CLINICAL MANIFESTATION AND TREATMENT OF NON-SEVERE FALCIPARUM MALARIA IN THAI CHILDREN

SUPROTIK GHAGRA

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ABSTRACT

A retrospective study was conducted to assess the effects of three different treatment regimens on non-severe falciparum malaria, and to review the clinical features of falciparum malaria in Thai children. A total of 116 children, ages ranging from 11 months to 13 years with uncomplicated falciparum malaria, who had been admitted to the Hospital for Tropical Diseases, Bangkok and Thongphaphum Hospital during the period 1991-2003, were evaluated. Most of the symptoms and signs of non-severe falciparum malaria in children were non-specific. Weakness (88%), headache (74%), chills (58%), hepatomegaly and splenomegaly, other than fever, were commonly found clinical features. Out of 116 patients, 54 cases received quinine (Q) 10 mg base/kg for 4 days, then 15 mg base/kg for the next 4 days, 32 cases received artesunate suppositories 10-19 mg/kg once daily for 3 days followed by mefloquine 25 mg base/kg in two divided doses (AS-MQ); and 30 children received artemether-lumefantrine (AT-L) in a fixed combination (artemether 1.5 mg/kg and lumefantrine 9 mg/kg) at 0, 8, 24 and 48 hours. Both rectal artesunate-mefloquine and artemether-lumefantrine exerted rapid initial therapeutic response. Parasite clearance times were significantly shorter with AS-MQ (50.4 hours) and AT-L (37.5 hours) than with Q (78.5 hours) ($p<0.001$). The mean fever clearance times were also shorter in AS-MQ (41 hours) and AT-L (39.8 hours), than in Q (66 hours) groups ($p<0.05$). The 28-day cure rate was higher in AS-MQ (92%) than in AT-L (71%) and Q (75%) groups. However, there was no statistically significant difference in cure rate among the groups. All three treatment regimens were well-tolerated; no serious adverse effects were observed. AS-MQ is more effective than AT-L and Q, a large scale prospective study to confirm the results of this study is warranted.

KEY WORDS: FALCIPARUM MALARIA/ TREATMENT/ CHILDREN
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LIST OF ABBREVIATIONS

Abbreviations	Terms
AP	Alkaline phosphatase
ALT	Alanine aminotransferase
AS	Artesunate
AST	Aspartate aminotransferase
AT	Artemether
BP	Blood pressure
^{o}C	Degree Celsius
Cl^-	Chloride
cm	Centimeter
d	Day
D/M/Y	Day/month/year
dl	Decilitre
FCT	Fever clearance time
g	Gram
G-6PD	Glucose 6 phosphate dehydrogenase
h	Hour
Hb	Hemoglobin
HCO_3^-	Bi-carbonate
Hct	Hematocrit
K^+	Potassium
kg	Kilogram
L	Lumefantrine
mEq/l	Milli equivalent per litre
mg	Milligram
mm	Millimeter
mmHg	Millimeter of mercury

LIST OF ABBREVIATIONS (cont.)

Abbreviations	Terms
mmol/l	Millimol per litre
Na^+	Sodium
PCT	Parasite clearance time
Pf.	*Plasmodium falciparum*
PO	Per oral
Pv.	*Plasmodium vivax*
Q	Quinine
qid	Four times daily
RBC	Red blood cell
SD	Standard deviation
T	Tetracycline
Temp	Temperature
tid	Three times daily
TNF	Tumor necrosis factor
U/l	Unit per litre
WHO	World Health Organization
WBC	White blood cell
%	Percent
µl	Microlitre

CHAPTER I
INTRODUCTION

Malaria is a life threatening parasitic disease transmitted from person to person through the bite of female anopheles mosquitoes. It is one of the major public health challenges eroding development in the poorest countries in the world. Malaria accounts for one of the top five causes of childhood mortality in Africa. Anemia, low birth weight, convulsion and neurological problems, all frequent consequences of malaria, compromise the health and development of millions of children throughout the tropical world. The estimated annual global incidence of malaria is 300 to 500 million clinical cases, although many cases are not seen by the health care providers (Snow et al., 1999; Murphy and Breman, 2001).

In general, the clinical symptoms of malaria are caused by the development of asexual parasites in infected erythrocytes. Clinical manifestation of malaria, in particular, non-severe falciparum malaria may be different in many aspects between children and adults. The common clinical features of non-severe falciparum malaria are fever, headache, restlessness, nausea, vomiting, cough, reluctant to food, convulsion and feeling of chills (Gilles and Warrel, 1993; Luxemburger et al., 1998). On the other hand non-severe falciparum malaria may mimic vivax malaria and can not be differentiated in the absence of laboratory confirmation and sound knowledge of clinical features of malaria which may subsequently account for undue loss of many lives. Specific treatment of non-severe falciparum malaria generally comprise of drugs such as quinine, tetracycline, mefloquine and artesunate or artemether (Wilairatana et al., 2002; Looareesuwan et al., 1998; White, 2003).

In Thailand, in spite of significant achievements in malaria control in the past two decades, about 51,849 malaria cases still occur each year (Anonymous, 2000). The provinces of Trat (Thai-Cambodian border), Tak (Thai-Myanmar border) and Kanchanaburi remained the highest incidence area of malaria cases (Thimasan et al., 1995) in Thailand. One of the major problems is the increasing frequency of falciparum malaria strains highly resistant to chloroquine and

sulfadoxine/pyrimethamine, and to mefloquine in the border areas of Trat and Tak, while sensitivity to quinine is also diminishing in certain areas of Thailand (Thimasan, 1992; Wongsrichanalai et al., 2001; Karbwang and Harinasuta, 1992). Although the combination of quinine and tetracycline has been shown to be effective against chloroquine resistant falciparum malaria in the hospital base, patient's compliance to the 7-day regimen is low due to the side effect (cinchonism) with subsequently high recrudescent rate in ambulatory setting and as a consequence, the risk of development of resistance to quinine (Karbwang and Harinasuta, 1992). Artemisinin derivatives (artesunate, artemether) combined with mefloquine have been introduced to clinical use in Thailand to cope with this situation. Artemisinin derivatives combined with mefloquine have been recommended as a standard regimen for the treatment of multi-drug resistant falciparum malaria in Thailand (Looareesuwan et al., 1998; Wilairatana et al.; 2002). Although every country has its own treatment strategy for the treatment of malaria, there is still no universal agreement concerning the most appropriate doses or treatment regimen. Thus it is a necessity to have an intensive search for the appropriate treatment regimen as well as to assess the trend of efficacy of available standard regimen.

The majority of death from falciparum malaria in children is caused by delayed diagnosis and administration of effective antimalarial treatment. There may be relentless deterioration in clinical condition of a young child with falciparum malaria who fails to get effective treatment in time, with death ensuing a matter of hours or days. Early diagnosis and treatment with potent antimalarials are fundamental components of prevention of high mortality associated with the disease.

Therefore, understanding of up-to-date knowledge of treatment regimens and clinical features of non-severe falciparum malaria in children is a clinical and public health importance. This study was conducted retrospectively to review the clinical manifestations and clinical outcome of non-severe falciparum malaria in Thai children treated with different antimalarial regimens.

CHAPTER II
OBJECTIVES

Primary objective:

To determine the effects of different treatment regimens on non-severe falciparum malaria in Thai children.

Secondary objectives:

1. To describe the clinical features of non-severe falciparum malaria.
2. To determine the relationship between initial parasitemia and therapeutic response.

CHAPTER III
REVIEW OF LITERATURE

History (White**,** 2003; Gilles and Warrel, 1993**)**

The word ‘malaria’ comes from the Italian, and means literally ‘bad air’. Indeed the cause of the seasonal periodic fever was a continuous source of debate until the late nineteenth century. The work of Meckel, Virchow and Frerichs had established that the pigment observed in the blood of some patients with periodic fever were resulted from the destruction of red blood corpuscles. This same pigment caused the characteristic grey discoloration of the internal organs in patients dying from this disease. In the 1870s, medicine slowly moved towards the germ theory of disease following the pioneering work of Koch, a French Army surgeon working in Algeria, claiming that malaria was caused by a parasite, and it was treated initially with some scepticism. On the 6 November 1880 Charles Louis Alphonse Laveran was examining the fresh blood of a patient with ague, and observed moving bodies (he was probably watching gametocyte exflagellation) which he surmised correctly were parasite of the red blood cells. The transmissibility of the infection in blood was proved fours years later by Gerhardt but the route of natural infection was not discovered until the next decade. Following the suggestion of Patrick Manson, Ronald Ross, a young Scottish physician reported in 1897 the presence of pigmented bodies in the certain species of brown ‘dapple winged’ mosquito that had fed on patients with malaria. He speculated that these might represent the parasite stage in the mosquito (the oocysts). After many years of study, Ross finally proved the existence of complete life cycle involving a mosquito in the malaria of canaries. Ross finally had the opportunity to demonstrate *Plasmodium falciparum* sporogony in anopheline mosquitoes in Sierra Leone. Bignami and his colleagues, following the pioneering work of Grassi, had succeeded in infecting a healthy volunteer with *P. falciparum* from mosquito bite in Rome. Both Laveran and Ross received Nobel Prizes for their respective discoveries.

Etiology and life cycle

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female anopheles mosquitoes. *Plasmodium falciparum*, the etiologic agent of the most deadly malaria exists in a variety of forms and has a complex life cycle that enables it to survive in different cellular environment in the human host (asexual phase) and the mosquito vector (sexual phase) (Duorado, 1992). A marked amplification of plasmodium organisms from approximately 100 to as many as 10^{14} occurs during a two step-process in humans (Krause, 2000). The first occurs in the cells of liver (exoerythrocytic phase) and the second in the red cells (erythrocytic phase). The exoerythrocytic phase begins with the inoculation of sporozoites into the blood stream by the bite of a female *anopheles* mosquito. Within minutes, the sporozoites enter the hepatocyte of the liver, where they develop and multiply asexually. The parasite is referred as a schizont at this stage. However, as only a few liver cells are infected, this phase is asymptomatic for the human host. After few days to two weeks, the hepatocytes rupture and release thousands of merozoites into the circulation (Miller et al., 2002; Gilles and Warrel, 1993). The tissue schizonts of *P. falciparum* rupture once and none persists in the liver. The erythrocytic phase of *Plasmodium* sp. development begins when the merozoites from the liver penetrate erythrocyte. Once invades the erythrocyte, the parasite transforms into the ring form which then enlarges to become a trophozoite. These later two forms can be identified with Giemsa stain on blood smear, the primary means of confirming diagnosis of malaria. The trophozoite multiplies asexually to produce many small merozoites. They are released into the blood stream when the erythrocyte membrane ruptures, a process associated with fever. Overtime, some of merozoites develop into male and female gametocytes. It is the gametocytes that complete the *Plasmodium* sp. life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a zygote in the stomach of mosquito. After a series of further transformation, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Pathogenesis

Four important pathologic processes have been identified in patients with falciparum malaria**: fever, anemia, immunopathologic events, and tissue anoxia** resulted from cytoadherence of infected erythrocytes (Wassmar et al., 2003; Benson and Brown, 2002; Krause, 2000). Fever occurs when erythrocytes rupture and release merozoites into the circulation. Anemia is caused by hemolysis, sequestration of erythrocytes in the spleen and other organs, and suppression of erythrocyte production in the bone marrow. Immunopathologic events that have been documented in patients with malaria include polyclonal antibodies activation resulting in both hypergammaglobulinemia and formation of immune complexes, immunosuppression, and release of cytokines such as tumor necrosis factor (TNF) that may be responsible for many of the pathologic features of the disease (Grau et al., 1989; Clark et al., 1989). Cytoadherence of infected erythrocytes to vascular endothelium occurs in *P. falciparum* malaria. It may lead to obstruction of blood flow and capillary damage with resultant vascular leakage of protein and fluid, and edema and tissue anoxia in the brain, heart, lungs, intestine and kidneys (de Kossodo and Grau, 1993; Miller et al., 2002).

