Clinical Comparison of Artemether and Quinine Treatment of Severe and Complicated Falciparum Malaria Patients in Indonesia A Preliminary Report*

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Abstrak

Dalam rangka mempersiapkan obat antimalaria alternatif untuk pengobatan malaria berat dan malaria falsiparum dengan komplikasi, telah dilakukan penelitian multisenter uji perbandingan acak antara pengobatan artemeter dan kina di RS Bethesda, RSU Balikpapan dan RSU Mataram, Indonesia sejak tahun 1994. Tujuan penelitian ini adalah untuk mengetahui manifestasi klinis, menilai dan membandingkan efikasi dan keamanan artemeter intramuskular dan kina dihidroklorida intravena pada penderita dewasa malaria berat dan malaria falsiparum dengan komplikasi. Lima puluh dua orang dari 180 penderita malaria berat dan malaria falsiparum dengan komplikasi yang direncanakan, dipilih secara acak untuk diobati dengan artemeter intramuskular 1,6 mg/kg BB/dosis setiap 12 jam pada hari 0 dan dilanjutkan dengan dosis tunggal pada hari 1-4, atau diobati dengan 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 setiap 8 jam dan secepatnya diganti dengan kina peroral apabila penderita dapat menelan obat. Pengobatan diteruskan sampai total mencapai 21 dosis. Mereka dirawat minimal selama 14 hari atau sampai sembuh secara klinis dan parasitologis. Dari 52 kasus malaria berat ditemukan 30 (57,7%) kasus dengan 1 komplikasi. Komplikasi yang sering ditemukan adalah hiperbilirubinemia (50%), malaria serebral (26,9%) dan hiperparasitemia (25%). Walaupun demikian angka kematian tertinggi berhubungan dengan edema paru (100%), syok septik (100%), perdarahan (100%) dan hiperkreatinemia (83,3%). Angka kematian penderita malaria berat dan malaria falsiparum dengan komplikasi adalah 19,2% (10/52), pada kelompok artemeter dan kina adalah 14,3% (4/28) dan 25% (6/24). Perbedaan tersebut secara statistik tidak bermakna. Kecenderungan kematian meningkat dengan jumlah komplikasi dan kematian 100% bila terdapat >3 komplikasi. Sampai dengan hari ke 14, tidak ada perbedaan bermakna diantara ke dua kelompok tersebut pada angka kesembuhan (100% vs 100%), angka rata-rata waktu bebas panas (34±33 jam vs 33±17 jam) dan bebas parasit (35±14 jam vs 46±26 jam); sedangkan angka rata-rata waktu kesadaran baik dari kelompok artemeter adalah lebih cepat dibandingkan kelompok kina (29,6±8,4 jam vs 105,3±66,6 jam). Artemeter mempunyai kelebihan dalam mempercepat waktu kesadaran (3,5 kali), kecenderungan menurunkan angka kematian, sedikit dan ringan efek samping, dan lebih mudah pemberiannya.

Abstract

In order to evaluate artemether as an alternative to quinine in the treatment of severe and complicated falciparum malaria, a multicenter randomized comparative study of artemether and quinine treatment was being conducted at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia. This study began in 1994. The objectives of this study were to determine the clinical manifestations of severe and complicated falciparum malaria, to assess and compare the efficacy and tolerance of intramuscular artemether and intravenous quinine dihydrochloride. Fifty-two out of 180 targetted severe and complicated falciparum malaria patients were randomized to receive artemether intramuscularly 1.6 mg/kg b.w/dose bid on day 0 and followed by a daily dose on day 1-4 or quinine dihydrochloride intravenously 20 mg salt/kg b.w in 5% dextrose 10 ml/kg b.w in 4 hours followed by 10 mg salt/kg b.w tid until the patient was able to swallow oral quinine up to 21 doses. They were hospitalized for at least 14 days or until clinically and parasitologically cured. The single complication cases were found in 30 (57.7%) of the 52 severe falciparum malaria patients. The most common complications were hyperbilirubinaemia (50%), cerebral malaria (26.9%) and hyperparasitaemia (25%). While the highest fatality rates were associated with septic shock (100%), pulmonary edema (100%), bleeding (100%) and hypercreatinaemia (83.3%). The overall case fatality rate was 19.2% (10/52), 14.3% (4/28) in the artemether group and 25% (6/24) in the quinine group. This difference was not statiscally significant. The risk of death increased with the number of complications and was 100% if there were more than 3 complications. Until day 14, between the treatment groups, there were no significant differences in the cure rates (100% vs 100%), mean fever clearance times (34±33 h vs 33±17 h) and mean parasite clearance times (35±14 h vs 46±26 h). However, the mean coma

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resolution time was faster in the artemether group than in the quinine group (29.6±8.4 h vs 105.3±66.6 h). This 3.5-fold reduction in coma duration, suggestive reduced fatality, few and mild side effects and convenience of intramuscular treatment indicated advantages of intramuscular artemether therapy.

