Original Article

Randomized Control Trial of Quinine and Artesunate in Complicated Malaria

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Abstract. ***Objective:*** To study the comparative efficacy of the quinine and artesunate in complicated malaria in children. ***Methods:*** All cases admitted to the Pediatrics ward of our hospital with clinical features of complicated malaria (WHO criteria) having asexual forms of *P. falciparum* in the peripheral smear, were included in the study. Relevant investigations were carried out for confirmation of diagnosis and to assess the prognosis. The patients were sub-grouped into 6 categories as per clinical presentations and each subgroup received alternatively either quinine or artesunate by systematic random sample method. Every odd number received quinine (Group-1) and every even number received artesunate (Group-2). 40 cases in each group were considered for the study and the data obtained were compiled and analyzed by suitable statistical tests. ***Results:*** 80 children with complicated malaria enrolled in the present study, of which 48 were boys and 32 were girls. The mean age was 7.93+3.56 years. The most common presentations were fever, splenomegaly and altered sensorium. The CRT, FCT and PCT were significantly less in the artesunate group (50.4 ± 31.49hrs; 43.55 ± 20.12 hrs, and 41.67 ± 16.78 hrs respectively) as compared to the quinine group (70.15 ± 17.56 hrs, 62.23 ± 16.99 hrs, and 52.24 ± 12.69 hrs respectively) ($p<0.05$) No side effects were observed in the artesunate treated group. ***Conclusion:*** Artesunate is a much better drug than quinine in complicated malaria in terms of rapid coma resolution,fever clearance,parasite clearance and better tolerability.
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Key words : *Artesunate; Complicated malaria; Children; Quinine; Randomized control trial*

Malaria continues to be a major global health problem, affecting over 40% of world's population worldwide. Prevalence of malaria is estimated to be around 300-500 million people in some 101 countries with a global death rate over 3.5 million/year. In Asia maximum incidence is from India.[1]

P. falciparum is responsible for most severe, complicated often-fatal form of the disease. Multiple manifestations can occur singly or more commonly in combinations in the same patient. Quinine is the mainstay of treatment of complicated malaria. But also it is associated with several adverse effects. Because of the emergence of resistance to quinine, its effectiveness is declining in most part of Africa and Southeast Asia. [2,3,4]

Thousand years ago *qinghao* (Sweet wormwood) was in use in China as a herbal remedy for fever.[5] But during 1970s the Chinese scientists identified the active antimalarial ingredient, *qinghaosu* (Extract of *qinghao*) or artemisinin.[6] Since 1979 several derivatives of artemisinin have been synthesized and studied in China. Artemisinin suppositories, artesunate (oral or parenteral), intramuscular artemether and dihydroartemisinin tablets have all proved rapidly effective.[7] Taylor *et al*[8] and Murphy *et al*[9] in their study of cerebral malaria in Malawian children and African children respectively had noted rapid coma resolution and parasite clearance with artemether compared with those treated with quinine.We present our study on the comparative efficacy of quinine and artesunate with reference to clinical and biochemical profile in children with severe malaria.

MATERIALS AND METHODS

The present study was undertaken in the Department of Pediatrics, SCB Medical College and Hospital, Cuttack, Orissa, India, a tertiary care referral hospital from Jan 2000 to Jan 2002. The study protocol was approved by the Ethics committee of the Institute and parent's written consent was taken before the drug trial.

Criteria for Inclusion

Cases with clinical features suggestive of complicated malaria (According to WHO criteria, Table 1) having asexual forms of *P. falciparum* in the peripheral smear were included in the study.[10]

Criteria for Exclusion

- The cases having no asexual form of *P. falciparum* in peripheral smear were not taken in our study.
- Renal failure due to other causes.
- Hepatitis due to other causes.