Clinical features of non-severe falciparum malaria

Falciparum malaria is responsible for almost all the 1 million or more deaths attributed to malaria each year worldwide (Snow et al., 1999; Murphy and Breman, 2001). People who live in endemic areas and have been frequently infected acquire some immunity so that they can tolerate *P. falciparum* parasitaemia with trivial or no symptoms. However, in non-immune people, such as expatriate travelers in malarious regions, falciparum infection nearly always causes debilitating symptoms and must be regarded as a potentially fatal disease. Clinical features in infants and children can be classified according to the endemicity of the disease.

In areas of low or unstable endemicity of falciparum malaria, where the immunity in the indigenous population is low, severe life threatening malaria may occur in all age groups. The classical febrile malarial paroxysm followed by an afebrile asymptomatic interval is not a feature of falciparum infection (Gilles and Warrell, 1993). The illness starts with headache, dizziness, pain in the back and limbs,

malaise, anorexia, nausea, vague abdominal pain, vomiting or mild diarrhea and feeling of chills. There are intermittent chills rather than a clearly circumscribed cold phase and the fever is continuous or irregular. The physical findings like symptoms are non-specific and include fever, anemia, prostration, postural hypotension, jaundice and hepatosplenomegaly (Luxemburger et al., 1998; Fernando and Wickremasinghe, 2002).

Clinical manifestation is even more variable in the area where endemicity for malaria is high. However, fever and anemia is a combination of symptoms frequently seen. After an acquired primary infection, a small proportion of infants may show a low grade parasitemia with few clinical symptoms, if any. There might be slight restlessness, decreased appetite, sweating, anemia, and occasional rise of temperature. After few days to months, inherited immunity declines and the clinical attack become more severe and many of them die either of cerebral malaria or of an acute general infection (Angyo et al., 1996; Harinasuta and Bunnag, 1988).

In highly endemic areas, there is an increase in infection rate from 0-2% during the first three months of life, to 80-90% by one year of age, and the rate persists at a high level during early childhood. By school age, a considerable degree of immunity has been developed and asymptomatic parasitemia could be as high as 75% in primary school children (Maitland et al., 1997; Luxemburger et al., 1996; Kamolratanakul et al., 1992).

Clinical features of severe and complicated malaria

Severe manifestations of falciparum malaria include (WHO, 2000):

1. Prostration (inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit)
2. Impaired consciousness
3. Respiratory distress (acidotic breathing)
4. Multiple convulsions (2 or more in a 24 hours)
5. Circulatory collapse
6. Pulmonary edema
7. Severe anemia (Hct < 15% or Hb < 5g/dl)
8. Abnormal bleeding

9. Jaundice
10. Hemoglobinuria (rare)
11. Hypoglycemia (blood glucose <2.2 mmol/l or <40 mg/dl)
12. Acidosis (plasma HCO_3 <15 mmol/l or arterial/capillary pH <7.35)
13. Hyperlactatemia (plasma lactate >5 mmol/l)
14. Hyperparasitemia (≥4% in non-immunes)
15. Renal impairment (urine output <12 ml/kg/24 h or serum creatinine >3 mg/dl)

Outline classification of severe malaria in children (WHO, 2000)

Group A

Children at immediately increased risk of dying who require parenteral antimalarial drugs and supportive therapy:

1. Prostrated children: Three subgroups of increasing severity should be distinguished.
   1.1 Prostrated but fully conscious
   1.2 Prostrated with impaired consciousness but not in deep coma
   1.3 Coma (the inability to localize a painful stimulus)
2. Respiratory distress:
   2.1. Mild; sustained nasal flaring and/or mild intercostal indrawing
   2.2. Severe; the presence of either marked indrawing of the bony structure of the lower chest wall or deep (acidotic) breathing.

Group B

Children who, though able to be treated with oral antimalarial drugs, require supervised management because of the risk of clinical deterioration but who show none of the features of group 'A' (above)

1. Children with a Hb level < 5 g/dl or Hct < 15%
2. Children with 2 or more convulsions within a 24 hour period

Group C

Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of group 'B' (above).

Laboratory findings

The diagnosis of malaria is established by identification of the organism on Giemsa or Wright's stained smears of peripheral blood. Both thick and thin blood smears should be examined (Bhatt, 1994; Van der et al., 1998). Normochromic normocytic anemia is the rule. The white blood count is usually normal but may be raised in severe malaria. The differential count is usually normal. Erythrocyte sedimentation rate is normal to high. Platelet count is reduced in all acute malarias, usually around 100,000/µl but thrombocytopenia is profound in some cases (Looareesuwan et al., 1992; White, 2003). In severe infection, the prothrombin time and partial thromboplastin time may be prolonged (Rojanasthien et al., 1992; Sharma et al., 1992). There may be mild hyponatremia, but the serum potassium is remarkably normal. Serum bicarbonate is often reduced and serum calcium may be low. Hypoglycemia may occur even in the absence of quinine treatment. The total and conjugate bilirubin may be elevated; the transaminase concentrations are often raised. Creatine phosphokinase (CPK), myoglobin, plasma urate levels are elevated in children with severe malaria. Hypergammaglobulinemia is usual in immuned and semi-immuned patients (White, 2003).

Treatment of non-severe falciparum malaria

Chloroquine still remains the drug of choice for blood schizontocidal treatment of malaria other than *P. falciparum*. At the dose of 10 mg base/kg initially, then 5 mg base/kg at 6, 24 and 48 hours, it eliminates the blood schizonts. But its effectiveness on *P. falciparum* is very disappointing in most malaria endemic countries. In Thailand, chloroquine is not recommended in the treatment of falciparum malaria as the cure rate is 0% and RII response is more than 45% (Karbwang and Harinasuta, 1992). Sulphadoxine/pyrimethamine combination was effective against chloroquine resistant strains of *P. falciparum* during early 1970's. Resistance to this combination is now well established in several countries of

Southeast Asia. It is given as a single oral dose of sulphadoxine 25 mg base/kg and pyrimethamine 1.25 mg base/kg . In Thailand, the cure rate of this combination in 1979-80 was only 22%. The combination of sulphadoxine- pyrimethamine in single dose with quinine for 7 days gives a cure rate of 76% (Karbwang and Harinasuta, 1992). In the face of chloroquine and sulphadoxine-pyrimethamine resistance, amodiaquine is used in many settings like Liberia and Papua New Guinea. A study in the south-eastern Liberia, with a 3day supervised course of 25 mg/kg amodiaquine showed a failure rate of 19.8% and its introduction is recommended in combination with artesunate as a first-line antimalarial in Liberia. Quinine is the drug of choice and widely available antimalarial in many malaria endemic countries for the treatment of chloroquine resistant *Plasmodium falciparum*. In Thailand decreasing sensitivity to quinine has been reported in many areas, with a cure rate at the dose of 10 mg (salt)/kg every 8 hours for 7 days being only 75 % (Bunnag and Harinasuta, 1988). Adding tetracycline to this regimen at 5mg/kg 4 times daily for 7 days has been shown to increase the cure rate to 95-100% (Karbwang et al., 1994). But the patient's compliance to this regimen in uncomplicated malaria is low due to side effects with the subsequent risk of development of resistance to quinine. In children less than 7 years, quinine sulphate at the dose of 10 mg base/kg tid for 4 days, then 15 mg base/kg tid for next 4 days can be used with a cure rate of 87 % (Chongsuphajaisiddhi et al., 1983). Mefloquine has been used for the oral treatment of uncomplicated multi-drug resistant falciparum malaria. Resistance to mefloquine has been reported increasingly in Thailand, Myanmar and Cambodia. The dose is 15 mg base/kg initially then, 10 mg base/kg 6-12 hours later. Treatment failure with this regime is 27% (Smithuis et al., 1993). Since mefloquine has a long half-life, its indiscriminate use could induce further resistance and it should be given in combination with an artemisinin derivative. Halofantrine has been shown to be effective against multi-drug resistant *Plasmodium falciparum*. The cure rate at the dose of 8mg/kg tid for 3 days is 89% (Krudsood et al., 2001). Unfortunately it is associated with rare but potentially lethal ventricular tachycardia which has curtailed its use. Artimisinin derivatives currently play an important role in the treatment of multi-drug resistant falciparum malaria in several parts of the world. It induces a rapid therapeutic response with rapid resolution of fever. However, because of its very short half-life, treatment with

artemisinin alone will result in high recrudescence rate if it is administered for a short period. In Thailand, combination of artemisinin derivatives with a longer-acting drug is recommended to increase overall cure rates and to prevent resistance (Looareesuwan and Viravan, 1995). Several studies showed that artesunate, at the dose of 10-12 mg/kg over 3 days followed by mefloquine 15 mg base/kg initially then, 10 mg base/kg exerts a high cure rate ranging from 89%-100% (Price et al., 1997; Vugt et al., 2000; Mueller, 2002). Artemether-lumefantrine also provides a highly effective and very well-tolerated treatment for multi-drug resistant falciparum malaria. The 6-dose regimen of artemether 1.5 mg/kg and lumefantrine 9 mg/kg per dose is as effective as artesuanate-mefloquine with a cure rate of 96-99% (Vugt et al., 2000; Vugt et al., 1999). Malarone (atovaquone-proguanil) is established as a safe and effective prophylactic antimalarial drug for travelers because it is effective everywhere (White, 2003) However, its use in the treatment of malaria is limited because of its high cost. The dosage is 15-20/6-8 mg/kg/day of atovaquone/proguanil for 3 days. It is well tolerated and 100% effective in the treatment of acute uncomplicated falciparum malaria (Looareesuwan et al., 1999).