***Keywords** : severe malaria, treatment, artemether, quinine.*

Currently, there are chloroquine or multidrug resistant *P. falciparum* malaria cases in Indonesia. However, the proportion of resistant cases is still low except in certain parts of Indonesia[1-2] (Annex 1). This phenomena is a serious public health problem. The new drugs with better efficacy need to be studied.

Severe and complicated falciparum malaria has been reported in more than 10% out of patients with falciparum malaria, with a mortality rate between 18.8 - 50.0%.[3-4] An alternative drug to reduce the complications and mortality is needed.

Artemether is an oil-based methyl ether of artemisinin and can be given by intramuscular injection. It is a rapidly acting schizontocidal drug. Clinical trials of artemether have shown to have high efficacy against uncomplicated, severe and complicated falciparum malaria, vivax malaria, chloroquine and multidrug resistant *P. falciparum* respectively. No resistance to artemether has yet been demonstrated.[5-7] Because of its ease of administration and low toxicity, artemether has replaced quinine for the first-line treatment of severe and complicated falciparum malaria in some countries. However, this drug is not yet available commercially in Indonesia. Therefore, a clinical study of artemether and quinine treatment was being performed in Indonesia to reveal the clinical manifestations of severe and complicated falciparum malaria, 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 clinical study was a collaborative study between the Ministry of Health, Jakarta, the University of Indonesia, Jakarta, and several referral hospitals in endemic malaria areas in Tomohon, Balikpapan and Mataram, Indonesia.

Study site and time of study

The study was being carried out at the following referral hospitals: the Bethesda Hospital, Tomohon, North Sulawesi, the Balikpapan General Hospital, Balikpapan, East Kalimantan, and the Mataram General Hospital, Mataram, West Nusa Tenggara, Indonesia. The study began in 1994.

Study design

The study was an open, randomized and comparative study of intramuscular artemether versus intravenous quinine dihydrochloride in severe and complicated falciparum malaria patients.

Patients

To date 52 patients out of a target of 180 have been recruited. The patients fulfill the WHO criteria for *in vivo* antimalarial sensitivity testing[8]. These were :

1. Over 12 years of age.
2. Non-pregnant or non-lactating females.
3. 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 consent was obtained from the patients or their relatives.

The presence of one or more of the following manifestations was sufficient for the diagnosis of severe and complicated falciparum malaria[9-12] :

1. Cerebral malaria
   Glasgow Coma Scale (GCS) was used to assess the depth of coma. A total score of GCS less than 10 and persisting for more than 30 minutes after convulsion was considered unrousable coma.
2. Impaired consciousness
   The unconscious malaria patient was still rousable, responded to stimulus and could be awakened.

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3. Repeated generalized convulsions
   Malaria with more than two generalized convulsions within 24 hours although cooling had been done.
4. Prostration, extreme weakness
   The malaria patient could not sit or walk with unexplainable neuropathology.
5. Fluid, electrolyte and acid-base disturbances
   Malaria with dehydration and or acidosis with arterial blood pH < 7.25 and plasma bicarbonate < 15 mmol/l.
6. 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.
7. Spontaneous bleeding and clotting disorders or Disseminated Intravascular Coagulation (DIC).
   Malaria with retinal or subconjunctival haemorrhages, bleeding from the gums, epistaxis, melaena, haematemesis and / or signs of DIC such as increased plasma fibrinogen and decreased antithrombin III.
8. Pulmonary edema
   Malaria with cough, a feeling of oppression in the chest and difficulty in breathing, dyspnoea, crepitations, cyanosis, convulsions and deterioration of consciousness.
9. Gastro-intestinal symptoms
   Malaria with consistent vomiting and /or diarrhoea.
10. Hyperpyrexia
    Malaria with body temperature (axillary) above 40.5°C or 105°F.
11. Severe anaemia
    Malaria with a normocytic anaemia and haematocrit less than 15% or haemoglobin less than 5 g%.
12. Jaundice
    Malaria with jaundice, palpable liver and bilirubin more than 50 µmol/l or more than 3 mg%.
13. 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.
14. 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%.
15. Haemoglobinuria and blackwater fever
    Malaria with black urine rather than red or brown as in other cases of massive haemolysis and Combor test positive.
16. 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 for at least 14 days or until the patient was cured.