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TABLE 1. Case Definition of Severe Malaria.[10]

Major signs		
Cerebral malaria/Unarousable coma	:	Failure to localize or respond appropriately to noxious stimuli (Glasgow coma score <8).
Severe anemia	:	Hb < 5gm/dl, Hematocrit ≤ 15%
Hypoglycemia	:	Blood glucose < 40 mg/dl
Circulatory collapse	:	Syst. BP< 50 mmHg.in children aged 1–5 yrs, <80 mm Hg in adults, Core-skin temperature difference of >2.5°C.
Renal failure	:	Urine output < 12 ml/kg/24 hrs. with no improvement on rehydration and S. creatinine > 3 mg/dl
Spontaneous bleeding/DIC	:	
Repeated convulsion	:	> 2 times generalized convulsions in 24 hr despite cooling.
Acidosis or Acidemia	:	Arterial pH < 7.25, plasma HCO_3 < 15 meq/L or venous lactate >6 mMol/L.
Hemoglobinuria	:	Not drug induced
Pulmonary edema	:	Adult respiratory distress syndrome
Postmortem diagnosis of malaria on needle biopsy of brain.		
Minor signs		
Impaired consciousness. Depressed level of consciousness but can localize painful stimuli.		
Jaundice detected clinically or serum bilirubin >3mg/dl.		
Prostration : Patient cannot sit or walk with no obvious neurological explanation.		
Hyperpyrexia : Rectal temp. >40 °C		
Hyperparasitemia. Parasite count >250,000/µl or >5%		

All suspected cases were subjected to the following investigations at the time of admission. (Day 0)

(a) Simultaneously thin and thick blood films were prepared and stained with Giemsa stain. Thick smear used to show the presence of parasite. Parasite count was done from the thin film. Level of parasitemia was expressed as the number. of parasitised RBCS per 1000 RBCS. This figure was then converted to number per microliter of blood.
(b) Hemoglobin, total and differential blood count and total platelet count.
(c) Bloodsugar, *S. urea*, creatinine, bilirubin (Total and direct), transaminases, alkaline phosphatase, acid base analysis.
(d) In suspected cases of cerebral malaria, lumbar puncture was done and cerebrospinal fluid (CSF) was evaluated for pressure, cells, sugar, protein and culture sensitivity.
(e) Urine analysis for sugar, albumin, red blood cell, pus cells and benzidine test for hemoglobinuria.

All the above hematological and biochemical tests were repeated on day 3 and 7.

The patients were subgrouped into 6 categories as per clinical presentations and each subgroup patients received either quinine or artesunate by "systematic random sample", every odd number received quinine (Group 1), and every even number received artesunate (Group 2), in the following dose. (A Postgraduate student allocated the patient to receive either drug after obtaining written consent of parents.)

Group 1(Q): 40 cases of complicated malaria were treated with quinine, in the dose of 20 mg/kg iv loading, followed by 10 mg/kg iv slowly at 8 hourly interval till the patient was conscious and was able to take orally. Rest of the treatment was completed by oral preparation to complete 7 days therapy.

Group 2 (A): 40 cases of complicated malaria were treated with artesunate, in the dose of 2.4 mg/kg iv stat, followed by 1.2 mg/kg after 6 hrs, then once daily for 5 days (iv route).

Supportive care like antibiotics, antipyretics, anticonvulsant, intravenous fluid, blood transfusion were given as and when required. Another Postgraduate student administered the drugs.

Follow-up of Patients

The patients were assessed by one faculty member who was not included in the study, for

1. Fever clearance time (FCT) in hours. Defined as the period from administration of the first dose of antimalarial till the axillary temp remained at or below 37°C for 72 hours.
2. Coma resolution time (CRT) in hours.Defined as time taken from start of therapy till patient had become fully conscious, and responded to verbal commands.
3. Parasite clearance time (PCT) in hours.Defined as the time taken from administration of first dose till parasites were undetectable in peripheral blood films and remained so for 7 days.
4. All side effects of drugs were also recorded.

Patients were followed up in the hospital for 10 days. Their clinical examinations were done twice daily. Vitals were monitored 4 hrly, blood for malaria parasite was tested 8 hrly. Survivors were discharged from the hospital on 10th day with instructions for follow-up in the out patient clinic on day 14, 21 and 28. During these visits their clinical status were assessed and blood samples were collected for hematological and biochemical tests.