CHAPTER IV
MATERIALS AND METHODS

Study design: This is a descriptive retrospective study.

Study site: This study was carried out in the patients admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, or Thongpaphum Hospital, Kanchanaburi Province, Thailand.

Study period: October 2003 through March 2004.

Study population: Medical records of all pediatric patients diagnosed as non-severe falciparum malaria and treated as in-patient from 1991 to 2003, who met the inclusion criteria were reviewed.

Inclusion Criteria:

1. Age 15 years or less.
2. Parasitologically diagnosed as falciparum malaria.
3. Medical records are available.
4. Had non-severe falciparum malaria as defined by WHO, 2000 (Appendix - B).

Exclusion Criteria:

1. Absence of fever at the time of admission that remained for successive 2 days.
2. Known history of receiving antibiotics (appendix - C) within 3 days or antimalarial drugs within 1 month prior to admission.
3. Presence of concomitant systemic diseases.
4. Immunocompromised child.
5. No asexual phase of parasite was detected.

Parameters that were collected:

1. Demographic data: age, sex, admission number, height, weight, date of admission, date of illness, date of discharge.
2. Clinical data: maximum pretreatment temperature, headache, anorexia, nausea, vomiting, diarrhea, cough, chills/rigor, myalgia, abdominal pain, weakness, pulse, BP, hydration status, hepatomegaly, splenomegaly and itching.
3. Laboratory data (on the day of admission and at day 7±1 and 28± 2 after initiation of treatment): complete blood count, platelet count, G-6-PD status, total bilirubin, direct bilirubin, alkaline phosphatase, AST/ALT, blood glucose, serum electrolytes and parasite count.
4. Outcome data: fever clearance time, parasite clearance time and cure rate (appendix - C).

Data analysis

Descriptive statistics were used to describe the demographic characteristics, clinical symptoms and signs and laboratory data of the subjects. Pearson or Spearman Rank correlations test were used to determine the relationship between continuous variables. ANOVA or non-parametric statistics to compare the quantitative variables and Chi-square test to compare the categorical data were used as appropriate. The statistical software package SPSS version 10.0 and EPI INFO 6 were used for statistical analysis. Statistical significance in all tests were accepted at two-tailed p-value of <0.05.

Sample size calculation

By using EpiInfo 6 Epitable calculator, with predicted cure rate of 96% (96-98) in oral artesunate plus mefloquine and 75% in the quinine group (Bunnag and Harinasuta, 1988; Nosten et al., 1994), 52 patients in each treatment group were sufficient to detect the difference in cure rate between these treatment regimens with a confidence level of 95% and a power of 80%.

Research fund

Research fund was provided by the Faculty of Tropical Medicine, Mahidol University, Thailand.

CHAPTER V
RESULTS

1. General characteristics and demographic features:

A total of 116 medical records of non-severe falciparum malaria patients treated at the Hospital for Tropical Diseases, Bangkok or Thongpaphum Hospital, Kanchanaburi during 1991-2003 and who met the inclusion criteria were evaluated. The patients were mainly from the western region of Thailand near the Thai-Myanmar border. There were 62 male and 54 female children. Their age ranged from 11 months to 13 years (mean 8.9 years). Most of them (93.1%) were 5 years of age or older. The mean (SD) weight and height were 23.9 (8.0) kilogram (kg) and 123.25 (16.6) centimeter (cm) respectively. All of the cases had falciparum infection except one case who had dual vivax and falciparum infection. Fifteen patients (13.2%) had history of previous infection with *P. falciparum* at least once within the last 1 year while ninety-nine patients (86.8%) had no history of previous malaria infection within the aforementioned period. G-6PD deficiency was found in 11 (9.8%) children (Figure 1). The demographic and baseline characteristics are shown in table 1.

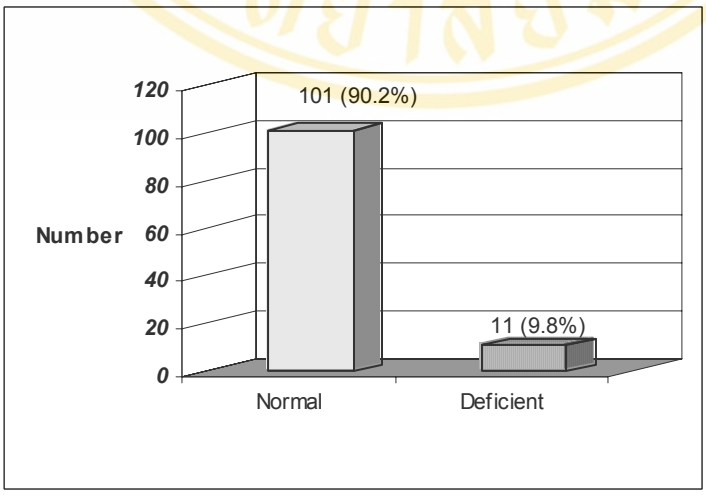

Figure 1. G-6PD status in 116 children with falciparum malaria

Table 1. The demographic and general characteristics of the 116 patients investigated

Characteristics	Values
Age (years)	
Range	0.92-13
Mean (SD)	8.9 (2.9)
No. (%) of patients	
Male	62 (53.4)
Female	54 (46.6)
Mean (SD) weight (kg)	23.9 (8.0)
Mean (SD) height (cm)	123.25 (16.6)
Duration of fever before treatment (day)	
Range	1-11
Mean (SD)	4.0 (2.2)
G-6 PD status [No. (%)]	
Normal	101 (90.2)
Deficient	11 (9.8)
Previous falciparum infection [No. (%)]	
Yes	15 (13.2)
No	99 (86.8)
Species of malaria infection [No. (%)]	
Falciparum	115 (99.1)
Mixed	1 (0.9)

2. Clinical manifestations

2.1 Symptoms:

Fever: In this study, only febrile patients who had temperature ≥37.5°C on admission or within 48 hours of admission were recruited. The temperature on admission ranged from 36.5 to 41.9°C (mean 38.7). The mean duration of fever before treatment was 4.0 days (minimum 1day, maximum 11 days).

The most commonly found symptoms were weakness (88.8%) followed by headache (74%) and chills (58%). Other common symptoms were anorexia (49.5%), nausea (32.4%), vomiting (30.8%), cough (46.4%), and myalgia (42.9%). Only 3.7% had diarrhea and 18.2% complained of abdominal pain. No data regarding itching and other symptoms were recorded. The clinical symptoms found in 116 children with malaria are shown in table 2 and figure 2.

Table 2. Clinical symptoms found in 116 Thai children with uncomplicated falciparum malaria

Symptoms	Number	%
Weakness	87/98	88.8
Headache	74/100	74.0
Chills	61/105	58.0
Anorexia	53/107	49.5
Cough	13/28	46.4
Myalgia	6/14	42.9
Nausea	33/102	32.4
Vomiting	33/107	30.8
Abdominal pain	16/88	18.2
Diarrhea	4/107	3.7

2.2 Clinical signs

Physical examination on admission revealed mean maximum temperature 38.6^{0}C, respiratory rate 29.7/minute, pulse rate 106/minute, BP 100/63 mmHg. Tachypnea (respiratory rate >40/minute for children 1 year-old or more) was found in 2.7% of children. It was difficult to determine the tachycardia because of a wide age difference. Hepatomegaly (57.4%) and splenomegaly (56.5%) were very common physical findings in children with malaria. Mild to moderate dehydration was also found in 35% of the patients. Any patient with jaundice (serum bilirubin >3 mg/dl) was excluded from the study according to the inclusion criteria. The clinical findings found in children with uncomplicated falciparum malaria in this study are shown in table 3 and figure 2.

Table 3. Clinical signs found in Thai children with uncomplicated falciparum malaria

Signs	Values
Mean (SD) max. temperature (^{0}C)	38.7 (1.0)
Mean (SD) max. resp. rate (per minute)	29.7 (3.3)
Mean (SD) max. pulse (per minute)	106.3 (13.0)
Mean (SD) BP (mm Hg)	
Systolic	100.4 (10.7)
Diastolic	62.7 (9.4)
Hepatomegaly [No. (%)]	66/106 (57.4)
Splenomegaly [No. (%)]	65/106 (56.5)
Mild to moderate dehydration [No. (%)]	7/20 (35.0)
Tachypnea [No. (%)]	3/106 (2.7)