Investigation

A thorough history was taken and physical examinations performed on study subjects from time of admission onwards. During hospitalization, daily axillary temperatures were taken 4 hourly at 2^{00}, 6^{00}, 10^{00}, 14^{00}, 18^{00} and 22^{00} until the patient became afebrile at < 37.5°C for 24 hours. Thereafter temperatures were taken daily.

Thick and thin blood smears were taken 12 hourly at 8^{00} and 20^{00} for parasite counts until the asexual forms were cleared for 3 consecutive examinations. Thereafter, smears were done daily until discharged.

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, ECG, chest X-ray and electrolyte analysis.

Patients were reviewed at least once a day.

Treatment

Twenty-eight patients were treated with intramuscular artemether at 1.6 mg/kg b.w, 12 hourly on day 0 and daily on day 1-4. Another 24 patients were treated with intravenous quinine dihydrochloride 20 mg salt/kg b.w or 16.7 mg base/kg b.w in 10 ml/kg b.w of 5% dextrose infused in 4 hours followed by 10 mg salt or 8.3 mg base/kg b.w, 8 hourly. As soon as the patient could swallow the medication, intravenous quinine was replaced by oral quinine sulphate 10 mg salt/kg b.w, 8 hourly, up to a total of 21 doses.

In addition all patients were also treated with primaquine 30 mg, single dose 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 b.w, 8 hourly for 7 days and tetracycline 500 mg, 8 hourly for 7 days. They followed up for 14 days after treatment.

Statistical analysis

Chi-square (X^2) and Fisher's exact tests were used to compare the characteristics, clinical events and cure rate of artemether and quinine groups. Unpaired Student's t-test was used to compare the characteristics, haematology and biochemistry values, fever and parasite clearance time and coma resolution time of those groups.

RESULTS

During the study, of the total 180 targetted severe and complicated falciparum malaria patients, 52 patients have been recruited. Among them, 36, 11 and 5 cases were from Balikpapan, Tomohon and Mataram Hospital respectively. Of the 52 severe and complicated falciparum malaria, 28 cases were in the artemether group and the other 24 cases were in the quinine group. There were 40 males and 12 females; ranging in age and weight between 13 and 70 years, and 39 and 65 kg. Less than 50% were indigenous peoples and only a few (7.7%) had previously experienced malaria with frequency in the last 6 month ranging between 1 and 2 times. Duration of illness, axillary temperatures and parasite counts on admission ranged between 1 and 14 days, 36 and 40.6°C, and 313 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 month, weight, axillary temperature and parasite count) revealed no significant differences between the two groups (Table 1).

Table 1. Comparison of characteristics of severe and complicated falciparum malaria patients between the treatment groups on admission at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Characteristic	Artemether group*	Quinine group**	Student's t or X- test
Age =(x ± SD)year	27 ± 12	33 ± 16	NS
Sex =male:female	21 : 7	19 : 5	NS
Race =native:others	12 : 16	9 : 15	NS
Duration of illness =(x ± SD)day	8 ± 5	7 ± 5	NS
Malaria previously =yes:no	2 : 26	2 : 22	NS
Malaria frequency in last 6 mo=(x ± SD)time	1 ± 0	2 ± 1	NS
Weight =(x ± SD)kg	51 ± 6	51 ± 3	NS
Axillary temperature =(x ± SD)°C	38.5 ± 1.1	38.4 ± 1.3	NS
Parasite count =(x ± SD) /µl	47,223 ± 60,050	78,318 ± 105,013	NS

* N = 28
** N = 24
NS = Not Significant

Comparative clinical events between treatment groups

The most frequent (>50%) clinical symptoms and signs in both groups were fever, pallor, jaundice, nausea, hepatomegaly and splenomegaly. However, there were statistically no significant differences between the two groups (Figure 1).

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 statistically no significant differences between the two groups (Table 2).