Results: A total of 80 cases were enrolled in the study. Mean age of patients was 7.93 ± 3.56 years. Maximum number of cases were in the age group 4–7 yrs. (32.5%). The male to female ratio was 1.5 : 1 (48 boys and 32 girls).

Most common presentation in the present study was fever, splenomegaly and altered sensorium. Less common presentations were respiratory distress, hemoglobinuria, bleeding diathesis. The base-line characteristics were compared in two groups (Table 2).

Table 2. Clinical Profile of the Patients Under Trial

Sl. No.	Symptoms and Signs	Group–1 (Q) n=40	Group–2 (A)n=40	P value
1	Mean age ± SD	8.1±3.23	7.31±3.47	
2	Sex Boys	22	26	
	Girls	18	14	
3	Fever	40	40	
4	Splenomegaly	34	38	>0.05
5	Anemia	30	38	<0.05
6	Altered sensorium	33	33	
7	Hepatomegaly	28	34	>0 05
8	Jaundice	23	23	
9	Convulsion	14	22	>0.05
10	Oliguria	15	15	
11	Loose motion	3	9	>0.05
12	Resp. distress	3	3	
13	Bleeding diathesis	3	3	
14	Hemoglobinuria	3	3	
15	Malnutrition	8	13	>0.05

The mean modified Glasgow coma score (MGCS) at presentation and after 3 days of treatment in both the groups was similar (p >0.05).

Coma resolution time, fever clearance time and parasite clearance time favoured artesunate group as compared to quinine group, and the differences observed was statistically significant (p<0.05) (Table 3).

There was definite improvement of renal function and liver function after 3 days of treatment in both the groups, but the difference of improvement was not statistically significant. (p>0.05) (Table 4).

In quinine treated group nausea was observed in 50% cases, headache in 40% cases, vomiting in 30% cases, tinnitus in 20% cases vertigo in 10% cases, circulatory failure in 5% cases and sudden blindness in 1 case only, whereas no complication was observed in artesunate group (Table 5).

Table 3. Comparison of MGCS, CRT, FCT, PCT in Group 1 and Group 2 Patient

	Group 1 (Q) (n=40)	Group 2 (A) (n=40)	P value
Mean* MGCS ± SD			
At admission	7.68 ± 2.09	8 ± 2.29	
After 3 days of therapy	14.4 ± 1.68	14.07 ± 1.67	>0.05
** CRT ± SD	70.15 ± 17.56	50.4 ± 31.49	<0.05
*** FCT ± SD	62.23 ± 16.99	43.55 ± 20.12	<0.05
**** PCT ± SD	52.24 ± 12.69	41.67 ± 16 78	<0.05

*MGCS –Modified Glasgow Coma Score,** CRT–Coma resolution time ***FCT–Fever clearance time, ****PCT–Parasite clearance time

Eight (20%) patients died in the quinine group and 5 (12.5%) patients in the artesunate group. But the difference was not statistically significant (p>0.05). One patient was a dropout during the follow up in the quinine group. But in the rest of the patients there was 100% cure rate in the 28 day follow up (Table 6). (No drug resistance in either group). The clinical status, hematological and biochemical parameters were normal during the follow up period in both groups of patients.

Table 4. Comparison of Renal Function and Liver Function in Both Groups of Patients.

	Group 1 (Q)	Group 2 (A)	P value
S. urea (mg/dl) Mean ± SD			
At Admission	88.35 ± 52.57	89.05 ± 15.85	
After 3 days of treatment	46.18 ± 14.56	49.72 ± 43.73	>0.05
S. Creatinine (mg/dl) Mean ± SD			
At Admission	1.55 ± 0 61	2.085 ± 1.33	
After 3 days of treatment	0.94 ± 0.21	1.08 ± 1.06	>0.05
S. Bilirubin (mg/dl) (T), Mean ± SD			
At Admission	7.9 ± 8.05	5.68 ± 5.03	
After 3 days of treatment	2.18 ± 1.89	1.65 ± 0.62	>0.05

