Comparative Study of Artemether and Quinine Treatment in Severe and Complicated Falciparum Malaria at Balikpapan General Hospital

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Abstrak

Untuk mendapatkan obat antimalaria alternatif yang dapat mengurangi komplikasi dan kematian, telah dilakukan uji klinis perbandingan artemeter dan kina pada penderita dewasa malaria falsiparum berat dan dengan komplikasi di RSU Balikpapan, Kalimantan Timur, Indonesia, pada tahun 1993 - 1995. Tujuan penelitian ini adalah untuk mengukur dan membandingkan efektivitas dan toleransi artemeter intramuskulus dan kina dihidroklorida intravena. Enam puluh penderita malaria falsiparum berat dan dengan komplikasi yang memenuhi syarat, diacak untuk mendapat artemeter intramuskular 1,6 mg/kg BB/dosis, 2X/hari pada hari 0 dan dilanjutkan 1X/hari pada hari 1-4; atau kina dihidroklorida intravena 20 mg garam/kg BB dalam 10 ml/kg BB dextrosa 5% dalam 4 jam, dilanjutkan dengan 10 mg garam/kg BB/dosis, 3X/hari dan secepatnya diganti dengan kina peroral apabila penderita dapat menelan obat sampai total mencapai 21 dosis. Mereka dirawat minimal selama 14 hari atau sampai sembuh secara klinis dan parasitologis. Dari 60 penderita tersebut ditemukan kasus 47% dengan 1 komplikasi, 28% dengan 2 komplikasi, 17% dengan 3 komplikasi dan 8% dengan >3 komplikasi. Komplikasi yang sering ditemukan adalah hiperbilirubinemia (50%), hiperparasitemia (28%) dan malaria otak (25%). Angka kematian tertinggi berhubungan dengan hiperkreatininemia, perdarahan, oedema paru, asidosis dan syok septik. Angka kematian menyeluruh adalah 18,3% (11/60), pada kelompok artemeter 13,3% (4/30), dan pada kelompok kina 23,3% (7/30), tapi perbedaan ini tidak bermakna. Angka kematian karena malaria otak adalah 53,3% (8/15). Kecenderungan kematian meningkat dengan meningkatnya jumlah komplikasi. Sampai dengan hari ke 14, tidak ditemukan perbedaan bermakna di antara ke 2 kelompok tersebut pada angka kesembuhan (87% vs 77%), angka bebas parasit (100% vs 100%), rata-rata waktu bebas panas (35,5±23,3 jam vs 37,4±24,7 jam), waktu bebas parasit (38,9±16,9 jam vs 41,8±14,7 jam) dan waktu kesadaran baik (32±14,1 jam vs 62,8±19,2 jam). Artemeter intra muskulus adalah aman dan sama efektivitasnya dengan kina intravena pada pengobatan malaria falsiparum berat dan dengan komplikasi. Obat ini baik sebagai pengganti kina, terutama di daerah yang terpencil dimana fasilitas perawatan dan pengobatan dengan infus atau intravena tidak tersedia.