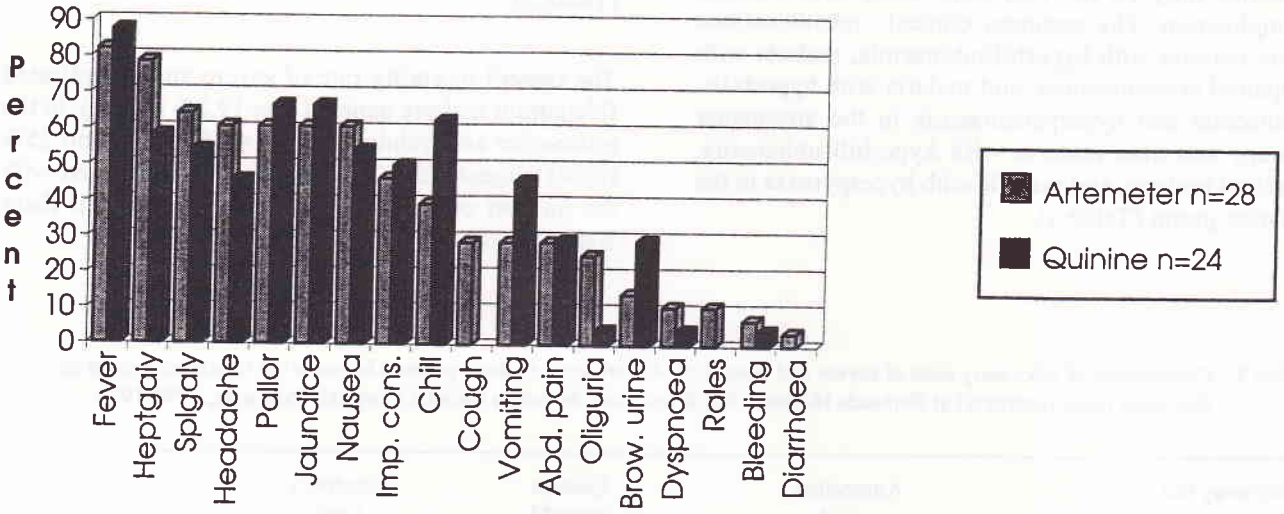

Figure 1. Comparison of clinical events of severe and complicated falciparum malaria patients between the treatment groups on admission at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia 1994-1995.

Table 2. Comparison of laboratory tests of severe and complicated falciparum malaria patients between the treatment groups on admission (pre-treatment) at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Laboratory test	Artemether group* (x ± SD)	Quinine group** (x ± SD)	Student's t-test
Haematocrit (%)	31 ± 8	28 ± 9	NS
Haemoglobin (g%)	9.5 ± 3.0	8.6 ± 3.1	NS
Red cell count (/pl)	3.4 ± 1.2	3.1 ± 0.9	NS
White cell count (/nl)	8.3 ± 3.5	7.5 ± 3.7	NS
Platelet (/nl)	207.1 ± 97.0	177.5 ± 45.8	NS
SGOT/ASAT (IU)	52 ± 50	51 ± 39	NS
SGPT/ALAT (IU)	41 ± 41	37 ± 26	NS
Alkaline phosphatase (IU)	234 ± 312	164 ± 73	NS
Total bilirubin (mg%)	5.9 ± 7.6	4.0 ± 3.7	NS
Protein (mg%)	6.1 ± 1.0	6.2 ± 0.3	NS
BUN (mg%)	95 ± 114	65 ± 54	NS
Creatinine (mg%)	2.1 ± 2.2	1.5 ± 1.5	NS
Glucose (mg%)	109 ± 81	109 ± 29	NS

* N = 28
** N = 24
NS = Not Significant

The results of all laboratory tests from both groups improved and became normal on discharge (post-treatment). There were also no significant difference between the two groups (Table 3).

Clinical manifestations and outcomes of the treatment groups

Among 52 severe and complicated falciparum malaria patients, only 30 (57.7%) were cases with a single complication. The common clinical manifestations were malaria with hyperbilirubinaemia, malaria with impaired consciousness, and malaria with hyperbilirubinaemia and hyperparasitaemia in the artemether group; and also malaria with hyperbilirubinaemia, cerebral malaria, and malaria with hyperpyrexia in the quinine group (Table 4).

The most common complications of severe and complicated falciparum malaria patients were hyperbilirubinaemia (50%), cerebral malaria (26.9%) and hyperparasitaemia (25%). However, the highest fatality rates were associated with pulmonary edema (100%), bleeding (100%), septic shock (100%) and hypercreatinaemia (83.3%). No fatal cases were found in patients with severe anemia and hyperpyrexia (Table 5).

The overall mortality rate of severe and complicated falciparum malaria patients was 19.2% (10/52), in the artemether and quinine group 14.3% (4/28) and 25% (6/24) respectively. The risk of death increased with the number of complications and was 100% if there were more than 3 complications (Table 4).