max. = maximum, resp. = respiratory

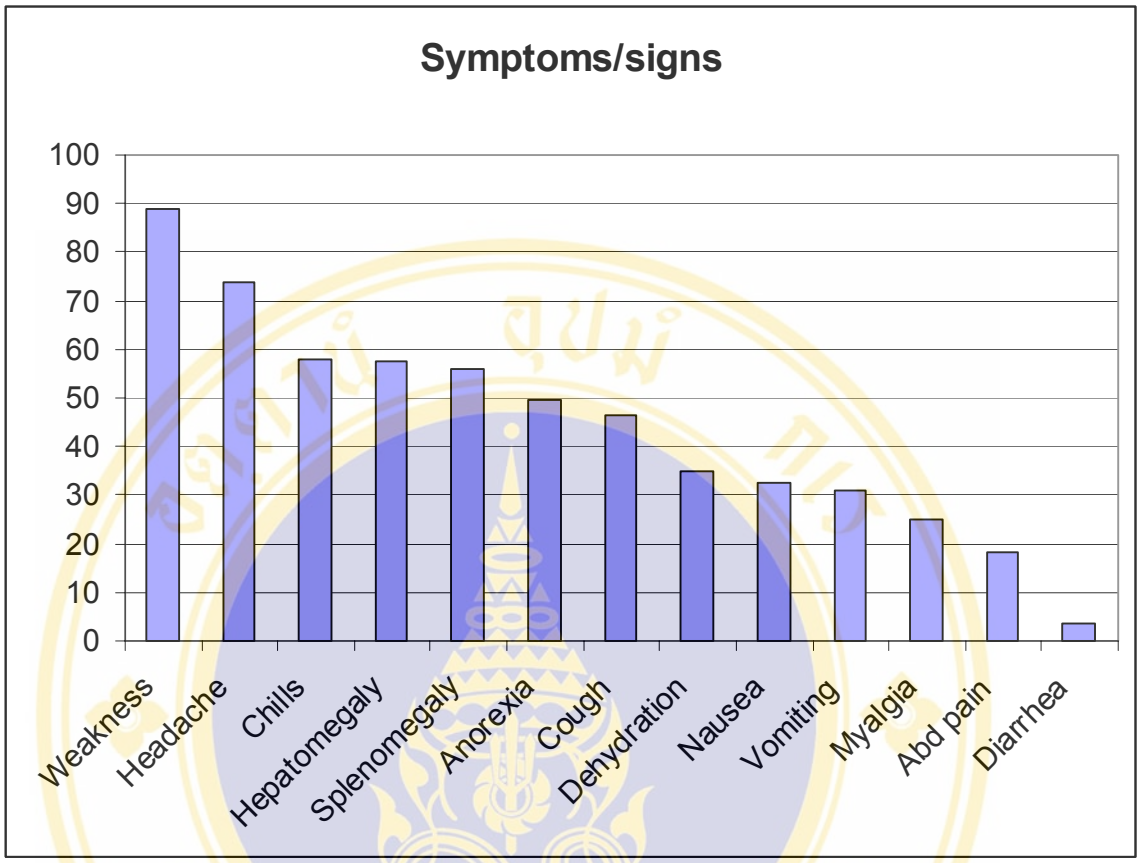

Figure 2. Clinical manifestations of falciparum malaria in 116 Thai children

2.3 Laboratory findings

The laboratory findings are shown in table 4 and 5. It was found that the mean hemoglobin, hematocrit and Na^+ of all study population were below the normal limit (10.65 g/dl, 33.06% and 134.1 mEq/l respectively). Leucopenia (WBC $<4.0 \times 10^3/\mu l$) was found among 8 (6.9%) patients while 13 (11.2%) patients showed leucocytosis (WBC $>10 \times 10^3/\mu l$). The most frequent findings were anemia and thrombocytopenia. Fifty-seven (69.5%) patients had hemoglobin less than 11.5g/dl (Figure 3). Reduced platelet ($<150 \times 10^3 /\mu l$) count was found in 53.5% (61/114) of the patients (Figure 4). Another common laboratory finding was abnormal serum electrolytes. Overall 48.5% (48/99) of the patients had mild to moderate hyponatremia (Na <135 mEq/l) and serum potassium was reduced to less than 3.5 mEq/l in 21 (21.4%) patients. Serum bicarbonate and chloride were remarkably normal. Hypoglycemia was an exclusion criteria in this study. However, only 7.3% of the patients (8/109) had blood sugar less than 60 mg/dl. Elevated total bilirubin (>2mg/dl)

was found in 11.9% (13/109) of the cases. Increased AST, ALT and alkaline phosphatase were observed in 26.5%, 10.6% and 7.8% of the patients respectively.

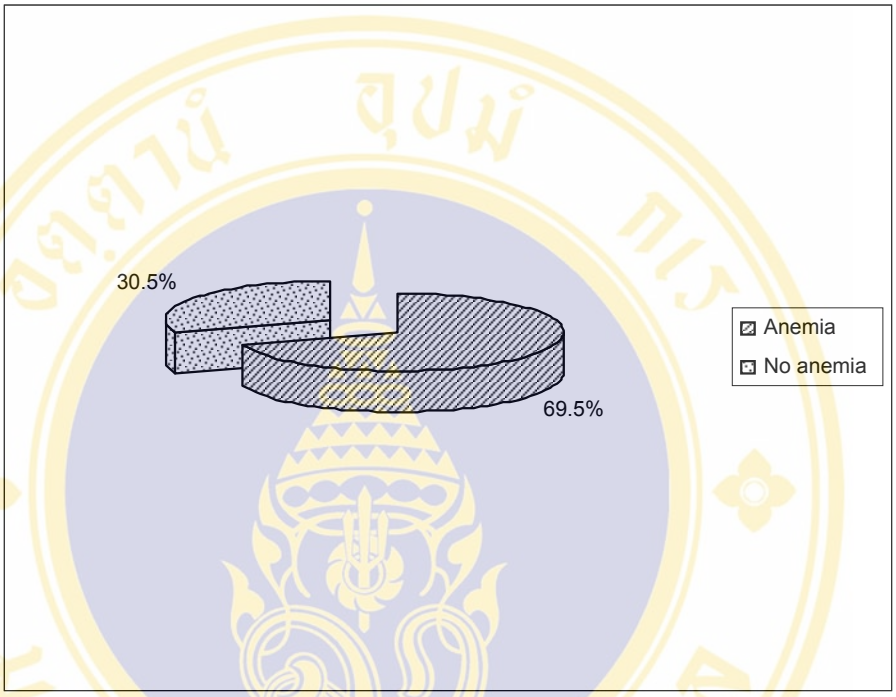

Figure 3. The proportion of children with falciparum malaria who had anemia (Hb <11.5g/dl)

Table 4. Laboratory findings in 116 children with uncomplicated falciparum malaria

Findings	Minimum	Maximum	Mean (SD)
Parasite count (n=116)			
Pf density/µl	3,750	252,000	75,512.4 (61158.6)
Other laboratory findings			
WBC ($\times 10^3$/µl)	1.0	18.0	6.9 (2.7)
RBC ($\times 10^6$/µl)	1.8	8.3	4.4 (1.0)
Hemoglobin (g/dl)	5.0	14.4	10.7 (1.8)
Hematocrit (%)	16.6	45.0	33.1 (5.8)
Platelet ($\times 10^3$/µl)	18.0	460.0	154.3 (97.4)
Band (%)	00	5.0	0.21 (0.8)
Neutrophil (%)	25.0	91.0	61.8 (14.9)
Eosinophil (%)	00	19.0	1.8 (2.8)
Basophil (%)	00	2.0	0.3 (0.5)
Lymphocytes (%)	7.0	66.0	30.9 (13.0)
Abn. Lymphocytes (%)	00	6.0	0.2 (0.8)
Monocytes (%)	00	16.0	4.9 (3.8)
Na^+ (mEq/l)	116.7	145.5	134.1 (5.4)
Cl^- (mEq/l)	98.0	109.0	103.3 (3.0)
HCO_3^-(mEq/l)	18.0	29.0	22.2 (2.9)
Blood sugar (mg/dl)	43.0	341.0	99.9 (34.5)
Total bilirubin (mg/dl)	0.3	3.0	1.2 (0.7)
Direct bilirubin (mg/dl)	0.08	0.6	0.3 (0.1)
AP (U/l)	31.0	851.0	187.6 (173.7)
AST (U/l)	3.0	163.0	40.0 (25.7)
ALT (U/l)	4.0	166.0	27.6 (25.7)

Table 5. Abnormal laboratory findings in 116 children with uncomplicated falciparum malaria

Laboratory findings	Values
Leucopenia (<4×10^3/µl) [No. (%)]	8 (6.9)
Leucocytosis (>10×10^3/µl) [No. (%)]	13 (11.2)
Anemia (Hb<11.5 g/dl) [No. (%)]	57 (69.5)
Thrombocytopenia [No. (%)]	
Platelet <50×103/µl	16 (14.0)
50-100×103/µl	23 (20.2)
100-150×103/µl	22 (19.3)
Hyponatremia (serum sodium <135mEq/l) [No. (%)]	48 (48.5)
Elevated bilirubin (total bilirubin>2mg/dl) [No. (%)]	13 (11.9)
Elevated AST (>45U/l) [No. (%)]	30 (26.0)

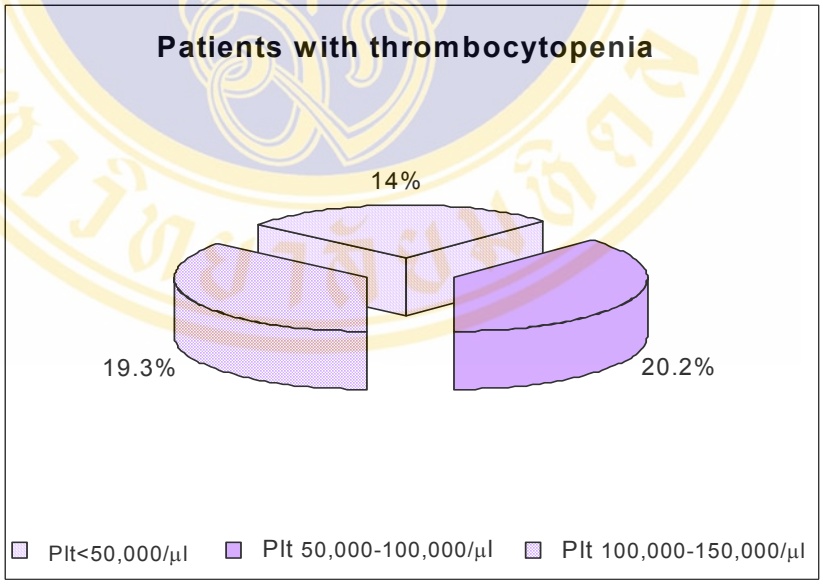

Figure 4. The proportion of children with falciparum malaria who had thrombocytopenia

3. Effects of treatment with three different regimen

Among 116 cases that were recruited, 54 patients were treated with quinine (Q), 32 patients received artesunate suppository combined with mefloquine (AS-MQ) and 30 patients received artemether combined with lumefantrine (AT-L). Only 45 (83%), 25 (78%) and 28 (93%) patients in the Q, AS-MQ and AT-L group respectively completed the 28-day follow-up period (Figure 5). Quinine was given at the dosage of 10 mg/kg/d 3 times a day for 4 days, then 15 mg/kg/d 3 times a day for the next 4 days; rectal artesunate was administered 10-19 mg/kg/d for 3 days followed by mefloquine 25mg base/kg in two divided doses; and artemether-lumefantrine was used in a dosage of artemether 1.5 mg/kg and lumefantrine 9 mg/kg at 0, 8, 24 and 48 hours. The baseline demographic, clinical and laboratory characteristics are shown in table 6 and 7. There were no significant differences among the treatment groups in the baseline clinical and demographical features except the history of previous malaria infection. Ten children (31.2%) in AS-MQ group had history of previous malaria infection while only one child (3.3%) in AT-L group and 4 (7.4%) in quinine group experienced prior malaria infection (p= 0.01). The laboratory findings were also comparable among different treatment groups. The mean parasite counts before treatment were comparable among the three treatment groups without statistically significant difference in parasite count before treatment (p= 0.9).

