The Myanmar Health Sciences Research Journal, Vol. 18, No. 3, 2006

Comparing the efficacy of initial single dose rectal artesunate versus single dose intravenous artesunate at 24 hours and after full consolidation treatment in both groups with intravenous artesunate in severe falciparum malaria in adults

**Win Win Myint, *Khin Phyu Pyar, **Myat Phone Kyaw,*
**Than Htut, *Khin Nyo & ***Marlar Than*

*Defence Services General Hospital
**Experimental Medicine Research Division
Department of Medical Research (LM)
***Clinical Research Unit (Malaria)
Defence Services General Hospital

The mortality rate of severe falciparum malaria, once vital organ dysfunction occurs, is as high as 30%. In remote areas, transport problems lead to high morbidity and mortality. Rectal artesunate, single dose is recommended for initial management of severe falciparum malaria especially in remote areas, to be followed by consolidation treatment at the nearest health care facility. A randomized controlled trial of rectal artesunate and parenteral artesunate was studied on 60 severe falciparum malaria cases admitted to DSGH. Test drug was Plasmotrim 50 mg rectocap 200 mg stat dose. Control drug was injection Artesunate 120 mg intravenous infusion, both arms followed at 24 hours by injection Arte-sunate 60 mg intravenous infusion, repeated 12 hourly (total=480 mg), plus tetracycline or clindamycin 250 mg 6 hourly for 7 days. Parasite clearance time in rectal artesunate was 46.3 hours and IV artesunate group was 49.1 hours and the 24 hours parasite clearances were 81.7% and 76.3% respectively ($p>0.5$). There was no difference in the 48 hour parasite clearance which were 96.2% and 96.9% respectively. Fever clearance time (FCT) was 51.5 hours with rectal artesunate compared to 30.3 hours with IV artesunate ($p>0.1$). The clinical success rate for rectal artesunate was similar to that of parenteral artesunate at 24 hours in this study, highlighting that it can be used effectively prior to definitive treatment to reduce malaria morbidity and mortality.

INTRODUCTION

Falciparum malaria remains a major cause of death in the tropics. Cerebral malaria,the most prominent manifestation of severe malaria carries at 16-20% mortality [1]. Once multiple vital organ dysfunction occurs, the mortality rate, even after treatment, is as high as 30%(WHO, 2000) [2]. Despite many treatment trials, no interventions have been shown conclusively to reduce this high figure.

The artemisimine derivatives are now the most rapidly acting, safe and potent of all the antimalarial drugs for treatment of *P. falciparum* malaria. In rural areas, where the transport facilities are poor, the mortality and morbidity rate is higher because of late referrals. The early initiation of artemisinin compound can save lives. WHO (UNDP, World Bank, and WHO Special Program for Tropical Diseases Research) selected rectal artesunate for investigation as a candidate to provide therapeutic cover for the initial 24 hours after presentation. Studies in Africa reported artesunate in rectal preparation in adults and children had a median parasitaemia reduction of 99% at 24 hours [3]. Rectal artesunate single dose

has now been approved by the United States Food and Drug Administration (US-FDA), for the initial management of severe falciparum malaria patients, who are unable to take oral medication and where parenteral anti-malarial treatment is not available. It was to be followed by further consolidation treat-ment at nearest health care facility. Hence, rectal artesunate makes a good stopgap until patient reaches health facilities [4].

In Myanmar, the usefulness of artesunate suppositories (Plasmotrim^{TM} rectocaps) in severe falciparum malaria (including patients in un-rousable coma) has been reported by our group in a prospective double blind randomized controlled study on 100 adult patients, on two dosage regimens. Artesunate suppository total dose 800 mg and 1200 mg given over 3 days each, was well tolerated, effective and cleared parasitaemia within 60 hours in both dosage regimens. The addition of mefloquine ensured a satisfactory 28 day cure-rate of 100 % [5].

However, there are no reported data on the 24 hours efficacy of single dose rectal artesunate in Myanmar yet. This study was aimed to determine whether administration of single dose rectal artesunate would provide beneficial initial antimalarial cover, indicated by a rapid fall in the density of parasitaemia and clinical improvement without serious adverse reactions, compared to a standard i.v. artesunate regimen. It will also look into the outcome at 14 days, after giving consolidation treatment of i.v. arte-sunate (in accordance with the National malaria treatment guidelines for severe malaria).