Table 3. Comparison of laboratory tests of severe and complicated falciparum malaria patients between the treatment groups on discharge (post-treatment) at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Laboratory test	Artemether group* (x ± SD)	Quinine group** (x ± SD)	Student's t-test
Haematocrit (%)	35 ± 5	31 ± 8	NS
Haemoglobin (g%)	10.6 ± 2.8	10.0 ± 2.3	NS
Red cell count (/pl)	3.6 ± 0.9	3.6 ± 0.8	NS
White cell count (/nl)	7.1 ± 1.7	7.0 ± 2.8	NS
Platelet (/nl)	336.3 ± 158.7	233.6 ± 160.7	NS
SGOT/ASAT (IU)	35 ± 29	40 ± 23	NS
SGPT/ALAT (IU)	33 ± 23	37 ± 27	NS
Alkaline phosphatase (IU)	147 ± 67	158 ± 39	NS
Total bilirubin (mg%)	0.8 ± 0.4	0.7 ± 0.3	NS
Protein (mg%)	6.8 ± 0.9	6.1 ± 0.6	NS
BUN (mg%)	25 ± 15	26 ± 7	NS
Creatinine (mg%)	0.8 ± 0.2	0.9 ± 0.5	NS
Glucose (mg%)	93 ± 38	103 ± 29	NS

* N = 23
** N = 18
NS = Not Significant

Table 4. Clinical manifestations and outcomes of the treatment groups of severe and complicated falciparum malaria patients at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Clinical manifestation	Artemether		Quinine		Total	
	#	dead	#	dead	#	dead (%)
Single complication :						
Hyperbilirubinaemia	5	0	5	0	10	0
Impaired consciousness	4	0	2	0	6	0
Hyperpyrexia	2	0	3	0	5	0
Severe anaemia	2	0	2	0	4	0
Cerebral malaria	1	0	3	1	4	1
Hyperparasitaemia	1	0	0	0	1	0
Subtotal	15	0	15	1	30	1(3.3)
Two complications :						
Hyperbilirubinaemia and hyperparasitaemia	4	0	0	0	4	0
Cerebral malaria and hyperbilirubinaemia	1	1	2	0	3	1
Cerebral malaria and hyperparasitaemia	2	0	1	1	3	1
Hyperbilirubinaemia and hypercreatinaemia	2	1	0	0	2	1
Cerebral malaria and severe anaemia	1	0	0	0	1	0
Hyperbilirubinaemia and severe anaemia	1	0	0	0	1	0
Hyperbilirubinaemia and pulmonary edema	0	0	1	1	1	1
Subtotal	11	2	4	2	15	4(26.7)
Three complications:						
Cerebral malaria, hyperparasitaemia and septic shock	0	0	1	1	1	1
Hyperbilirubinaemia, hypercreatinaemia and pulmonary edema	0	0	1	1	1	1
Hyperbilirubinaemia, severe anaemia and hyperparasitaemia	0	0	1	0	1	0
Hyperbilirubinaemia, hyperparasitaemia and impaired consciousness	0	0	1	0	1	0
Hyperparasitaemia, hypercreatinaemia and impaired consciousness	0	0	1	1	1	1
Subtotal	0	0	5	3	5	3(60.0)
More than three complications :						
Cerebral malaria, hyperbilirubinaemia, hyperparasitaemia and hypercreatinaemia	1	1	0	0	1	1
Cerebral malaria, hyperbilirubinaemia, hypercreatinaemia, pulmonary edema and bleeding	1	1	0	0	1	1
Subtotal	2	2	0	0	2	2(100)
Total	28	4	24	6	52	10
%	100	14.3*	100	25*	100	19.2

* $p > 0.05$

Comparative efficacy between treatment groups

Of the 52 severe and complicated falciparum malaria patients, only 23 cases in the artemether group and 18 cases in the quinine group survived and had completed the study until day 14 (Table 5, 6). One case in the artemether group had not completed the study until day 14, but survived.

By day 14, the cure rates in both treatment group were 100% (23/23 and 18/18). The fever clearance times ranged from 0 to 118 hours in the artemether group and from 6 to 60 hours in the quinine group. The mean fever clearance times (34±33 hours vs 33±17 hours) were not significantly different between the two treatment groups. The parasite clearance times ranged from 17 to 57 hours in the artemether group and from 12 to 137 hours in the quinine group. The mean parasite clearance times between these groups (35±14 hours vs 46±26 hours) were not significantly different. The coma resolution times of those with cerebral malaria ranged from 18 to 36 hours in the artemether group and from 48 to 195 hours in the quinine group. The mean coma resolution times between these groups were 26.6±8.4 hours in the artemether group and 105.5±66.6 hours in the quinine group. There was a significant difference statistically with $p < 0.05$ (Table 6).

Comparative side effects between treatment groups

A side effect was defined as a symptom or sign appearing only after drug administration. There were mild and self-limiting symptoms reported in both groups. In the artemether group, these were diarrhoea, itching, nausea and vomiting. While in the quinine group, these were tinitus and vertigo (Table 7).