Table 6. Baseline demographic and clinical characteristics according to treatment groups

Characteristics	Q (n=54)	AS+MQ (n=32)	AT+L (n=30)	P-value
Mean (SD) age (years)	9.2 (2.7)	8.2 (3.1)	8.9 (2.8)	0.28
Sex [No. (%)]				
Male	26 (48.1)	18 (56.3)	18 (60.0)	0.54
Female	28 (51.9)	14 (43.7)	12 (40.0)	
Mean (SD) height (cm)	123.9 (16)	121.2 (19.4)	124.3 (15)	0.72
Mean (SD) weight (kg)	25.1 (8.3)	21.4 (6.7)	24.3 (8.2)	0.10
Patients who had previous malaria infection [No.(%)]	4 (7.4)	10 (33.3)	1 (3.3)	0.01
Patients who had G-6PD deficiency [No. (%)]	4 (7.4)	3(10.7)	4 (13.3)	0.7
Mean (SD) duration of fever before treatment (d)	3.7 (2.0)	4.6 (2.4)	3.6 (2.1)	0.18
Mean (SD) highest fever (°C) before treatment	38.6 (1.1)	38.4 (1.0)	39.0 (1.1)	0.08
Mean (SD) respiratory rate/minute	31 (7)	24 (3)	32 (8)	0.48
Mean (SD) pulse rate/minute	103 (14)	106 (12)	111 (13)	0.06
Mean (SD) BP (mmHg)				
Systolic	100 (8.3)	98 (10.7)	103 (10.6)	0.15
Diastolic	62 (9.7)	60 (9.4)	65 (8.3)	0.12
Patients with hepatomegaly [No.(%)]	33 (61.1)	13 (40.6)	20 (69.0)	0.06
Patients with splenomegaly [No.(%)]	32 (59.3)	17 (53.1)	16 (55.2)	0.84

Table 7. Baseline laboratory characteristics in three treatment groups

Characteristics	Q (n=54)	AS-MQ (n=32)	AT-L (n=30)	P-value
Mean (SD) Pf density/μl	75768.5 (66374.7)	74576.9 (49889.9)	76049.4 (64178.4)	0.90
RBC (× 10^6/μl)4.4	4.1	4.7	0.06	
WBC (× 10^3/μl)	6.8	6.67	7.2	0.65
Hb (g/dl)	10.9	10.2	10.9	0.22
Hct (%)	33.4	31.1	34.4	0.63
Mean platelet count (×10^3/μl)	149.7	142.6	175.4	0.38
Na^+ (mEq/l)	134.0	135.2	133.5	0.57
K^+ (mEq/l)	3.8	4.0	3.9	0.67
Blood sugar (mg/dl)	101.8	103.2	93.3	0.48
Total bilirubin (mg/dl)	1.1	1.0	1.2	0.51
AST (U/l)	38.9	34.6	49.7	0.06
ALT (U/l)	28.3	19.3	34.1	0.08
AP (U/l)	212.4	143.5	169.0	0.27

3.1 Efficacy of different treatment regimens

The primary parameter for evaluating the efficacy of antimalarials was the 28-day cure rate. Secondary efficacy endpoints were the parasite clearance time and the fever clearance time. Table 8 summarized the efficacy endpoints. Both rectal artesunate combined with mefloquine and artemether-lumefantrine cleared peripheral parasitemia significantly faster than quinine ($p < 0.001$). The mean (SD) parasite clearance times in quinine, artesunate-mefloquine and artemether-lumefantrine were 78.5 (35), 50 (18) and 37.5 (8.8) hours respectively (Figure 7). Fever clearance time was also significantly shorter in the artesunate-mefloquine and artemether-lumefantrine groups ($p = 0.002$) compared to the quinine group.

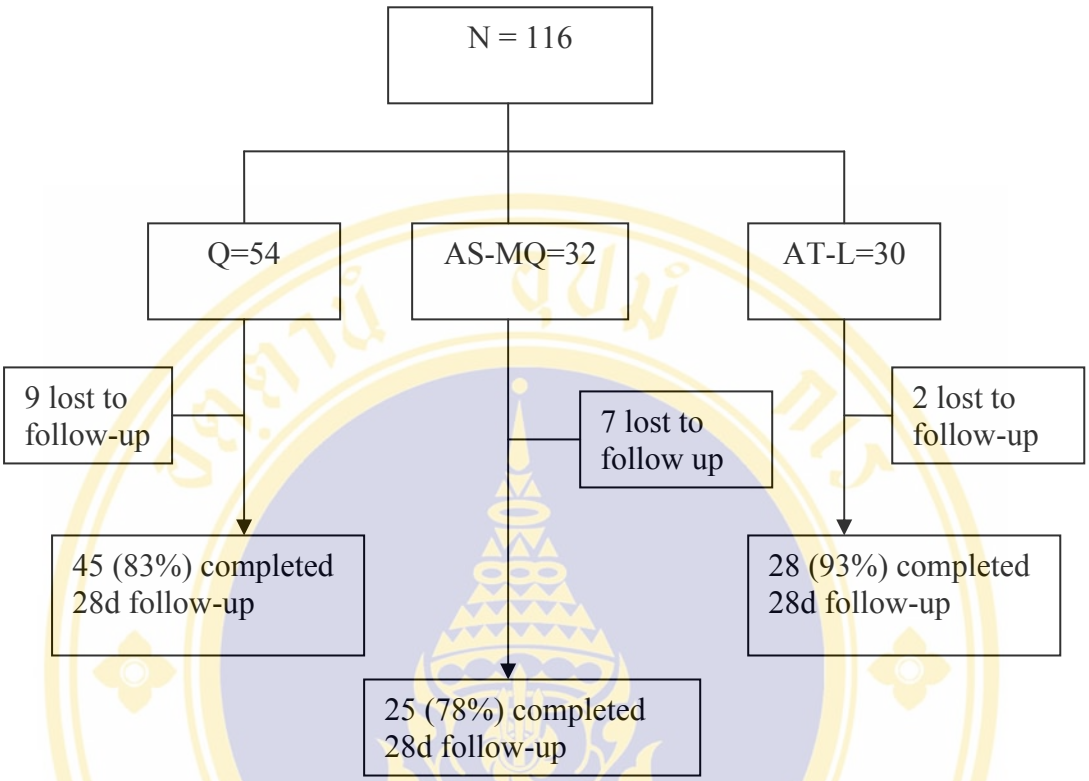

Figure 5. Study profile with different treatment regimens

The mean (SD) fever clearance times were 66.2 (41.7), 41.2 (27.1) and 39.9 (27.5) hours in quinine, artesunate-mefloquine and artemether-lumefantrine group respectively (Figure 6). Rectal artesunate-mefloquine and artemether-lumefantrine groups were comparable in terms of fever and parasite clearance time (p= 0.13 and 0.98 respectively). All patients cleared peripheral parasitemia within 7 days. There was no difference in cure rate at day 14. However, at day 28, it was observed that rectal artesunate combined with mefloquine group exerted a higher cure rate (92.0%) comparing to quinine and artemether-lumefantrine groups (75.6% and 71.4% respectively). Nevertheless, the cure rate was not statistically different among the three groups (p= 0.15).

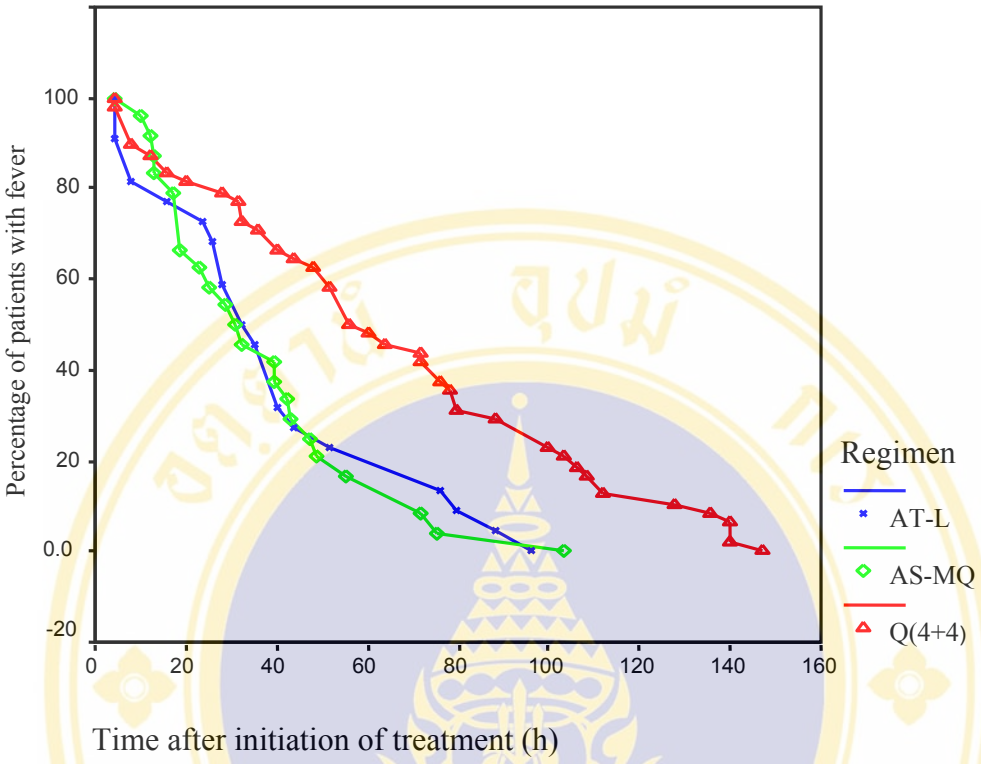

Figure 6. Fever clearance after treatment with 3 different regimens

Table 8. Efficacy of different regimens in Thai children with uncomplicated falciparum malaria

Outcome	Q (n=54)	AS-MQ (n=32)	AT-L (n=30)	P-value
Cure rate (%)	75.6	92.0	71.4	0.15
Mean (SD) FCT (h)	66.2 (41.7)	41.2 (27.1)	39.9 (27.5)	0.002
Mean (SD) PCT (h)	78.5 (34.8)	50.4 (18.2)	37.5 (8.8)	<0.001
Reappearance of parasitemia (%) in 28 d	24.4	8.0	28.6	0.27