Abstract

To obtain an alternative drug regimen to reduce the complications and mortality of malaria, a comparative clinical trial of artemether and quinine in severe and complicated falciparum malaria patients was carried out at Balikpapan General Hospital, East Kalimantan, Indonesia, in 1993-1995. The objectives of this study was to assess and compare the efficacy and safety of intramuscular artemether and intravenous quinine dihydrochloride in adult malaria patients. The sixty eligible severe and complicated falciparum malaria cases were randomized to receive either artemether intramusculary 1.6 mg/kg bw/dose bid on day 0 and followed by a daily dose on day 1-4 or quinine dihydrochloride intravenously 20 mg salt/kg bw in 5% dextrose 10 ml/kg bw in 4 hours, followed by 10 mg/kg bw tid which was switched to oral quinine when the patient was able to swallow oral quinine, for a total of 21 doses. They were hospitalized for at least 14 days or longer. One, two, three and more than three complications were found in 47%, 28%, 17% and 8% of the 60 patients respectively. The most common complications were hyperbilirubinaemia (50%), hyperparasitaemia (28%) and cerebral malaria (25%). The highest fatality rates were associated with hypercreatininaemia, bleeding, pulmonary edema, acidosis and septic shock. The overall mortality rate was 18.3% (11/60). It was 13.3% (4/30) in the artemether group and 23.3% (7/30) in the quinine group, but this difference was not statistically significant. The case fatality rate of cerebral malaria cases was 53.3% (8/15). The risk of death increased with the number of complications. As assessed on day 14, there were no significant differences between the treatment groups in the survival rate (87% vs 77%), parasite clearance rate (100% vs 100%), mean fever clearance time (35.5±23.3 h vs 37.4±24.7 h), mean parasite clearance time (38.9±16.9 h vs 41.8±14.7 h) and mean consciousness recovery time (32±14.1 h vs 62.8±19.2 h). Intramuscular artemether was well tolerated and as effective as intravenous quinine for the treatment of severe and complicated falciparum malaria. This drug is a good alternative to quinine, particularly in remote areas lacking hospitals and the capability for intravenous infusion.

Keywords : *severe malaria, comparative clinical trial*

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The development of resistance to antimalarial drugs poses a serious therapeutic challenge especially in the treatment of severe and complicated falciparum malaria. Multidrug resistant *P. falciparum* had been reported in East Kalimantan.[1-2] Therefore, new drugs with better efficacy need to be studied.

In Indonesia, severe and complicated falciparum malaria occur in about 10% of patients hospitalized with falciparum malaria. The mortality rate is up to 50%.[3-7] Though quinine is still considered a life-saving drug for severe malaria cases, an alternative drug to reduce the complications and mortality is desirable.

Artemisinin, a sesquiterpene lactone peroxide, was first isolated from the Chinese herb Qing-Hao *(Artemesia annua L)* in 1972. This drug and its derivates have powerful antimalarial activity, although their pharmacokinetic properties have not been well characterized. They have been widely and successfully used to treat severe falciparum malaria.[8] Studies performed in recent years in malarious areas have confirmed the efficacy and safety of artemisinin derivates in the treatment of severe and chloroquine resistant falciparum malaria.[9-10] However, it has not been established that these drugs offer advantages over quinine with regard to reducing mortality or sequelae in severe malaria.

Artemether, an oil-based methyl ether of artemisinin for intra muscular injection has a rapid schizontocidal effect in vivo. The ease of administration and the low toxicity of artemether have accounted for its replacing quinine for the first-line treatment of severe and complicated falciparum malaria in some countries.[11- 12] Since artemether is not yet available commercially in Indonesia, it appears worthwhile to perform an artemether clinical trial in Balikpapan, East Kalimantan to assess and compare the efficacy and safety of intramuscular artemether and intravenous quinine dihydrochloride in the treatment of severe and complicated falciparum malaria in adults.

METHODS

This study was a collaborative study between the Ministry of Health, Jakarta, the University of Indonesia, Jakarta, and Balikpapan General Hospital, Balikpapan.

Ethical clearance was obtained from The Committee of Health Research Ethics, National Institute of Health Research and Development, Ministry of Health, Jakarta, on January 14, 1993.

Study site and time of study

The study was carried out at Balikpapan General Hospital, Balik papan, East Kalimantan, Indonesia, during 1993-1995.

Study design

The study was an open label, randomized study comparing intramuscular artemether with intravenous quinine dihydrochloride for the treatment of severe and complicated falciparum malaria in adult patients.

Drugs

Artemether was supplied by Rhone Poulenc Rorer Doma, and packaged in 1 ml ampoule of 80 mg artemether. Quinine dihydrochloride was purchased from Kimia Farma and packaged in 2 ml ampoule of 250 mg base of quinine dihydrochloride/ml. Primaquine 15 mg base/ tablet and tetracycline 250 mg/capsule were also purchased from Kimia Farma.