Table 5. Complications and outcomes of the treatment groups of severe and complicated falciparum malaria patients at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Complication	Artemether		Quinine		Total	
	#	dead (%)	#	dead (%)	#	dead (%)
Hyperbilirubinaemia	15	4 (26.7)	11	2 (18.2)	26	6 (23.1)
Cerebral malaria	7	3 (42.9)	7	3 (42.9)	14	6 (42.9)
Hyperparasitaemia	8	1 (12.5)	5	3 (60.0)	13	4 (30.8)
Impaired consciousness	4	0	4	1 (25.0)	8	1 (12.5)
Severe anaemia	4	0	3	0	7	0
Hypercreatinaemia	4	3 (75.0)	2	2 (100)	6	5 (83.3)
Hyperpyrexia	2	0	3	0	5	0
Pulmonary edema	1	1 (100)	1	1 (100)	2	2 (100)
Septic shock	0	0	1	1 (100)	1	1 (100)
Bleeding	1	1 (100)	0	0	1	1 (100)

Table 6. Comparison of antimalarial efficacy in severe and complicated falciparum malaria patients between the treatment groups until day 14 at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Efficacy	Artemether group	Quinine group	Chi-square or Student's t-test
Cure Rate	23/23	18/18	NS
(%)	100	100	
Fever Clearance Time			
(x ± SD) hour	34 ± 33	33 ± 17	NS
Parasite Clearance Time			
(x ± SD) hour	35 ± 14	46 ± 26	NS
Coma resolution Time			
(x ± SD) hour	29.6 ± 8.4*	105.3 ± 66.6**	S

* N = 4
** N = 4
NS = Not Significant
S = Significant ($p < 0.05$)

Table 7. Comparison of side effects of antimalarial in severe and complicated falciparum malaria patients between the treatment groups until day 14 at Bethesda Hospital, Balikpapan and Mataram General Hospital, Indonesia, 1994-1995.

Side effects	Artemether group*		Quinine group**	
	#	%	#	%
Diarrhoea	1	4.3	0	0
Itching	1	4.3	0	0
Nausea	1	4.3	0	0
Vomiting	1	4.3	0	0
Tinitus	0	0	15	83
Vertigo	0	0	5	28

* N = 23
** N = 18

DISCUSSION

The continuing prominence of malaria as a cause of illness and death, and the spread of resistant parasites to antimalarial drugs has become a serious problem, justifying a major effort to obtain an alternative antimalaria drug for the treatment of severe and complicated malaria.

Previous study showed that despite treatment with intravenous quinine, severe and complicated falciparum malaria, had a fatality rate of 50%.[4] In clinical trials, artemether usually produced a more rapid therapeutic response than chloroquine, sulfadoxine-pyrimethamine and quinine.[13-16] Therefore, artemether is now considered as one of the antimalarial drugs of choice for severely ill patients.

This preliminary data was not sufficient to confirm the efficacy of artemether against severe falciparum measured by fever and parasite clearance times.[13-15] The cure rate on day 14, mean fever and parasite clearance times between the two groups (100%, 34±33 h and 35±14 h vs 100%, 33±17 h, and 46±26 h) were not significantly different. May be the sample was not large enough to show a statistically significant difference of these therapeutic responses. However, the mean coma resolution time was shorter in artemether group than in quinine group (29.6±8.4 h vs 105.3±66.6 h). Faster recovery of consciousness in cerebral malaria associated with artemether had also been reported in Malawi.[16]

In severe malaria, the pathological effects are due to sequestration of erythrocytes containing mature forms of parasite in the microvasculature of vital organs and causing organ damage.[17] Artemether is able to prevent parasite development to the stage at which cytoadherence will limit the pathophysiological processes in severe and complicated falciparum malaria.[18] However, the case fatality rate between the two groups (14.3% vs 25%) was not significantly different. The death cases in this study were mainly with more than 2 complications and associated with fatal complications such as pulmonary edema, septic shock, bleeding and hypercreatinaemia.

In a previous study with intravenous quinine, the death cases were also mainly of patients with more than 2 complications and associated with tachypnoe, hypercreatinaemia, hyperbilirubinaemia, hypoglycaemia, leucocytosis and hypotension. The case fatality rate was higher (39%) than the present study (19.2%).[4]

Due to limited budget and operational reason, the patients were followed up for only 14 days. Ideally, this should be 28 days to look for recrudescence as this most occurred within 4 weeks of treatment.[19-20] Hence, no recrudescence case was found up till day 14.

There were various signs and symptoms of drug intolerance in this trial. Other studies also showed that artemether had similar or no side effects, and quinine had side effects which were mild and self limiting.[20-22]

CONCLUSION

Artemether is a well tolerated and efficacious drug in the treatment of severe and complicated malaria. The 3.5-fold reduction in coma duration, trend toward reduced fatality, few and mild side effects, and convenience of intramuscular treatment indicate advantages of artemether therapy over intravenous quinine therapy.

