.d for 7 days. They were followed up for 14 days.

Patients who developed vivax malaria infection during the follow up days were treated with oral standard chloroquine 25 mg/kg BW for 3 days plus oral primaquine 15 mg base daily for 14 days.

Statistical analysis

Unpaired Student's t - test was used to compare hematology and biochemistry pre-treatment and post-treatment values.

RESULTS

Blood smear examinations

During the study, a total of 586 (18.6%) cases of malaria were detected through Active Case Detection (ACD) and Passive Case Detection (PCD). Of these 307 (52.4%) were *P. falciparum* infections, 261 (44.5%) were *P. vivax* infections, 9 (1.6%) were *P. malariae* infections and 9 (1.5%) were mixed infections of *P. falciparum* and *P. vivax* (Table 1).

In vitro sensitivity test

From the 307 *P. falciparum* cases, 66 patients were selected according to the protocol criteria. Of the 66 cases, 54 (88.5%) were *in vitro* resistant to chloroquine, 7 (11.5%) were sensitive to chloroquine and 5 (7.6%) had failed to grow. Only 44 of the 54 uncomplicated *in vitro* chloroquine resistant patients could be

recruited in this study. The other 10 patients dropped out because they refused to be further hospitalized (Table 2).

P. falciparum also showed resistance (82.7%) to sulfadoxine-pyrimethamine, however all isolates were sensitive to quinine and mefloquine. Among 51 uncomplicated falciparum malaria cases, 25 (49.0%) patients were resistant to chloroquine and sulfadoxine-pyrimethamine (Table 2).

Characteristics of patients

They were 25 males and 19 females, ranging in age and weight of between 13 and 48 years, and 25 and 84 kg

respectively. Less than 50% were native Irians and 59.1% had previously experienced malaria, with attack frequency in the last one year ranging between 1 and 12 times. Duration of illness, axillary temperatures and parasite counts on admission ranged between 11 and 90 days, 36.0 and 40.0°C, 560 and 99,220/ul respectively (Table 3).

Clinical events

The most frequent clinical symptoms and signs in uncomplicated *in vitro* chloroquine resistant falciparum malaria patients were headache, pallor, nausea, fever and chills (Table 4).

Table 1. Results of thick and thin blood smear examination in Timika, Irian Jaya, April - November 1994.

Result	ACD*	PCD**	Total
Number of negative cases (%)	2,166 (81.6)	397 (80.0)	2,563 (81.4)
Number of positive cases (%)	487 (18.4)	99 (20.0)	586 (18.6)
<i>P. falciparum</i> infection	252 (9.5)	55 (11.1)	307 (8.7)
<i>P. vivax</i> infection	222 (8.4)	39 (7.9)	261 (8.3)
<i>P. malariae</i> infection	6 (0.2)	3 (0.6)	9 (0.3)
Mixed infection	7 (0.3)	2 (0.4)	9 (0.3)
Number examined	2,653 (100.0)	496 (100.0)	3,149 (100.0)

* ACD = Active Case Detection

** PCD = Passive Case Detection

Table 2. Results of *in vitro* sensitivity test to 4 antimalarial drugs in uncomplicated falciparum malaria cases in Timika, Irian Jaya, April - November 1994.

Antimalarial	Number examined	Failure (%)	Sensitive (%)	Resistant (%)
Chloroquine	66	5 (7.6)	7 (11.5)	54 (88.5)
Sulfadoxine-pyrimethamine	64	12 (18.8)	9 (17.3)	43 (82.7)
Quinine	64	5 (7.8)	59 (100.0)	0
Mefloquine	66	5 (7.6)	61 (100.0)	0

Note : 25 out of 51 (49.0%) cases were resistant to chloroquine and sulfadoxine -pyrimethamine.

Table 3. Characteristics of uncomplicated *in vitro* chloroquine resistant falciparum malaria patients at Freeport Hospital, Tembagapura, Irian Jaya, April - November 1994.

Age = $x \pm SD$ year	22 \pm 9
Sex = male : female	25 : 19
Race = Irian : others	18 : 26
Duration of illness = $x \pm SD$ day	10 \pm 14
Malaria previously = yes : no	26 : 18
Malaria frequency in the last 1 year = $x \pm SD$ time	3 \pm 3
Weight = $x \pm SD$ kg	47 \pm 12
*Axillary temperature = $x \pm SD$ °C	37.6 \pm 1.0
*Parasite count = $x \pm SD$ / μ l	12,158 \pm 23,282

* on admission
Total number of patients = 44.