Objectives

1. To compare the therapeutic efficacy at 24 hours, of a single dose rectal artesunate with a single dose iv. artesunate.
2. To compare the final outcome between the two groups at 14 days, after giving identical consolidation treatments of i.v. artesunate.

PATIENTS AND METHODS

Laboratory confirmed, severe falciparum malaria patients admitted to Clinical Research Unit (Malaria) Defence Services General Hospital were recruited for the study.

Inclusion criteria

- Both sexes
- Age between 10 - 60 years
- Positive peripheral blood film for trophozoite forms of pure *Plasmodium falciparum*
- Informed consent

Exclusion criteria

- Patients who received parenteral anti-malarials (quinine >1200 mg) within the past 24 hours
- Patients with other concomitant diseases
- Patients with severe diarrhoea, bleeding per rectum, dysentery

Withdrawal criteria

- Patient's request
- Any serious adverse effects to drugs
- Serious or repeated non-compliance with protocol specifications

Sample size

60 patients

Study design

A hospital–based randomized controlled study.

Study period

July 2004 to September 2005

Drug regimens

A. Initial treatment

Test drug (30 patients)

- Plasmotrim 50 rectocap (Mepha-Switzerland. Batch No. 0250638
- 200 mg (4 rectocaps) single stat dose

Control drug (30 patients)

- Artesunate injection 60 mg (Guilin – pharma, China, Batch No. 020702)
- 120 mg single dose i.v. infusion

B. Consolidation treatment at 24 hours followed by full course of treatment

Artesunate injection 60 mg (Guilin pharma-China) 60 mg i.v. infusion at 24 hours and then 12 hourly (total dose for full course: - 480 mg) was given for both arms of treatment.

C. Combination drug

For adults:- Tetracycline 250 mg (MPF-Myanmar) 6 hourly for 7 days

For pregnant females & children: -

Clindamycin (Kalbe - Farma, India)

250 mg 6 hourly for 7 days was given when the patient could take by mouth

Procedure

Eligible patients were subjected to the following procedure. Routine history taking , clinical examination and relevant investigations were done and recorded in the standard proforma. Patients were randomized to the drug regimens, using sealed envelopes.

The following assessments were made.

1. *Clinical* (Day 0,1,2,3,4,7 and 14)
   - Symptoms review
   - Adverse effect review (according to the check-list)
   - Physical examination
   - Body temperature recorded 4 hourly until normal for 24 hours and then daily up to Day 14.

2. *Parasitology* (Day 0,1,2,3,7 and 14)

   Giemsa's stained thick and thin blood smears were examined and parasite counts performed 6 hourly until negative for 24 hours and daily up to 3 consecutive negatives, then weekly up to Day14.

3. *Haematology* (Day 0, 3,7 and 14)
   - Hb%, T & DC

4. *Biochemistry* (Day 0, 3,7 and 14)
   - Serum bilirubin
   - Blood urea, sugar

5. *ECG* (Day 0,3, 7 and 14)

Therapeutic response was assessed as follows:

a) For clinical response at 24 hours
   Parasite clearance
   Fever clearance
   Development of severe symptoms and signs
   Mortality
   Adverse effects
   Tolerability of drug

b) For final outcome after consolidation treatment (at 14 days)
   Early treatment failure (ETF)
   Late treatment failure (LTF)
   Adequate clinical and parasitoligical response (ACPR)
   Mortality
   Sequelae
   Adverse effects

Adverse effects were noted by means of a check - list clinically, haematologically, biochemically and ECG in the proforma.

Ethical considerations

The protocol was approved by the Ethical Committee, Department of Medical Research (Lower Myanmar). Informed written consent was obtained from all the patients/ relatives.

Statistical evaluation

Statistical evaluation comparing the regimens was done by computer using EPI-INFO software. Categorical data were compared by calculating the chi-square value with Yates' correction or by Fischer's

exact test. Normally distributed continuous data were compared by the Student's t test and analysis of variance. Data not conforming to a normal distribution were compared by the Mann-Whitney U test.

Retreatment of failure

ETF cases were retreated with standard i.v. quinine dihydrochloride (10 mg of salt / kg 8 hourly).

LTF cases were retreated with standard oral quinine sulphate (10 mg of salt/kg three times a day).

RESULTS

Age, weight, initial temperature and initial parasite counts were comparable in the two groups. Initial parasitaemia was Mean (Range) 70,819 (1200 - 250,000) in artesunate rectocap and 50,933 (800 - 250,000) per microlitre in i.v. artesunate group. (p> 0.5) (Table 1).