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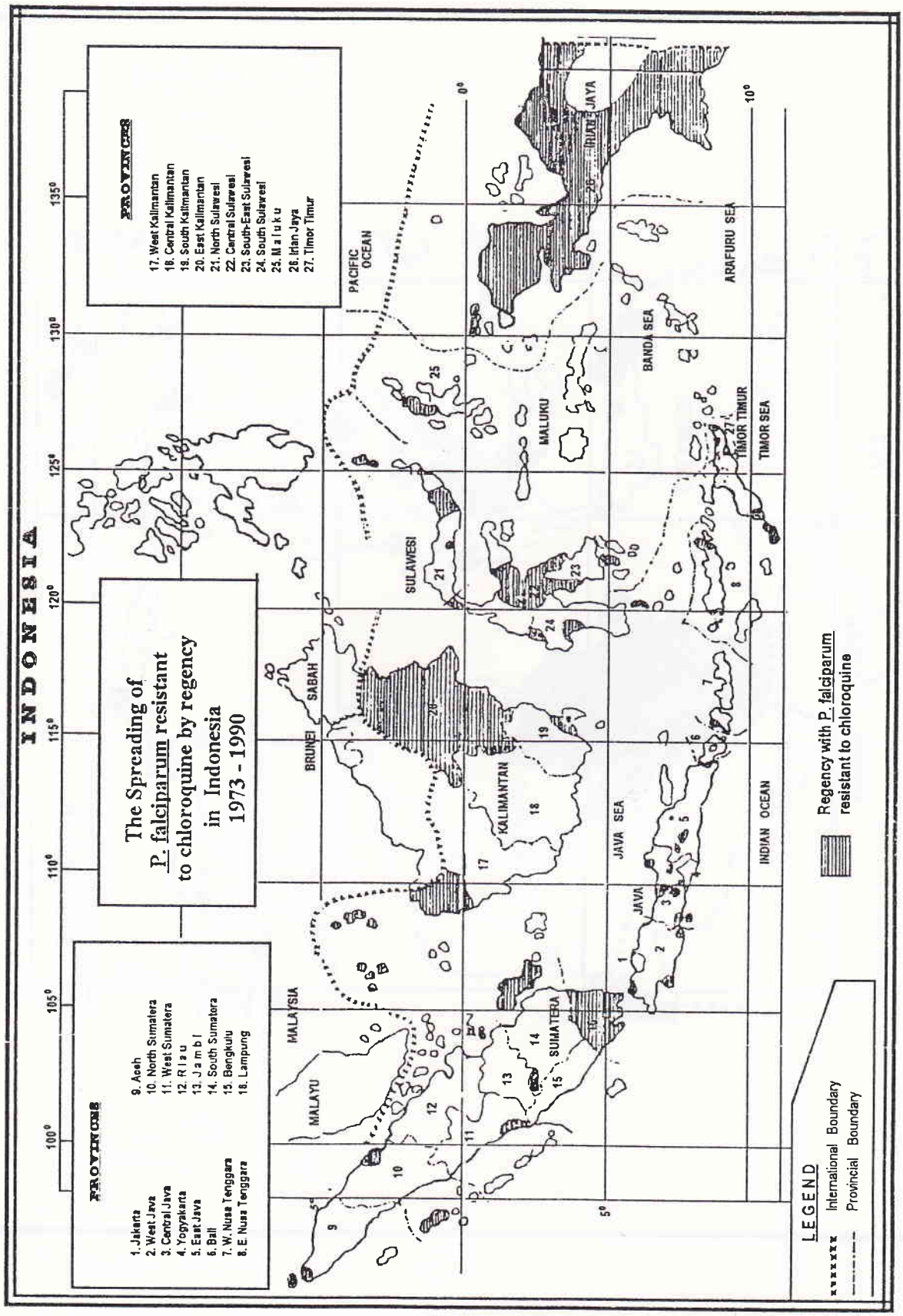
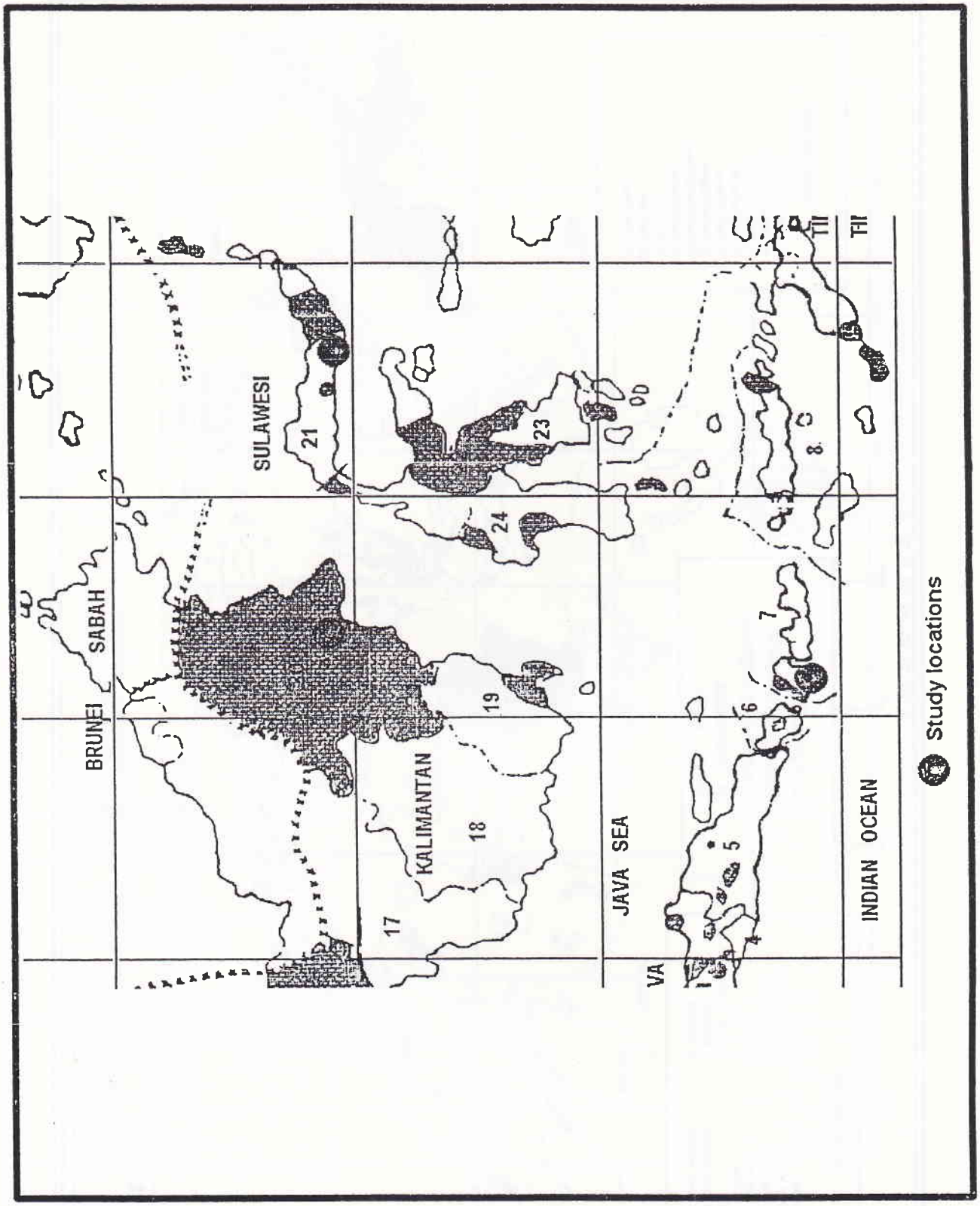