Table 4. Clinical events of uncomplicated *in vitro* chloroquine resistant falciparum malaria patients at Freeport Hospital, Tembagapura, Irian Jaya, April - November 1994.

Clinical event	Number of patient (%)
Headache	36 (82)
Pallor	24 (55)
Nausea	24 (55)
Fever	18 (41)
Chill	17 (39)
Abdominal pain	16 (36)
Splenomegaly	14 (32)
Vomiting	7 (16)
Hepatomegaly	5 (11)
Diarrhoea	4 (9)
Oliguria	4 (9)
Dyspnea	4 (9)
*Others	7 (16)

* Jaundice, brownish urine, cough, myalgia and chest pain.
Total number of patients = 44.

Laboratory test results

The results of the routine haematology and biochemistry examinations were generally within normal values on admission (pre-treatment) and discharge (post-treatment) except the mean platelet counts, which were low (< 150 /nl) on admission. However,

some laboratory test results on admission and discharge showed significant differences: mean platelet counts, serum bilirubin, protein, creatinine and glucose, improved or remained within normal values during hospitalization (Table 5).

Table 5. Result of laboratory tests of uncomplicated *in vitro* chloroquine resistant falciparum malaria patients at Freeport Hospital, Tembagapura, Irian Jaya, April - November 1994.

Laboratory test	On admission* $x \pm SD$	On discharge** $x \pm SD$	Student's* t-test
Hematocrit (%)	32.7 \pm 5.0	33.4 \pm 5.1	NS
Hemoglobin (g%)	11.2 \pm 1.8	11.3 \pm 2.0	NS
Red cell count (/pl)	4.3 \pm 0.8	4.3 \pm 0.6	NS
White cell count (/pl)	8.1 \pm 3.0	8.1 \pm 3.1	NS
Platelet (/nl)	118.9 \pm 79.5	253.7 \pm 121.6	S
Reticulocyte (%)	1.4 \pm 0.5	1.7 \pm 0.8	NS
SGOT/ASAT (IU)	31 \pm 18	29 \pm 17	NS
SGPT/ALAT (IU)	27 \pm 17	30 \pm 21	NS
Alkaline phosphatase (IU)	149 \pm 60	142 \pm 40	NS
Total bilirubin (mg%)	1.1 \pm 0.8	0.7 \pm 0.2	S
Protein (mg%)	5.9 \pm 0.7	6.3 \pm 0.8	S
BUN (mg%)	30 \pm 17	28 \pm 8	NS
Creatinine (mg%)	0.8 \pm 0.2	0.7 \pm 0.2	S
Glucose (mg%)	103 \pm 39	89 \pm 22	S

* Total number of patients = 44

** Total number of patients = 38

NS = Not Significant

S = Significance level at $p < 0.05$.

Efficacy of artemether

Of the 44 patients treated with artemether, 38 cases completed the study. One patient requested to withdraw from the study, one patient had a urinary tract infection and 4 patients had parasite counts less than 500 / μ l on admission.

The Parasite Clearance Rate (PCR) of artemether was 100 % on day 7 (38/38) and day 14 (38/38). On day 21, 7 patients developed *P. vivax* malaria, however the *P. falciparum* PCR was still 100 % (31/31). The PCR was 90.3% (28/31) on day 28 because of the presence of 3 (9.7%) recrudescence cases (Table 6).

The Fever Clearance Time (FCT) ranged from 0 to 30 hours, and the mean FCT was 9 ± 10 hours on day 7 and 14, and 8 ± 10 hours on day 21 and 28. The Parasite Clearance Time (PCT) ranged from 11 to 47 hours and the mean PCT was 31 ± 10 hours on day 7 and 14, 30 ± 9 hours on day 21, and 29 ± 9 hours on day 28 (Table 6).

Side effects

A side effect was defined as a symptom or sign appearing only after drug administration. During treatment, abdominal pain (7.9%) and diarrhoea (5.3%) were noted as side effects of artemether, which were mild and self-limiting (Table 7).

DISCUSSION

Previous studies have shown that Irian Jaya is the worst area affected by chloroquine resistant *P. falciparum* in Indonesia.^{1-4,7} The spread of parasites resistant to antimalarial drugs and the ability of *P. falciparum* to develop resistance to antimalarial drugs poses a therapeutic challenge.