Patients

Sixty severe and complicated falciparum malaria patients were selected according the WHO criteria for in vivo antimalarial sensitivity testing.[13] These criteria were:

1. Over 12 years of age.
2. Female should be non-pregnant or non-lactating.
3. The presence of asexual forms of *P. falciparum* in blood smears.
4. No ingestion of antimalarial drug in the previous 12 hours.
5. No history of hypersensitivity to antimalarials.
6. The absence of any other serious illness.
7. Informed consents were obtained from the patients or their relatives.

The presence of one or more of the following manifestations in falciparum malaria patients was sufficient for the diagnosis of severe and complicated falciparum malaria:[14-17]

Cerebral malaria

Glasgow Coma Scale (GCS) was used to assess the depth of coma in cerebral malaria. A total score of GCS less than 9 and persisting for more than 30 minutes after convulsion was considered unrousable coma.

Impaired consciousness

The unconscious malaria patient was still rousable, responded to stimulus and could be awakened.

Repeated generalized convulsions

Malaria with more than two generalized convulsions within 24 hours despite fever control.

Prostration, extreme weakness

The malaria patient could not sit or walk with unexplainable neuropathology.

Fluid, electrolyte and acid-base disturbances

Malaria with dehydration and or acidosis with arterial blood PH < 7.25 and plasma bicarbonate < 15 mmol/l.

Circulatory collapse (algid malaria)

Malaria with hypotension (systolic BP less than 70 mm Hg in supine position) and signs of peripheral circulatory failure such as cold, clammy, cyanotic skin and constriction of peripheral vessels.

Spontaneous bleeding and clotting disorders or disseminated intravascular coagulation (DIC)

Malaria with retinal or subconjunctival haemorrhages, bleeding from the gums, epistaxis, melena, haematemesis and/or signs of DIC such as increased plasma fibrinogen and decreased antithrombin III.

Pulmonary edema

Malaria with cough, a feeling of oppression in the chest and difficulty in breathing, dyspnea, crepitations and cyanosis.

Gastrointestinal symptoms

Malaria with persistent vomiting and/or diarrhoea.

Hyperpyrexia

Malaria with body temperature (axillary) above 40.5°C or 105°F.

Severe anaemia

Malaria with a normocytic anaemia, haematocrit less than 15% or haemoglobin less than 5 g%.

Jaundice

Malaria with jaundice, palpable liver and bilirubin more than 50 µmol/l or more than 3 mg%.

Hypoglycaemia

Malaria with blood sugar less than 40 mg% or less than 2.2 mmol/l, symptoms of anxiety, confusion, breathlessness, sweating and neurological symptoms.

Renal failure

Malaria with urine output less than 400 ml in 24 hours after rehydration and a serum creatinine more than 265 µmol/l or more than 3 mg%.

Haemoglobinuria and blackwater fever

Malaria with black urine rather than red or brown as in other cases of massive haemolysis.

Hyperparasitaemia

Malaria with the density of asexual forms of *P. falciparum* in the peripheral blood smears exceeding 5% of the erythrocytes (more than 250,000 parasite per µl at normal red cell counts).

Setting

All patients were hospitalized and observed clinically and parasitologically for at least 14 days or untill the patient was cured.

Clinical evaluation

A thorough history was taken and physical examination was performed on each study subjects at the time of admission. Physical examination was repeated daily during hospitalization. Daily axillary temperatures were taken 4 hourly at 2^{oo}, 6^{oo}, 10^{oo} a.m. and p.m. until the patient became afebrile (< 37.5°C) for 24 hours. Thereafter, temperatures were taken daily.

Thick and thin blood smears were taken 12 hourly at 8^{oo} a.m. and p.m. for parasite counts until the asexual forms were cleared for 3 consecutive examinations. Thereafter, smears were performed daily until discharge.