FCT= fever clearance time, PCT= parasite clearance time, h=hour

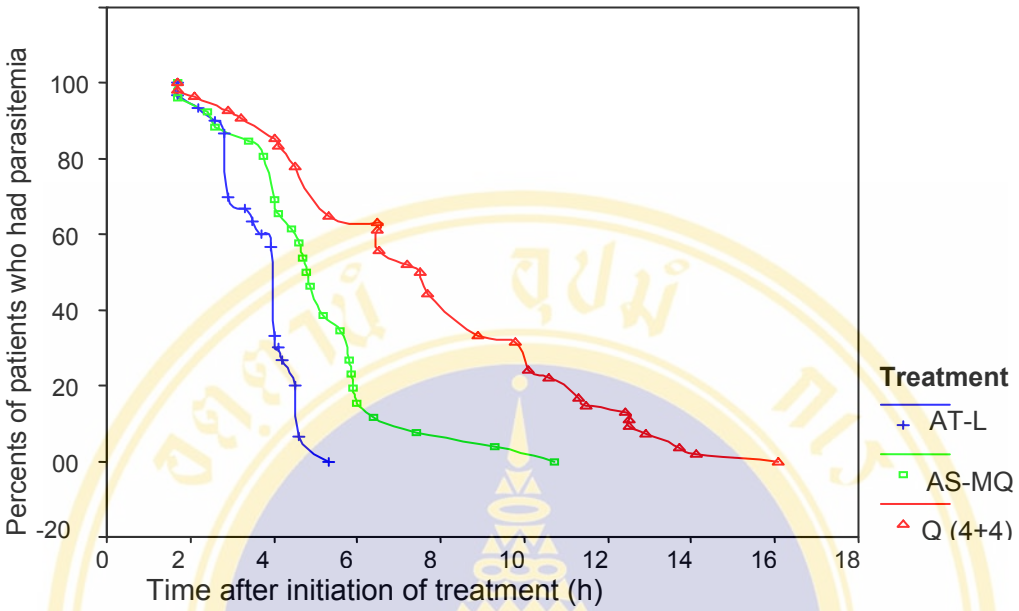

Figure 7. Parasite clearance after treatment with 3 different regimens

3.2 Adverse effects of antimalarial drugs

It was difficult to distinguish between symptoms of acute malaria and drug related side effects. We defined the side effects as the new symptoms or signs that did not exist on admission but appeared after initiation of treatment. Patients in the three treatment groups tolerated the drugs well. No major adverse effects were observed. No clinically significant changes in vital signs were noted during the study. Most adverse events were mild in intensity. The common adverse effects were anorexia, vomiting, nausea and headache (Table 9 and Figure 8)). It was observed that artesunate-mefloquine was better tolerated than quinine and artemether-lumefantrine although it was not statistically significant. Eleven patients had G-6-PD deficiency, but no clinical evidence suggesting significant hemolysis was noted. No patient died or developed severe malaria during the study. No data for tinnitus, dizziness or other side effects were recorded.

Table 9. Adverse effects of antimalarial treatment with 3 different regimens

Adverse effects	Q n (%)	AS-MQ n (%)	AT-L n (%)	P-value
Anorexia	4/48(8.3)	0/12(0)	1/26(3.8)	0.47
Vomiting	3/49(6.1)	0/12(0)	4/26(15.3)	0.20
Nausea	2/47(4.2)	0/12(0)	3/25(12)	0.26
Headache	2/49(4)	0/12(0)	4/28(14.2)	0.13
Chill	2/47(4.2)	1/12(8.3)	1/29(3.4)	0.80
Abdominal pain	2/42(4.7)	0/12(0)	0/25(0)	0.40
Itching	(-)	1/12(8.3)	(-)	(-)
Cough	0/2 (0)	1/12(8.3)	0/1(0)	0.90

(-) = No data were available

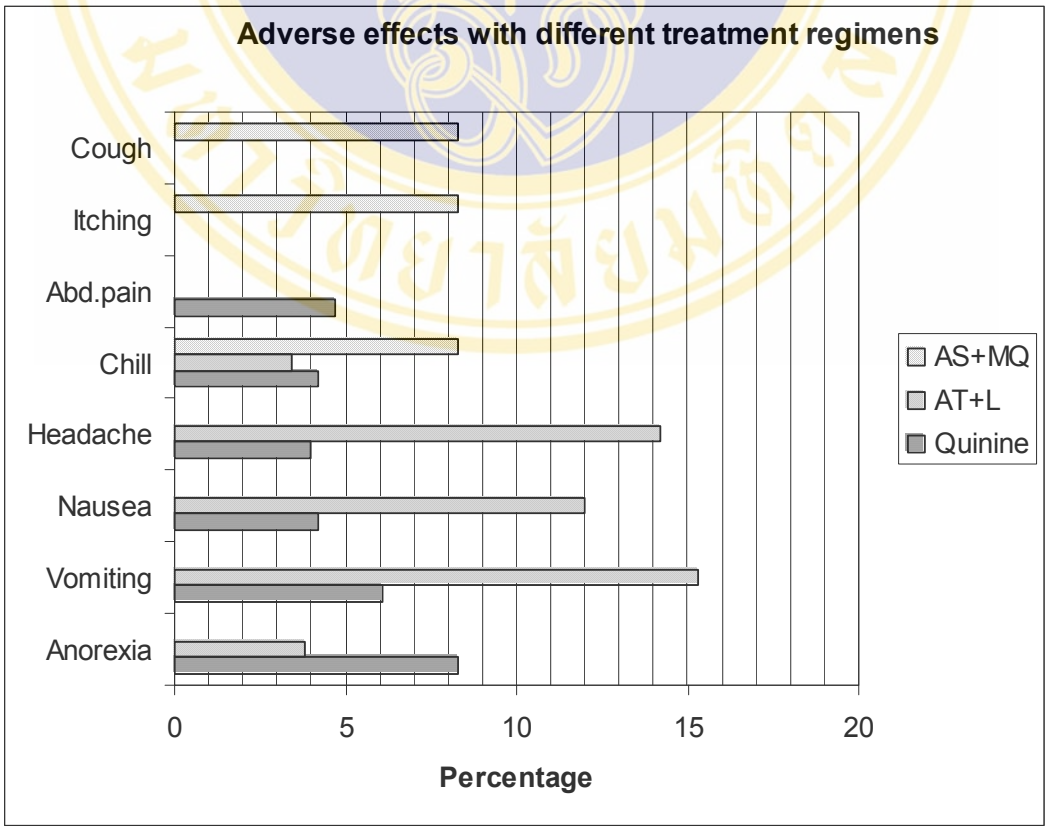

Figure 8. Adverse effects observed in different treatment groups

3.3 Effects of treatment on laboratory values

Table 10 shows the mean changes in laboratory values on day 7 after initiation of treatment. No significant differences in changes of mean laboratory values were found except AST which significantly decreased on day 7 comparing to day 0. No untoward hematological effects of the three treatment groups occurred. Mean WBC counts in AS-MQ and AT-L groups increased about 2.0 × 10^3/µl but not beyond the normal limit. Thrombocytopenia (platelet <150 × 10^3/µl) was a common finding (53% of children) at baseline platelet count. On day 7 a remarkable increase in platelet counts were observed in all three groups with a mean change of 129.2, 139.2 and 120.6 × 10^3/µl in quinine, artesunate-mefloquine and artemether-lumefantrine group respectively (Table 10 and Figure 10). These changes were similar among different treatment groups. Serum electrolytes, particularly the proportion of patients who had mild to moderate hyponatremia (Na^+ <135 mEq/l), decreased from 48% at baseline to 7.0% on day 7. Elevated AST and ALT (>45U/l) were found in 26.5% and 10.6% of the patients before treatment while only 10% and 5 % of the patients had elevated AST and ALT on day 7 respectively. Figure 11 shows the percentages of patients who had elevated AST (>45 U/l). The mean reduction of AST was 11 U/l, 4 U/l and 23 U/l in quinine, artesunate-mefloquine and artemether-lumefantrine group respectively (p= 0.01). Hematocrit and hemoglobin changed more slowly. A negative trend of hemoglobin and hematocrit changes within the first seven days were observed in all three groups but most of them gradually recovered later. On follow-up at day 28 the mean hemoglobin was 12.1g/dl, 11.3g/dl and 11.8g/dl in quinine, artesunate-mefloquine and artemether-lumefantrine groups respectively (Figure 9).

Table 10. Mean changes in laboratory values between the day of admission and day 7 (D_7-D_0) after treatment

Lab. values	Quinine	AS-MQ	AT-L	P-value
WBC ($\times 10^3/\mu l$)				
Initial	6.86	6.66	7.2	
Mean change	0.7	2.4	2.0	0.07
Hemoglobin (g/dl)				
Initial	10.9	10.2	10.9	
Mean change	-1.0	-1.0	-0.4	0.41
Platelet ($\times 10^3/\mu l$)				
Initial	149.7	142.6	175.4	
Mean change	129.2	139.2	120.6	0.89
Na^+ (mEq/l)				
Initial	134.0	135.2	133.5	
Mean change	5.56	3.5	7.0	0.40
AST (U/l)				
Initial	38.9	34.6	49.7	
Mean change	-11	-4.5	-23.3	0.01
ALT (U/l)				
Initial	28.3	19.3		34.1
Mean change	-6.5	0.00	-10.0	0.35
Eosinophil (%)				
Initial	1.5	2.1	1.8	
Mean change	4.4	4.2	4.4	0.99
Glucose				
Initial	101.8	103.2	93.3	
Mean change	22.9	17.9	13.1	0.57

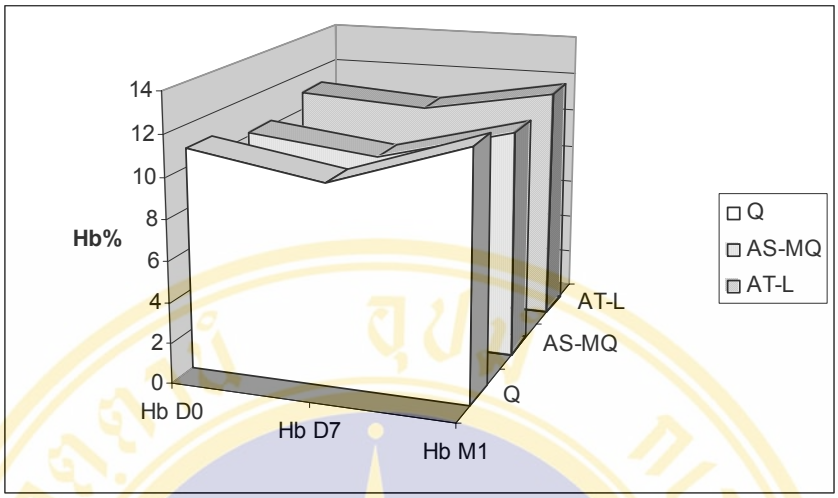

Figure 9. Mean hemoglobin in three treatment groups before and after treatment

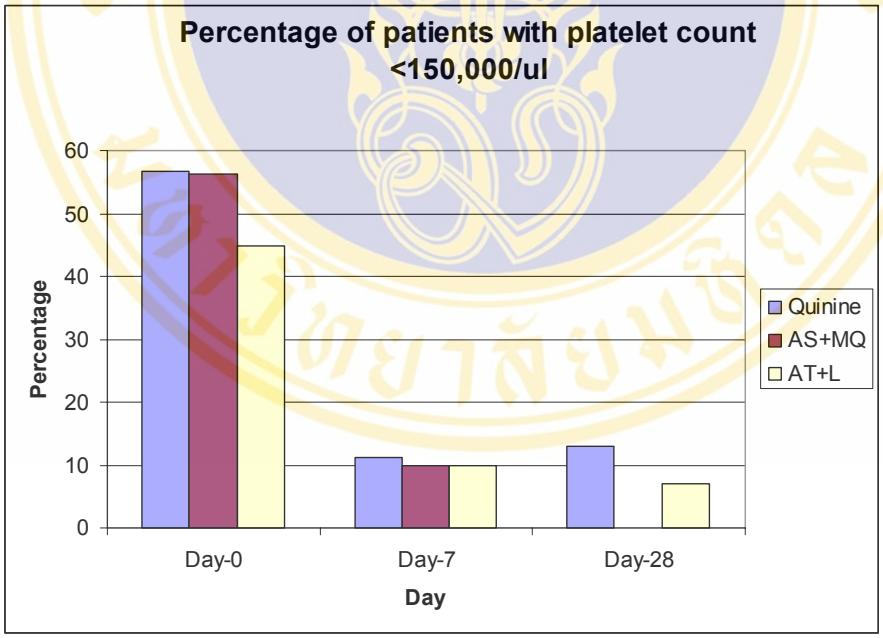

Figure 10. Percentage of patients who had thrombocytopenia before and after treatment

There was an interesting observation regarding the changes of eosinophil count. On admission the overall mean percentage of eosinophil (i.e. mean for all groups) was 1.7% which increased to 6.1% and 8.5% at day-7 and day-28 after treatment respectively. There was no statistical difference in changes of mean eosinophil percentage among the treatment groups.