INDONESIA
The Spreading of P. falciparum resistant to chloroquine by regency in Indonesia 1973 - 1990
PROVINCES
1. Jakarta
2. West Java
3. Central Java
4. Yogyakarta
5. East Java
6. Bali
7. W. Nusa Tenggara
8. E. Nusa Tenggara
9. Aceh
10. North Sumatera
11. West Sumatera
12. Riau
13. Jambi
14. South Sumatera
15. Bengkulu
16. Lampung
PROVINCES
17. West Kalimantan
18. Central Kalimantan
19. South Kalimantan
20. East Kalimantan
21. North Sulawesi
22. Central Sulawesi
23. South-East Sulawesi
24. South Sulawesi
25. Maluku
26. Irian Jaya
27. Timor Timur
MALAYSIA
BRUNEI
SABAH
SULAWESI
KALIMANTAN
MALUKU
IRIAN JAYA
TIMOR TIMUR
PACIFIC OCEAN
BANDA SEA
ARAFURU SEA
TIMOR SEA
JAVA SEA
INDIAN OCEAN
MALAYU
SUMATERA
JAVA
Regency with P. falciparum resistant to chloroquine
LEGEND
International Boundary
Provincial Boundary


BRUNEI
SABAH
SULAWESI
KALIMANTAN
JAVA SEA
INDIAN OCEAN
17
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19
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Study locations