Routine haematology (haematocrit, haemoglobin, red cell count, white cell count, platelet count and reticulocyte count) and biochemistry (SGOT, SGPT, alkaline phosphatase, bilirubin, protein, BUN, creatinine and glucose) were done on admission (pretreatment), on discharge (post-treatment), and at other times depending on the clinical state of the patient. Other investigations were done if clinically indicated e.g.: lumbar puncture, EKG, chest X-ray and electrolyte analysis.

Patients were reviewed at least once a day.

Treatment

Thirty patients were treated with intramuscular artemether 1.6 mg/kg bw, 12 hourly on day 0 and daily on day 1-4. Another 30 patients were treated with

intravenous quinine dihydrochloride 20 mg salt/kg bw or 16.7 mg base/kg bw in 10 ml/kg bw of 5% dextrose infused in 4 hours followed by 10 mg salt or 8.3 mg base/kg bw, 8 hourly. As soon as the patient could swallow medication, intravenous quinine was replaced by oral quinine sulphate 10 mg salt/kg bw/dose, 8 hourly, up to a total of 21 doses.

In addition, all patients were also treated with primaquine 30 mg, single dose, to get radical cured. It was given when the patients could swallow the drug or on the last day of treatment.

Patients who had persistent positive blood smears or negative smears followed by positive smears on day 7, or day 14, were treated with quinine sulphate orally 10 mg salt/kg bw, 8 hourly for 7 days and tetracycline 500 mg, 8 hourly for 7 days. All patients were followed up for 14 days after treatment.

Data analysis

The efficacy or therapeutic response of these antimalarial drugs was measured by survival rate (SR), parasite clearance rate (PCR), fever clearance time (FCT), parasite clearance time (PCT) and recovery time (RT).

SR was defined by the survival at the end of the hospitalization period (14 days). PCR was the proportion of cases showing clearance of asexual forms of parasites by day 14.

The rapidity of the response was based on FCT, PCT and RT. FCT was the time (hours) after treatment required for body temperature to return to normal (< 37.5°C). PCT was the time (hours) after treatment required for parasite count to fall below the level of microscopic detection. RT was the time taken for the cerebral malaria patients to completely recover from unconsciousness.

A side effect was defined as a symptom or sign appearing only after drug administration, that was not the classic symptom or sign of malaria infection.

Statistical analysis

Chi-square (X^2) and Fisher's exact tests were used to compare the characteristics, clinical presentations, survival rate, parasite clearance rate and case fatality rate in the artemether and quinine groups. Unpaired Student's t-test was used to compare the characteristics, haematology and biochemistry values, fever and parasite clearance times and consciousness recovery time between the two groups.

RESULTS

Of the 60 severe and complicated falciparum malaria patients, there were 51 (85%) males and 9 (15%) females, ranging in age and weight between 15 and 64 years, and 40 and 71 kg respectively. Among them, only 8 (13%) were native and only 3 (5%) had previously experienced malaria in the last 6 months with frequency ranging between 1 and 3 times. Duration of illness, axillary temperatures and parasite counts on admission ranged between 3 and 16 days, 36 and 40.8°C, and 174 and 384,780/µl respectively.

Comparative characteristics between treatment groups

Comparison of the characteristics (age, sex, race, duration of illness, previous history of malaria, malaria frequency in the last 6 months, weight, axillary temperature and parasite count) revealed no significant differences between the two groups (Table 1).

Comparative clinical presentations between treatment groups at enrollment

The most frequent (>50%) clinical symptoms and signs in both groups were fever, hepatomegaly, jaundice, pallor and splenomegaly. Oliguria or anuria and cough were more common in the artemether group, abdominal pain in the quinine group, and these differences were statistically significant (Table 2).