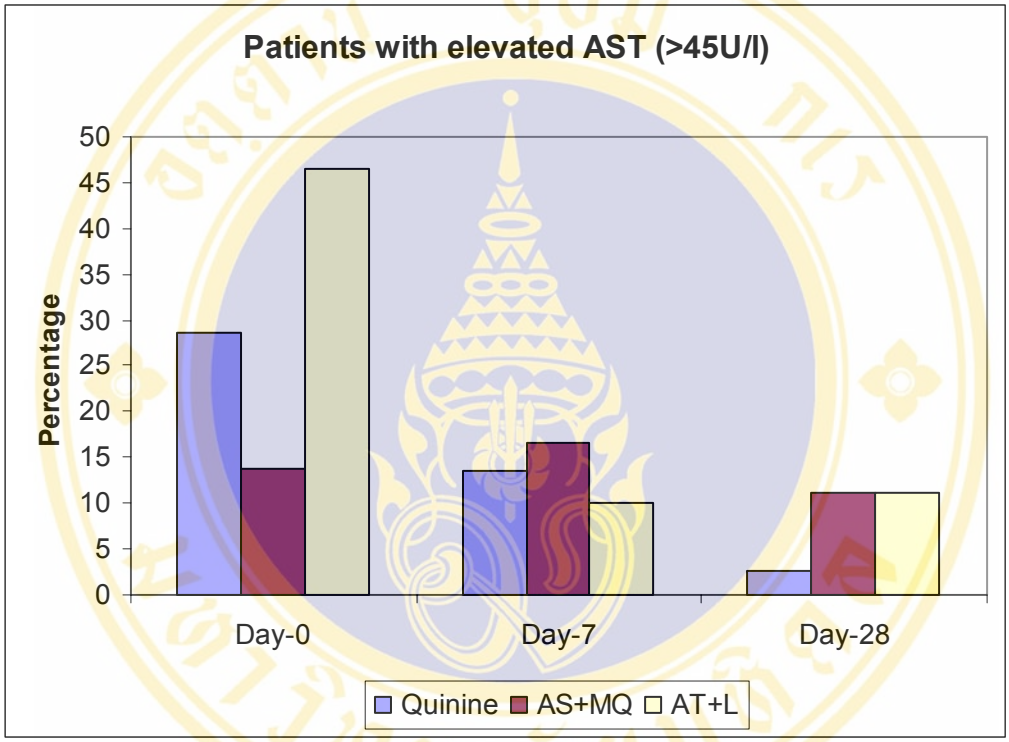

Figure 11. The percentage of patients who had elevation of AST before and after treatment with different antimalarials

4. Relationship between initial parasitemia and therapeutic response.

To determine the relationship between initial parasite count and 28-day cure rate, each treatment group was divided into two subgroups: patients who had initial parasitemia <100,000/µl and who had parasitemia >100,000/µl. The 28-day cure rate was compared between two subgroups in each treatment regimen. There was no significant difference in cure rate between the two subgroups of different initial parasite density (Table 11). The fever clearance time in quinine had positive linear correlation to the initial parasite density but there was no correlation between the

fever clearance time and initial parasitemia in AT-L (Table 12). On the other hand, there was negative correlation between fever clearance time and initial parasite density in AS-MQ group. Parasite clearance times in all three treatment regimens were independent from initial parasite density.

Table 11. Relationship between initial parasite density and 28-day cure rate

Regimen	Pf<100,000/µl Cure rate [No. (%)]	Pf>100,000/µl Cure rate [No. (%)]	P-value*
Q	21/28 (75.0)	13/17 (76.5)	0.84
AS-MQ	17/18 (94.4)	6/7 (85.7)	0.86
AT-L	15/20 (75.0)	5/8 (62.5)	0.96

* Chi-square with Yates correction

Table 12. Correlations between initial parasitemia and therapeutic response

Outcome	Correlation coefficient	P-value*
Q		
FCT	0.41	0.004
PCT	0.19	0.15
AS-MQ		
FCT	- 0.39	0.03
PCT	0.10	0.57
AT-L		
FCT	0.20	0.36
PCT	0.28	0.13

* Spearman's correlation

CHAPTER VI
DISCUSSION

Treatment of acute falciparum malaria in Southeast Asia especially in Thailand is becoming difficult because of increasing resistant to all available antimalarials. In 1982 quinine used for 7 days yielded cure rate of 75%. A modified eight days regimen in children improved the cure rate to 85% in 1982-85 (Chongsuphajaisiddhi et al., 1983). The cure rate decreased again to 75% in 1996 (Sabchareon et al., 1998). Artemisinin derivatives (e.g. artesunate, artemether) are potent, rapidly acting antimalarials that can reduce parasitemia by 90% within 24 hours after treatment in uncomplicated malaria. However, recrudescence within 28 days may range from 10 to 100% depending upon the dosage, duration of treatment and severity of diseases if artemisinin derivatives are used alone (Bunnag et al., 1991; Hien et al., 1991). Therefore, these drugs should be combined with mefloquine or other long acting antimalarials. Artesunate combined with mefloquine has been used as the standard regimen for the treatment of multi-drug resistant falciparum malaria in Thailand. Recently artemether in combination with lumefantrine has been successfully introduced for the treatment of uncomplicated falciparum malaria with a cure rate of 97% (Vugt et al., 1999). Continuous investigation on the efficacy of existing antimalarials and alternative drugs is necessary to cope with the problem of increasing resistance of falciparum malaria.

In this study, it was found that both artesunate-mefloquine and artemether-lumefantrine cleared the peripheral parasitemia significantly faster than quinine (p-value <0.001). The mean parasite clearance time in quinine, artesunate-mefloquine and artemether-lumefantrine groups were 78.5, 50.4 and 37.5 hours respectively. Fever clearance time was also significantly shorter in AS-MQ and AT-L groups than in quinine group (p= 0.002) which reiterated the previous studies (Vugt et al., 1999; Pukrittayakamee et al., 2000). Artesunate-mefloquine and artemether-lumefantrine were comparable in terms of PCT (p= 0.13) and FCT (p= 0.98).

A study in 1981 involving children aged from 2 to 12 years showed that quinine in a modified 7-day regimen (10 mg base/kg 3 times a day for first 4 days then, 15 mg base/kg 3 times a day next 3 days) yielded a cure rate of 87% (Chongsuphajaisiddhi et al., 1983). This regimen (Q4-4), probably based on that study, is now practiced in Thailand especially for the treatment of uncomplicated falciparum malaria in children below 7 years old. The 28-day cure rate with quinine in present study was 75% which was lower than that of the previous study. This lower efficacy, slower clearance of parasite (78.5 hours) and longer fever clearance time (66 hours) with quinine (Q4-4) may suggests that sensitivity to quinine reduced again in Thailand or the dosing schedule used may be facing problem. Further prospective studies are needed to confirm the results of this study.

Vugt et al, (1999) in a study found that 4-dose regimen of AT-L was less effective (cure rate 83%) than 6-dose regimen (cure rate 97%). Treatment with artemether-lumefantrine in present study led to a cure rate of 71%, which was below the recommended threshold of 75% for an effective antimalarial drug (WHO, 2000) and lower than the cure rate reported in that study. It might be because of small sample size or due to re-infection that could not be excluded since genotyping was not done in this study. Further studies should be done and if drug resistant really occurred, further studies for readjustment of the dosing schedule of the drug should be done.

The results of this study demonstrate that rectal artesunate at the dose of 10-19 mg/kg once daily for 3 days combined with mefloquine 25 mg base /kg in two divided doses is highly effective in treating children with uncomplicated multi-drug resistant malaria with a cure rate of 92% which is consistent with previous study (Sabchareon et al., 1998). The evidence from this study suggests that a daily (24 hour) dosing intervals of rectal artesunate are adequate for children with uncomplicated falciparum malaria. The wide variation of doses (10-19 mg/kg) was because of unavailability of appropriate formulation of suppositories according to age during the treatment period. Suppositories are easy to administer and rapidly absorbed. One problem with suppositories is that the drug could be spontaneously extruded without being noticed. Patients need to rest in bed for approximately 1 hour after administration to avoid the expulsion. However no such incidence was recognized during this study. This study suggests that artesunate suppositories could be very

useful in the treatment uncomplicated falciparum malaria and in preventing malaria related mortality in children. This regimen may be particularly valuable for children with falciparum malaria who can not tolerate oral medication and in situations where safe administration of parenteral antimalarials is not available

All three treatment regimens were well tolerated and there were no significant differences in the incidence of adverse events among the groups. The commonly found side effects were mild and comprised nausea, vomiting, headache, anorexia, abdominal pain and cough. In general, vomiting (15%), headache (14%) and nausea (12%) were more frequent in artemether-lumefantrine group than in quinine and artesunate-mefloquine groups. No signs of cardio-toxicity or hypotension were observed although no data of electrocardiographic monitoring was available. No untoward hematological change or drug related hypoglycemia was recorded.

The fever clearance time correlated to the initial parasite density in patients treated with quinine while there was no such correlation in patients treated with AT-L and negative correlation in the patients treated with AS-MQ. The correlation between fever clearance time and initial parasite density is therefore inconclusive and need further studies. Parasite clearance times were independent from initial parasite density irrespective of the treatment regimen. This study could not show any relationship between initial parasite count and 28 day cure rate.