Currently, quinine is still the first drug of choice for chloroquine resistant falciparum malaria in Irian Jaya. The present study shows that *P. falciparum* is still sensitive to quinine and also to mefloquine.

Patient's compliance is a problem for quinine treatment, due to impractical quinine administration and unpleasant side-effects. Poor compliance results in treatment failure and lessens the drug's utility.

Artemether is a promising antimalarial for multiple drug resistant falciparum malaria. Data on the use of oral artemether are limited. This trial has demonstrated the good efficacy of artemether in the treatment of uncomplicated *in vitro* chloroquine resistant falciparum malaria. The 90.3% cure rate (PCR) was similar to that reported in other studies (88 - 98%).¹⁵⁻¹⁷ Different dosage (480 mg/5d vs 700-750 mg/5d) and additional primaquine might influence this therapeutic response. Other therapeutic responses, the mean FCT and PCT were shorter (8 and 29 hours) than previous studies (30-42.6 and 34-39.9 hours).¹⁵⁻¹⁷ This differences might be due to different characteristics and conditions of patients on admission (Table 8).

Table 6. Efficacy of capsule artemether in uncomplicated *in vitro* chloroquine resistant falciparum malaria patients at Freeport Hospital, Tembagapura, Irian Jaya, April - November 1994.

Day of observation	Number of cases	PCR = S/(S+R)%	FCT = (x±SD)h	PCT (x±SD)h	Note
7	38	38/38 (100)	9±10	31±10	6 out of 44 cases were dropped out
14	38	38/38 (100)	9±10	31±10	
21	31	31/31 (100)	8±10	30±9	7 out of 38 cases developed Pv infection 3 out of 31 cases developed recrudescences
28	31	28/31 (90.3)	8±10	29±9	

PCR = Parasite Clearance Rate

FCT = Fever Clearance Time

PCT = Parasite Clearance Time

S = Sensitive cases

R = Recrudescence cases

Table 7. Side-effects of artemether in uncomplicated *in vitro* chloroquine resistant falciparum malaria patients at Freeport Hospital, Tembagapura, Irian Jaya, April - November 1994.

Side effect	Number of cases (%)*
Abdominal pain	3 (7.9)
Diarrhoea	2 (5.3)

* Total number of patients = 38

Table 8. Reported clinical trials of oral artemether in uncomplicated falciparum malaria from Thailand and Indonesia, 1992 - 1995.

References	Karbwang et al 1992	Karbwang et al 1993	Looreesuwan et al in press	Tjitra et al 1995
Country	Thailand	Thailand	Thailand	Indonesia
Follow-up period (days)	28	28	28	28
Dose (mg)	700/5d	700/5d	750/7d	480/5d
No of evaluable cases	34	50	58	38
FCT (min-max hours)	30 (4-108)	42.6 (8-182)		8 (0-30)
PCT (min-max hours)	34 (18-84)	39.9 (20-68)		29 (11-47)
Cure rate (%)	97	88	98	90.3

The correct dose of artemether for treatment of multiple drug resistant falciparum malaria has yet to be defined. In the dose ranging study, the total dose and duration of drug administration correlated with the cure rate but not with PCT.¹⁸ The 1.6 mg/kg BW/dose or the total of 480 mg recommended by Kunming Pharmaceutical Factory may not be suitable to effect radical cure in Irian Jaya where multiple drug resistance is common. Increasing the dose and /or prolonging the duration of artemether administration may be needed to cure falciparum malaria, but these are not the solution because these measures are not practical in the field and will reduce patient's compliances. Modification of artemether dosage and schedule or combination of artemether with other antimalarial drugs which produce synergistic effect might solve this problem.

In this study, vivax malaria cases were found on day 21. Rapid elimination of artemether may be responsible for the appearance of *P. vivax*.¹⁵ Several previous studies also reported vivax malaria occurred in artemether-treated patients.^{9,15,19}

Laboratory findings showed no evidence of toxicity by artemether either hematologically or biochemically. There was evidence of only mild intolerance of artemether (abdominal pain and diarrhoea), which proved self-limiting. This present study had similar clinical side-effects to other studies.^{15,20}

CONCLUSION

Oral artemether at about 480 mg given over 5 days is effective and well tolerated for treatment of uncomplicated *in vitro* chloroquine resistant falciparum malaria in Timika, Irian Jaya. A larger sample size is needed to evaluate various possible dosage schedules for artemether. To achieve a radical cure, modification of the

artemether dosage and schedule or combination of artemether with other antimalarial drugs which have synergistic effect should be studied.

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