Comparative laboratory test results between treatment groups

Most results of routine haematology and biochemistry examinations were abnormal on admission (pre-treatment), except the white cell and platelet counts, serum protein and glucose which were within normal values. There were no differences between the two groups except for a lower platelet count in the quinine group (Table 3).

The results of all laboratory tests from both groups improved and became normal on discharge from the hospital (post-treatment). There were no significant differences between the two groups (Table 4).

Clinical manifestations and morbidity rates in the treatment groups

Among 60 severe and complicated falciparum malaria patients, 28 (47%), 17 (28%), 10 (17%) and 5 (8%) were cases with single, two, three and more than three

Table 1. Comparison of characteristics of severe and complicated falciparum malaria patients between the treatment groups on admission at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Characteristic	Artemether group*	Quinine group†	Student's t or chi-square test
Age = ($\bar{x}$ ± SD) year	28 ± 10	28 ± 10	NS
Sex = male : female	26 : 4	25 : 5	NS
Race = native : others	4 : 26	4 : 26	NS
Duration of illness = ($\bar{x}$ ± SD) day	8 ± 5	9 ± 4	NS
Malaria previously = yes : no	1 : 29	2 : 28	NS
Malaria frequency in the last 6 mo = ($\bar{x}$ ± SD) time	1 ± 0	2 ± 1	NS
Weight = ($\bar{x}$ ± SD) kg	51 ± 4	52 ± 6	NS
Axillary temperature = ($\bar{x}$ ± SD)°C	38.6 ± 1.3	38.8 ± 1.5	NS
Parasite count = ($\bar{x}$ ± SD) /µl	57,673 ± 62,551	80,335 ± 100,465	NS

* N = 30
† N = 30
NS = Not Significant ($P > 0.05$)

Table 2. Comparison of clinical presentations of severe and complicated falciparum malaria patients between the treatment groups on admission at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Clinical events	Artemether group (%)*	Quinine group (%)†	Chi-square test
Fever	23 (77)	28 (93)	NS
Hepatomegaly	22 (73)	19 (63)	NS
Jaundice	20 (67)	24 (80)	NS
Pallor	18 (60)	15 (50)	NS
Splenomegaly	18 (60)	15 (50)	NS
Headache	16 (53)	13 (43)	NS
Nausea	13 (43)	17 (57)	NS
Impaired consciousness	9 (30)	11 (37)	NS
Chill	9 (30)	16 (53)	NS
Vomiting	7 (23)	14 (47)	NS
Brownish/blackish urine	7 (23)	10 (33)	NS
Oliguria/anuria	6 (20)	1 (3)	S
Cough	5 (17)	1 (3)	S
Abdominal pain	4 (13)	10 (33)	S
Ronchi/crepitation	2 (7)	2 (7)	NS
Convulsion	1 (3)	1 (3)	NS
Diarrhoea	1 (3)	0	
Bleeding	0	2 (7)	
Dyspnoea	0	1 (3)	

* N = 30
† N = 30
NS = Not Significant ($P > 0.05$)
S = Significant ($P < 0.05$)

Table 3. Comparison of laboratory tests of severe and complicated falciparum malaria patients between the treatment groups on admission (pre-treatment) at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Laboratory test	Artemether group* ($\bar{x} \pm SD$)	Quinine group† ($\bar{x} \pm SD$)	Student's t-test
Haematocrit (%)	30 ± 8	28 ± 11	NS
Haemoglobin (g%)	9.2 ± 3.2	9.1 ± 3.6	NS
Red cell count (/pl)	3.2 ± 0.9	3.1 ± 1.1	NS
White cell count (/nl)	8.4 ± 5.5	7.4 ± 4.2	NS
Platelet (/nl)	219.4 ± 68.6	188.0 ± 32.2	S
Reticulocyte (%)	4.6 ± 3.1	4.1 ± 3.0	NS
SGOT/ASAT (IU)	52 ± 38	44 ± 32	NS
SGPT/ALAT (IU)	48 ± 40	41 ± 25	NS
Alkaline phosphatase (IU)	229 ± 311	187 ± 73	NS
Total bilirubin (mg%)	5.1 ± 6.6	4.7 ± 4.5	NS
Protein (mg%)	6.2 ± 1.1	6.3 ± 0.2	NS
BUN (mg%)	78 ± 105	67 ± 62	NS
Creatinine (mg%)	1.9 ± 2.1	1.5 ± 1.3	NS
Glucose (mg%)	119 ± 42	112 ± 41	NS