Table 1. Baseline characteristics of the two groups

Parameters	Regimens		*'P'*
	PR Artesunate	IV Artesunate	
Age (years), mean	25.37	28.13	>0.5
(S.D.)	(8.71)	(11.37)	
Height (inches), mean	166.5	164.86	>0.1
(S.D.)	(10.09)	(8.28)	
Body weight (Kg) mean	49.22	50.79	>0.5
(S.D.)	(4.99)	(9.32)	
Initial temperature (°C) mean	38.7	38.67	>0.5
(S.D.)	(0.88)	(1.07)	
Initial parasitaemia / µl Geom mean(range)	70,819 (1200-250,000)	50933.33 (800-250,000)	>0.5

The rectal forms of artesunate were well tolerated and not expelled in adults, hence none were needed to be reinserted. At 24 hour after start of treatment, 43.3% of 30 patients who received rectal artesunate had a parasite density below 10% of baseline, compared with 36.7% of 30 on i.v. artesunate group. Percentage mean parasite reduction at 24 hours was 79.83 ± 22.38 % in per rectal group and 76.27 ± 21.78 % in the intravenous group. The median fractional reduction of parasitaemia at 24 hours was 88% and 79% in patients treated with rectal and intravenous artesunate, respectively (Table 2).

Table 2. Response at 24 hours and 48 hours for two groups

Response	Regimens	
	PR Artesunate	IV Artesunate
Response at 24 hours		
Percentage of patients with parasitaemia below 10% of baseline	43 .3	36.7
Percentage parasite reduction, mean (S.D)	79.83 ± 22.38	76.27 ± 21.78
Median fractional reduction of parasitaemia %	**88**	**79**
Tolerability of treatment	Good	Good
Adverse effect of drug	Nil	Nil
Mortality	Nil	1
Response at 48 hours		
Percentage of patients with parasitaemia below 10% of baseline	90	93.3
Percentage parasite reduction-mean (S.D)	92.47 (22.36)	96.89 (5.98)
Median fractional reduction of parasitaemia (%)	**100**	**100**
Tolerability of treatment	Good	Good
Adverse effect of drug	Nil	Nil
Mortality	Nil **	Nil

**(1 death at 72 hours)

At 48 hours, i.v. artesunate consolidation treatment started in both groups, 90% of 30 patients who received initial rectal artesunate, had a parasite density below 10% of baseline, compared with 93.3% of 30 patients who received initial i.v. artesunate. Percentage parasite reduction at 48 hours was 92.47 ± 22.36% in per rectal group and 96.89 ± 5.98 % in the intravenous group (p>0.5). The median fractional reduction of parasitaemia at 48 hour was 100% in both groups (Table 2). Parasite clearance time was 46.01 ± 21.36 hours and 43.39 ± 26.90 hours, and Fever Clearance time was 56.67 ± 46.85 hours and 27.87 ± 32.43 hours, respectively in the rectal and intravenous regimens (Table 3).

Adequate Clinical and Parasitological Response (ACPR) was 96.7% in per rectal group and 86.6% in intravenous group at14 days. Early treatment failure (ETF) was

3.33% in per rectal group and. 6.7% in intravenous group. Late treatment failure (LTF) was 0% in per rectal group and 6.7% in intravenous group and the results were not statistically different (Table 4).

There were no serious clinical, haemato-logical, biochemical, and electrographic adverse effects of therapy in the both groups within the 14 days observation periods.

Table 3. Clearance of fever and parasitaemia in two groups

Response	Regimens		*'P'*
	PR Artesunate	IV Artesunate	
Fever clearance time (hours) Mean (S.D)	56.67 (46.85)	27.87 (32.43)	>0.5
Parasite clearance time (hours) Mean (S.D)	46.01 (21.36)	43.39 (26.90)	>0.1

Table 4. Cure rates and outcome at 14 days

	PR Artesunate (n=30)		IV Artesunate (n= 30)	
	No.	%	No.	%
Early treatment failure (ETF)	1	3.33	2	6.7
Late treatment failure (LTF)	0	0	2	6.7
Adequate clinical & parasitological response (ACPR)	29	96.7	26	86.6
Sequelae	Nil		Nil	
Total	30	100	30	100

There were two cases that deteriorated in our study:

A 43-year-old female admitted with fever and jaundice and diagnosed initially as cholangiohepatitis in the surgical ward, was referred to the physician for development of acute renal failure with serum creatinine of 3 mg%. Peripheral blood film showed *P. falciparum* parasitaemia of 120,000/µl. In spite of giving intravenous artesunate, the patient rapidly became comatose GCS 3/15, with severe anemia and hypotension 70/50 and died of septicaemic shock within 72 hours after receiving treatment.