Regarding clinical manifestation, differentiation of malaria from other causes of fever only on clinical background is extremely difficult because of non-specific signs and symptoms. Older children in hyperendemic area may present as asymptomatic parasitemia (Fernando and Wickremasinghe, 2002). In this study all children were febrile before treatment as per inclusion criteria with a mean (SD) temperature of 38.6^{o}C (1.1). The mean duration of fever before treatment was 4 days. In the present study, the most common clinical manifestations were weakness (88%), headache (74%), chill (58%), cough (30%), myalgia (46%), hepatomegaly (57%), splenomegaly (56%) and dehydration (35%). All these findings are similar to that of the previous studies (Luxemburger et al.,1998; Fernando and Wickremasinghe, 2002). Thrombocytopenia is a common finding of acute falciparum malaria which resolves synchronously with the resolution of infection (Pukrittayakamee et al., 1989) and seldom sufficient to cause major bleeding. Platelet activation and aggregation occur in

acute falciparum malaria with accelerated splenic removal of aggregated or degranulated platelets. Pooling of platelets in the vasculature of enlarged spleen and liver may be another contributory mechanism (Looareesuwan et al., 1992). The role of immune processes in the thrombocytopenia remains speculative (Kelton et al., 1983). In this study reduction in platelet count (<150,000/µl) was found in 53% of the patients on admission which gradually resolved to be only 10% on day 7 without any occurrence of bleeding manifestation. Anemia is another frequent finding in childhood falciparum malaria. White and Ho (1992) described anemia in falciparum malaria resulting from the destruction of parasitized erythrocytes, the shortened survival of un-parasitized erythrocytes and a variable degree of bone marrow dyserythropoiesis. We found that 69% of the patients had mild to moderate anemia (Hb <11.5 g/dl) before treatment. The fall in hematocrit and hemoglobin attributable to malaria in this study was greatest at day 7 of treatment (around 1-1.5 weeks after illness) with a mean fall of 1.7 g/dl from the pre-treatment period which is consistent with previous studies (Price et al., 2001). Following the initiation of treatment in this study, the eosinophil count increased from 1.7% (±2.8) at baseline to 6.1% (±6.0) and 8.5% (±7.8) at day 7 and day 28 respectively. The elevated eosinophil counts might be related to helminthic infections with transient suppression of pre-existing eosinophilia by *P. falciparum* parasitemia (Shanks and Wilaratanaporn, 1992). Hyponatremia (Serum sodium <135 mEq/L) was found in 48.5% of the patients which supports a previous study. Profuse sweating, decreased intake and increased loss of electrolytes with vomiting or diarrhea may be the reasons of hyponatremia. There is also a possibility of an inappropriate secretion of anti-diuretic hormone (Miller et al., 1967). In this study, mild elevation of liver enzyme (AST >45U/l) was found in 26% of the children. This elevated liver enzymes generally regarded as reflection of liver cell changes in acute malaria, also to some extent, contribution from enzymes released from lysed erythrocytes (Fletcher et al., 1988).

The limitation of this study was the study design (retrospective study) and time limitation. Only limited available data could be evaluated which resulted in an unequal sample sizes in each treatment group (54, 32 and 30 in quinine, artesunate-mefloquine and artemether-lumefantrine groups respectively). There might be difference in other characteristics such as malaria strain, time variation, etc. that might

influence the therapeutic outcomes and therefore make the comparison between different treatment groups inaccurate. A further, larger prospective study should be done.

CHAPTER VII
CONCLUSION

Differentiation of malaria from other causes of fever based only on clinical information is extremely difficult. Most of the symptoms and signs of childhood falciparum malaria in this study were very nonspecific. Malaria should be confirmed by microscopic examination of a blood slide as the result provides both malaria diagnosis and species differentiation. However clinical features found in this study along with epidemiological knowledge may serve as an important clue in early diagnosis of falciparum malaria.

Both artesunate suppositories in combination with mefloquine and artemether in combination with lumefantrine cleared fever and parasitemia faster than quinine although this study could not show any significant difference among the groups in terms of a 28-day cure rate. All three treatment regimens are well-tolerated. There were no significant systemic adverse effects or untoward hematological changes and no significant difference in adverse effects among the groups. Artesunate suppositories in combination with mefloquine are highly effective (cure rate of 92%) and best tolerated in treating children with uncomplicated multi-drug resistant falciparum malaria comparing to quinine and artemether-lumefantrine. This study suggests that artesunate suppositories could be very useful in the treatment of uncomplicated falciparum malaria and in preventing malaria related mortality in children especially those who can not tolerate oral medication. The lower efficacy (cure rate 75%) of quinine in this study is really a matter of concern. It suggests that sensitivity of *Plasmodium falciparum* to quinine with a modified 8-day regimen (Q4-4) proved in 1982-83 might reduce again or face a problem with dosing schedule. A further large scale prospective study to confirm the results of this study is warranted.

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APPENDIX A

DATA RECORD FORM

DATA RECORD FORM -A

1. Admission number [ ] [ ] [ ] [ ] / [ ] [ ]
2. Date of admission [ ] [ ] / [ ] [ ] / [ ] [ ] (D/M/Y)
3. Date of discharge [ ] [ ] / [ ] [ ] / [ ] [ ] (D/M/Y)
4. Age [ ] [ ] / [ ] [ ] (Y/M)
5. Sex (male = 1, female = 2) [ ]
6. Height (cm) [ ] [ ] [ ] . [ ] [ ]
7. Body weight (kg) [ ] [ ] [ ] . [ ] [ ]
8. Duration of fever before treatment (D) [ ] [ ]
9. Previous malaria infection [ ] No [ ] Yes If yes, last infection.....
10. Species of malaria infection [ ] Pv [ ] Pf [ ] Mixed
11. Antimalarial regimen
    - [ ] Quinine + Tetracycline
    - [ ] Quinine (Q4-4)
    - [ ] Artesunate + Mefloquine
    - [ ] Halofantrine
    - [ ] Artemether + Lumefantrine
    - [ ] Malarone
    - [ ] Chloroquine
    - [ ] Chloroquine+ Primaquine
    - [ ]

    Others_____

12. Onset of Treatment (D/M/Y) [ ] [ ]/ [ ] [ ] / [ ] [ ] hr:min [ ] [ ]:[ ] [ ] 13. Fever Clearance Time [ ] [ ] [ ] . [ ] [ ] hr [ ] Missing
14. Parasite clearance time Pf _____ hr. Pv _____hr. [ ] Missing
15. Cure [ ] Yes [ ] No [ ] Missing

DATA RECORD FORM -B

Symptoms and signs	D0	D1	D2	D3	D4	D5	D6	D7
Max. body temperature (^{o} C)								
RR (/minute)								
Pulse (/minute)								
Systolic blood pressure (mm Hg)								
Diastolic blood pressure (mm Hg)								
Weakness (N=0, Y= 1)								
Chill/Rigor (N=0, Y= 1) Headache (N=0, Y= 1)								
Myalgia (N=0, Y= 1)								
Abdominal pain (N=0, Y= 1)								
Diarrhea (N=0, Y= 1)								
Nausea (N=0, Y= 1)								
Vomiting (N=0, Y= 1)								
Anorexia (N=0, Y= 1)								
Cough (N=0, Y= 1)								
Hydration (No dehydration=0, Present dehydration = 1)								
Itching (N=0, Y= 1)								

Liver (cm) [ ] [ ].[ ] [ ]

Spleen (cm) [ ] [ ].[ ] [ ]

DATA RECORD FORM -C

Laboratory findings	**Do**	**D 7±1**	**D 28±2**
WBC count ($x10^9$/l)			
RBC count ($\times10^{12}$/l)			
Hb (g/dl)			
Hematocrit (%)			
Platelet count ($\times10^9$/l)			
Band (%)			
Neutrophil (%)			
Eosinophil (%)			
Basophil (%)			
Lymphocyte (%)			
Abnormal Lymphocyte (%)			
Monocyte (%)			
Sodium (mmol/l)			
Potassium (mmol/l) Chloride (mmol/l)			
Serum HCO_3 (mEq/l)			
Blood sugar (mg/dl)			
Direct bilirubin (mg/dl)			
Total bilirubin (mg/dl)			
Alk phosphatase (U/L)			
AST(U/L)			
ALT(U/L)			

G-6P D status [ ] Normal [ ] Deficient [ ] No data

DATA RECORD FORM-D

(Parasite count)

Actual date (D/M/Y)	**Actual time 24 hr (hr:min)**	***P. falciparum***		
		/1000RBC	**/200WBC**	**/µl**

APPENDIX B

WHO, 2000 CRITERIA FOR SEVERE AND COMPLICATED MALARIA

WHO, 2000 CRITERIA FOR SEVERE AND COMPLICATED MALARIA

1. Prostration (inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit)
2. Impaired consciousness
3. Respiratory distress (acidotic breathing)
4. Multiple convulsions (2 or more in a 24 hours)
5. Circulatory collapse
6. Pulmonary edema
7. Severe anemia (Hct < 15% or Hb < 5g/dl)
8. Abnormal bleeding
9. Jaundice
10. Haemoglobinuria (rare)
11. Hypoglycaemia (blood glucose<2.2mmol/L or <40 mg/dl)
12. Acidosis (plasma HCO_3 <15 mmol/L or arterial/capillary pH <7.35)
13. Hyperlactataemia (plasma lactate >5 mmol/L)
14. Hyperparasitemia ($\geq$4% in non immunes)
15. Renal impairment (urine output <12ml/kg/24 h or serum creatinine >3mg/dl)

* A patient will also be classified as severe malaria if schizontemia is detected in peripheral blood.

APPENDIX C

OPERATIONAL DEFINITIONS

OPERATIONAL DEFINITIONS

Fever: Body temperature $\geq 37.5^{0}$ C (oral)

Anemia: Hb < 11.5 gm/dl or hematocrit < 34.5%

Fever clearance time (FCT)**:** The time from beginning of antimalarial treatment until the body temperature falls to normal (<37.5^{o}C) and remained at that value for at least 48 hours.

Parasite clearance time (PCT)**:** The time from beginning of antimalarial treatment and the first negative blood slide which remained negative for at least 48 hours.

Cure: Negative peripheral blood smear for asexual parasite at 28-day of follow-up.

Antibiotics: Patients who had received any of the following antibiotics within 3 days prior to admission were excluded from the study:

sulfonamides, bactrim, tetracycline, doxycycline, macrolides, rifampicin, chloramphenicol and fluoroquinolones.

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