* N = 30
† N = 30
NS = Not Significant ($P > 0.05$)
S = Significant ($P < 0.05$)

Table 4. Comparison of laboratory tests of severe and complicated falciparum malaria patients between the treatment groups on discharge (post-treatment) at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Laboratory test	Artemether group* ($\bar{x} \pm SD$)	Quinine group† ($\bar{x} \pm SD$)	Student's t-test
Haematocrit (%)	32 ± 7	32 ± 8	NS
Haemoglobin (g%)	10.8 ± 2.3	10.5 ± 2.5	NS
Red cell count (/pl)	3.7 ± 0.7	3.6 ± 0.8	NS
White cell count (/nl)	6.9 ± 1.6	7.9 ± 2.6	NS
Platelet (/nl)	262.4 ± 103.4	256.9 ± 106.7	NS
Reticulocyte (%)	4.4 ± 3.6	5.3 ± 6.9	NS
SGOT/ASAT (IU)	40 ± 29	36 ± 23	NS
SGPT/ALAT (IU)	38 ± 17	32 ± 18	NS
Alkaline phosphatase (IU)	164 ± 97	130 ± 47	NS
Total bilirubin (mg%)	0.9 ± 0.4	1.7 ± 3.6	NS
Protein (mg%)	6.8 ± 0.5	6.4 ± 0.7	NS
BUN (mg%)	27 ± 9	41 ± 66	NS
Creatinine (mg%)	0.8 ± 0.2	1.2 ± 1.3	NS
Glucose (mg%)	97 ± 21	118 ± 59	NS

* N = 26
† N = 23
NS = Not Significant ($P > 0.05$)

complications respectively. The common clinical complications found in malaria were hyperbilirubinaemia, severe anaemia, and hyperbilirubinaemia and hyperparasitaemia in the artemether group; hyperpyrexia, hyperbilirubinaemia, severe anaemia, and cerebral malaria in the quinine group. The risk of death increased with the number of complications (Table 5).

The most common complications of severe and complicated falciparum malaria patients were hyperbilirubinaemia (50%), hyperparasitaemia (28%) and cerebral malaria (25%). However, the highest fatality rates were associated with hypercreatininaemia (100%), bleeding (100%), pulmonary edema (100%), acidosis (100%) and septic shock (100%). No fatal cases were found in patients with hyperpyrexia, and nausea and vomiting (Table 6).

The overall mortality rate of severe and complicated falciparum malaria patients was 18.3% (11/60), and in the artemether and quinine group were 13.3% (4/30) and 23.3% (7/30) respectively. This difference was not statistically significant (Table 5). The case fatality rates were also not significantly different when analysed in subgroups (hyperbilirubinaemia, hyperparasitaemia, cerebral malaria, severe anaemia and impaired consciousness). Most of the patients (3 out of 4 patients, range 1-3 days) died before day 3 in the artemether group and only a few (2 out of 7 patients, range 0-8 days)) died in the quinine group (Table 6).

Table 5. Number of complication and outcomes of the treatment groups of severe and complicated falciparum malaria patients at Balikpapan General Hospital, East Kalimantan, 1993-1995.