Table 5. Comparison of Side Effects of Treatment in Group-1 and Group–2 Patient

Side effects	Group 1 (Q) No. of Cases	Group 2 (A) No. of Cases
Nausea	20	0
Vomiting	12	0
Headache	16	0
Tinnitus	8	0
Vertigo	4	0
Circulatory failure	2	0
Sudden blindness	1	0

Table 6. Clinical Sub-groups (Baseline features), Outcome of Group-1 and Group-2 Patients

Clinical features and outcome	Group-1(Q) N=40	Group-2(A) N=40	P value
Cerebral malaria	8	8	
Cerebral malaria+jaundice	13	13	
Cerebral malaria+ARF	9	9	
Cerebral malaria+jaundice+ ARF+bleeding	3	3	
Jaundice	4	4	
Haemoglobinuria+ jaundice+ARF	3	3	
Death	8 (20%)	5 (12 5%)	>0.05
Lost to FU	1	0	
28 day cure rate	31/40	35/40	

ARF= Acute renal failure

DISCUSSION

In the present series total 80 cases of *Plasmodium falciparum* slide positive cases were studied. The age of the patients ranged from 2 years to 14 years with mean age of 7.93 ± 3.56 years. The male : female ratio was 1.5 : 1. Roger *et al*[11] in their study in Cameroon children had noted a similar male preponderance with male : female ratio being 59 : 43.

There was no significant difference of clinical profile of patients and baseline features in both groups, except anemia. This significant difference was contributed by mild and moderate anemia cases, which would not influence the outcome of drug therapy.

The significant less coma resolution time (CRT) in patients treated with artesunate could be due to its rapid schizonticidal effect leading to inhibition of cytokines and ultimately release of nitric oxide (which is neurotoxic). Also it prevents the rosette formation in the cerebral circulation.[12] Taylor *et al*[8] in their study of cerebral malaria in Malawian children and Salako *et al*[13] in a study of cerebral malaria in Nigerian children had found similar results with artesunate.

The significantly lower fever clearance time (FCT) for artesunate could be due to its rapid schizonticidal effect leading to suppression of cytokines and TNF-α production, which are responsible for fever.[12] In a study in China, Li GQ *et al*[7] reported mean FCT with quinine to be 63±40 hrs, and that with artemisinine derivative to be 30±22 hrs. Mishra *et al*[14] in a study in Orissa found out FCT of 52±27.09 hrs with artemisinine derivative. Myint *et al* [15] in their controlled trial in Burma found out FCT to be 46.85±20.96 hours with quinine and 31.26±22.71 hours with artemether.

The parasite clearance time was significantly less in artesunate group as compared to quinine group. In a study in Vietnam, Hien TT [16] reported mean PCT between 16–28 hrs for artesunate. Mishra *et al*[14] in a study in Orissa, found out it to be 8–72 hrs.

Stepalewaka *et al*[17] in a meta-analysis study group found out that the parasite clearance time (PCT) in artemether treated group was 16–24 hrs, compared with 28–32 hrs in quinine group.

In quinine treated group side effects like nausea, headache, vomiting, tinnitus, vertigo., circulatory failure and sudden blindness were observed, whereas no side effect was observed in artesunate group. Price *et al*[18] had similar observation that quinine was associated with a wide range of common side effects at therapeutic drug concentration, whereas artesunate had none.

Limitations of the study

As far as practicable, it was a double blind study.The doctor monitoring the patient did not know what the patient was getting. But the parents knew about the drugs their child was getting. Still then the results could not be biased in a small child (Mean age 7.93 ± 3.56 yrs) with altered sensorium (82.5% at admission), as the results are quantifiable. The nil side effects observed in artesunate group could not be related to the psychological set up of the patient.

CONCLUSION

Artesunate is a much better drug in complicated malaria in terms of rapid coma resolution, fever clearance, parasite clearance, well tolerability. Also it is more rapid schizonticidal than quinine. Artesunate is equally as effective as quinine in improving renal function and liver function in patients with renal failure and liver failure due to complicated malaria. Rather artesunate can be given easily without risk of fluid overload and consequent heart failure.