The second case was presented with jaundice, acute renal failure and serume
creatinine of 5 mg%, GCS 11/15 with peripheral parasitaemia of *P. falciparum* 9,000/ microlitre. He received i.v. artesunate and died at 24 hours after treatment.

DISCUSSION

Initial clinical outcome (Parasitaemia at 24 hours)

In Africa, Barnes *et. al* reported on 35 adults with moderately severe malaria, randomly assigned to rectal artesunate (single dose of about 10 mg/kg) or parenteral quinine treatment (10 mg/kg at 0, 4, and 12 hrs). Parasitaemia at 24 hours was less than 10% of baseline in 81% of patients allocated to artesunate, compared with 38% in the quinine-treated group. The median fractional reduction of parasitaemia at 24 hours was 99% and 72% in patients treated with artesunate and quinine, respectively [3].

In our study, on 30 adults receiving rectal artesunate 43.3% of patients had a parasite density below 10% of baseline, compared with 36.7% on i.v. artesunate group. The percentage of parasitaemia reduction at
24 hours from the initial baseline parasitaemia was 79.93% in per rectal group and 76.27% in intravenous group. The median fractional reduction of parasitaemia at 24 hours was 88% and 79% in patients treated with rectal and i.v. respectively. Hence, although the percentage of patients reaching below 10% baseline and median fractional reduction of parasitaemia are less than that of Barnes e*t. al*, the percentage reduction of parasitaemia at 24 hours in our study was quite satisfactory.

A single dose of artesunate suppositories at a dose of 200 mg was well tolerated in Myanmar adults, and as efficacious as a single dose of i.v. artesunate. There were no clinical, haematological, biochemical or

ECG adverse effects. After full consolidation treatment with standard therapy of i.v. artesunate, both treatment groups resulted in adequate parasite and fever clearance and satisfactory cure rates. Artesunate suppositories can be given safely and easily by anyone without need for much training, even in the home. However, as single administration, not a curative treatment for falciparum malaria, the need to watch for the expulsion of suppositories and to reinsert them, and of the need to ensure follow-up with an effective curative treatment should be properly informed to the care-givers.

It was concluded that per rectal artesunate is as effective as intravenous artesunate for rapid reduction of parasitaemia load at
24 hours, and is also as safe and effective as intravenous artesunate in the treatment of severe malaria in adults. Thus, single dose rectal artesunate in our study has equivalent clinical outcomes to that of single initial dose i.v. artesunate and also to those of Barnes *et al*. This treatment is of greatest relevance to communities in rural areas, where parenteral treatment is often not immediately available.

It was also recommended that in rural areas where facilities for parenteral treatment are unavailable, the single rectal artesunate which can be easily administered, may be used to serve as a stop gap treatment, before reaching health facilities for further consolidation treatment.

ACKNOWLEDGEMENT

We are greatly indebted to Major-General Than Aung, Director of Medical Services,

Ministry of Defence, for his kind permission and encouragement to carry out this study. We thank Professor Paing Soe, Director-General, Department of Medical Research, Lower Myanmar for his advice and support. Our gratitude goes to the Commanding Officer of D.S.G.H. 1000-Bedded Mingaladon for his supervision and to all staff of CRU (Malaria) D.S.G.H for their help and to all the patients for their co-operation.

REFERENCES

1. Management of severe malaria - *A practical handbook,* second edition WHO Geneva.
2. Severe falciparum malaria. WHO. *Transactions of the Royal Society of Tropical Medicine & Hygiene* 2000 (April); Vol: 94, Supplement.
3. Barnes KI, Mwenechanya J, Tembo M *et al.* Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomized study. *Lancet* 2004; 363:1598-605.
4. Breaking news 2004 Rectal artesunate makes a good stopgap. *www.who.int.tdr.malaria*.
5. Marlar Than, Zay Soe, Aung Zaw Oo, Aye Yu Soe, Kyi Kyi Tin, Khin Nyo & Myat Phone Kyaw. A double blind comparative trial of two dosage regimens of artesunate suppository in combination with oral mefloquine in severe falciparum malaria. *The Myanmar Health Sciences Research Journal* 2000;12 (1-3): 41-47.