Number of complication	Artemether group		Quinine group		Total	
	N	died (%)	N	died (%)	N	died (%)
1	13	0	15	1 (6.7)	28	1 (3.6)
2	12	2 (16.7)	5	2 (40.0)	17	4 (23.5)
3	3	0	7	3 (42.9)	10	3 (30.0)
>3	2	2 (100)	3	1 (33.3)	5	3 (60.0)
Total	30	4 (13.3)*	30	7 (23.3)*	60	11 (18.3)

* = No Significant Difference ($P > 0.05$)
N = Number of patients
Died = Number of patients died

Table 6. Complications and outcomes of the treatment groups of severe and complicated falciparum malaria patients at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Complication	Artemether group		Quinine group		Total		Chi-square
	N	died (%)	N	died (%)	N	died (%)	test
Hyperbilirubinaemia	16	4 (25)	14	2 (14.3)	30	6 (20)	NS
Hyperparasitaemia	9	1 (11.1)	8	3 (37.5)	17	4 (23.5)	NS
Cerebral malaria	8	3 (37.5)	7	5 (71.4)	15	8 (53.3)	NS
Severe anaemia	6	0	5	1 (20,0)	11	1 (9.1)	NS
Hyperpyrexia	4	0	7	0	11	0	
Nausea and vomiting	3	0	3	0	6	0	
Hypercreatininaemia	3	3 (100)	2	2 (100)	5	5 (100)	
Impaired consciousness	1	0	4	1 (25)	5	1 (20)	NS
Bleeding	1	1 (100)	1	1 (100)	2	2 (100)	
Pulmonary edema	1	1 (100)	1	1 (100)	2	2 (100)	
Acidosis	0	0	2	2 (100)	2	2 (100)	
Septic shock	0	0	1	1 (100)	1	1 (100)	

NS = Not Significant ($P > 0.05$)
N = Number of patients
Died = Number of patients died

Comparative efficacy between treatment groups

Of the 60 severe and complicated falciparum malaria patients, 26 (87%) cases in the artemether group and 23 (77%) cases in the quinine group were still alive on day 14. By day 14, the parasite clearance rates were 100% in both groups. The fever clearance time ranged from 0 to 82 hours in the artemether group and from 0 to 93 hours in the quinine group. The mean fever clearance time was not significantly different between the two groups (35.5±23.3 hours vs 37.4±24.7 hours). The parasite clearance time ranged from 11.5 to 77 hours in the artemether group and from 17 to 88 hours in the quinine group. The mean parasite clearance time showed 50%, 90% and 100% reductions when compared between these groups, and were not significantly different (16.9±10.3 hours vs 21.3±12.6 hours, 29.3±12.3 hours vs 29.4±10.7 hours and 38.9±16.9 hours vs 41.8±14.7 hours). The consciousness recovery time of the cerebral malaria patients (7 cases) ranged from 22 to 42 hours in the artemether group (5 cases) and from 37 to 90.5 hours in the quinine group (2 cases). The mean unconsciousness recovery time between these groups (32±14.1 hours vs 62.8±19.2 hours) was not significantly different (Table 7).

Comparative side effects between treatment groups

There were mild and self-limiting symptoms (side effect) reported in both groups. In the artemether group, no pain and abscess at the injection site were noted. While in the quinine group, tinnitus (22%), nausea (4%), and hickups (4%) were reported.

DISCUSSION

The mortality rate of severe malaria remains high despite prompt treatment with loading dose of quinine infusion. The unsatisfactory treatment outcomes with this regimen led to a multicenter study of artemether as an alternative antimalarial drug for the treatment of severe and complicated falciparum malaria, particul lary in multidrug resistant area such as East Kalimantan.

Table 7. Comparison of the efficacy of artemether and quinine in severe and complicated falciparum malaria patients at Balikpapan General Hospital, Balikpapan, East Kalimantan, 1993-1995.