So artesunate can be recommended as a good alternative therapy to quinine in complicated falciparum malaria in our state and country as most of the cases are reported from rural and tribal setup where monitoring facilities do not exist and it is very easy to administer the drug.

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CORRIGENDUM

In the picture of the month entitled *Branchio-Oto Renal Syndrome* by Kalpana Gowrisankar *et al* published in the *Indian J Pediatrics* 2004; 71 (3) : 276 the legends of Fig. 2 and Fig. 3 must be interchanged as shown below. The error is highly regretted.

— Editor

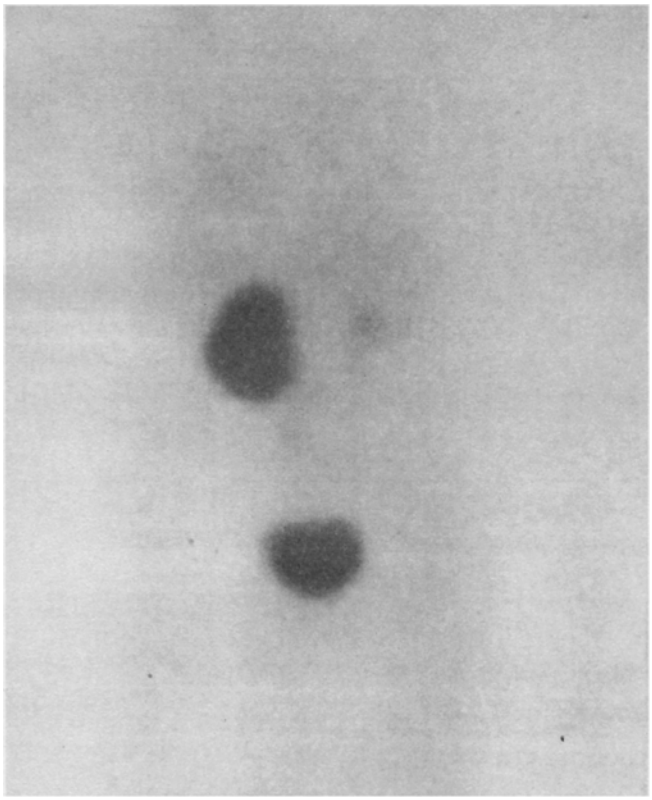

Fig 2. DTPA scan showing decreased size and function of the right kidney

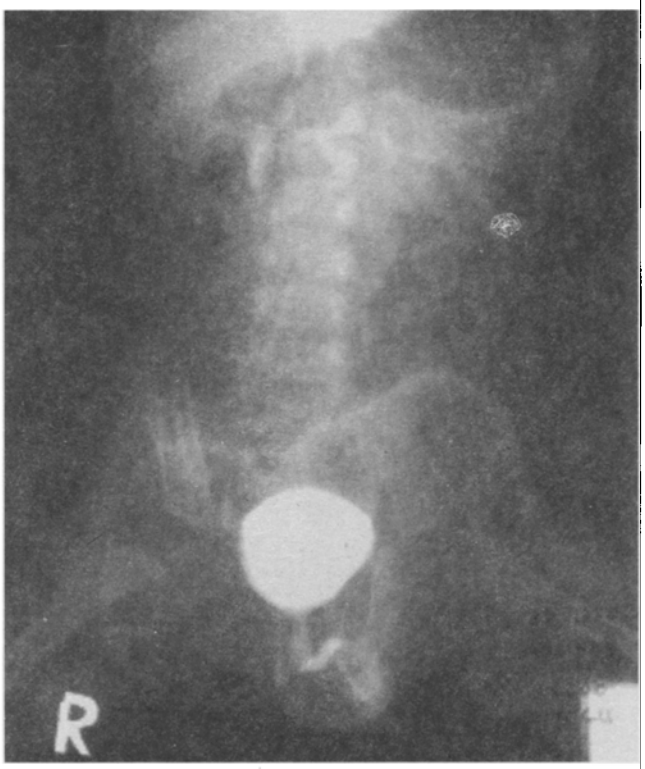

Fig 3. VCU documenting bilateral vasico ureteric reflux