Therapeutic response	Artemether group*	Quinine group †	Chi-square or Student's t-test
Survival Rate (%)‡	26/30 (87)	23/30 (77)	NS
Parasite Clearance Rate (%)‡	26/26 (100)	23/23 (100)	NS
Fever Clearance Time ($\bar{x}$ ± SD) hour	35.5 ± 23.3	37.4 ± 24.7	NS
Parasite Clearance Time (50%) ($\bar{x}$ ± SD) hour	16.9 ± 10.3	21.3 ± 12.6	NS
Parasite Clearance Time (90%) ($\bar{x}$ ± SD) hour	29.3 ± 12.3	29.4 ± 10.7	NS
Parasite Clearance Time (100%) ($\bar{x}$ ± SD) hour	38.9 ± 16.9	41.8 ± 14.7	NS
Recovery Time of Consciousness ($\bar{x}$ ± SD) hour	32 ± 14.1§	62.8 ± 19.2‖	NS
Case Fatality Rate of Cerebral Malaria (%)	3/8 (37.5)	5/7 (71.4)	NS

* N = 26
† N = 23
‡ = on day 14
§ N = 5
‖ N = 2
NS = Not Significant ($P > 0.05$)

Artemether's activity against the early forms of the parasite may be useful in preventing the sequestration of the later stages associated with severe malaria. In the preliminary report for this study and in most of the clinical trials in severe falciparum malaria, artemether was good. This drug was superior to chloroquine, sulfadoxine-pyrimethamine and quinine, as evi denced by the faster fever and parasite clearance time and recovery time of consciousness, and the lower mortality rate.[7,12,18-21] These reports suggest that artemether may stop tissue destruction and prevent death more efficiently than other antimalarials, although reduction in mortality related to intravenous quinine have not been demonstrated in randomized trial with a single exeption.

The present study did not confirm the superiority of artemether over quinine. The survival rate, parasite clearance rate, mean fever and parasite clearance time, recovery time of consciousness, and case fatality rate between the two groups were not significantly different. The number of cases in this study may be not sufficient to confirm the superior efficacy of artemether against severe and complicated falciparum malaria adult patients.

In Nigerian children with cerebral malaria, artemether also did not show superiority over quinine.[22] In Gambia, artemether and chloroquine had equally rapid action in the treatment of severe malaria in children.[19]

Death in the artemether group mostly (75%) occurred within the first 48 hours. While in the quinine group mostly (71%) occurred after the first 48 hours. This finding may be related to the pathogenesis of severe malaria. In severe malaria, a number of sequestered trophozoites and schizonts in capillaries in various tissues are expected, and artemether may be able to rapidly clear the parasites only in the circulation.[8,23]

The fatal cases in this study were mainly those with more than 3 complications and those associated with complications such as hypercreatininaemia, bleeding, pulmonary edema, acidosis and septic shock. In the preliminary report and a previous study with intravenous quinine, the fatal cases were those with more than 2 complications and those associated also with pulmonary edema, septic shock, bleeding, hypercreatininaemia, tachypnoea, hyperbilirubinaemia, hypoglycaemia, leucocytosis and hypotension.[7,21]

Most of the patients in this study were referred from outside Balikpapan and could be followed up for only 14 days. All of the surviving patients were cured. Ideally, the follow up period should be 28 days to look for recrudescence, which generally occured within 4 weeks of treatment.[24-25]

In the present study, the mortality rate of severe and complicated falciparum malaria patients was quite similar with that described in the preliminary report (18.3% vs 19.2%),[21] and lower than a previous study (18.3% vs 39%).[7] In Thailand, the mortality rates of severe malaria were between 8 and 25%.[26]

The case fatality rate of cerebral malaria in this study was higher than in the preliminary report (53.3% vs 42.9%),[21] and similar with a previous study (53.3% vs 50%).[7] The use of the Glasgow Coma Scale in this present study (GCS<9) might have influenced the outcome of the treatment.

CONCLUSION

Intramuscular artemether was well tolerated and as effective as intravenous quinine treatment of severe and complicated falciparum malaria. This drug is a good alternative to quinine, particularly in remote areas lacking hospitals and the capability for intravenous infusion.

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