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Complicated malaria - a randomized control study comparing the efficacy of quinine and artesunate in its management in western rajasthan, india

Abstract

Objective: To compare the effects of quinine and artesunate in management of complicated malaria: randomized control trial

Material and methods: Out of the total 100 patient enrolled, 77 patients who were having complicated malaria were treated either with quinine or artesunate. Reminder of the patients was treated with chloroquine.

Results: This is the secondary analysis of our study in which we analyse the effects of quinine and artesunate in management of complicated malaria. In the study group of 77 complicated malaria patients; 25 patients had *P. vivax* malaria, 37 patients had *P. falciparum* malaria and mixed malaria was detected in 15 patients. The splenic regression time was less for artesunate as compared to quinine but there was decreasing trend in fever defervescence time, mean duration of hospital stay, and mean blood volume requirement in quinine group as compared to artesunate.

Conclusions: Quinine still seems to be as effective as artesunate in management of complicated malaria in places where malaria is sensitive to quinine.

Keywords: complicated malaria, artesunate, quinine

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Introduction

Malarial infection, reported as early as 1570 BC from Egypt, still poses a diagnostic and therapeutic challenge in this modern anti-microbial era. It is one of the most important parasitic diseases of humans, affecting more than 1 billion people worldwide, causing more than 1 to 3 million deaths every year with prevalence in 103 countries.[1] India shares a large burden of this disease, especially drug resistant malaria.[2]

In spite of all developments, malaria remains an enormous international medical issue with 300- 500 million cases reported annually, resulting in 1.5- 2.7 million deaths. In absolute terms, malaria kills 3000 children aged less than 5 years every day.[3] An estimated 216 million cases of malaria occurred in 2010 causing an estimated 6, 55,000 deaths, mostly (91%) among African children. Majority (86%) of deaths were in children aged less than 5 years of age. A total of 106 countries were endemic for malaria in 2011. According to World Malaria Report 2011, in India confirmed malaria cases were 15,99,986 and malaria attributed deaths were 1023 in 2010.[4]

Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world. The emergence and spread of drug resistance in *P. falciparum* malaria causes a major problem in the management of malaria.

Quinine remains quite effective even after extensive use. It remains the drug of choice for complicated malaria. Reports of resistance to quinine are rare, but cases have been reported from Thailand and East Africa. High degree of resistance to quinine is not common. Artesunate is a prodrug which releases an active metabolite dihydroartemisinin on absorption. It is effective against schizonts of all four types of human malarial parasites. Recently some resistance to this drug has been reported from Thailand and Combodia.[5]

To overcome the problem of drug resistant in treatment of severe and complicated malaria intravenous artesunate is used in different part of world. But still we are using quinine for treatment of complicated malaria in children in most parts of western Rajasthan. The present study is therefore, planned keeping in mind the aforementioned facts and to conclude that which drug is more efficacious in the treatment of complicated malaria in children in present conditions of western Rajasthan.

Material and methods

The present study was conducted in Department of Paediatrics, Umaid hospital for women and children, regional institute of maternal and child health, Dr. S. N. Medical college, Jodhpur. This prospective study was conducted after getting proper clearance from ethics committee. Patient consent was taken prior to enrolment for studies.

This was a single centre non blinded, randomized control trial study in two parallel groups conducted in tertiary care hospital of India, Umaid hospital, Jodhpur from December 2010 to November 2011.

Eligible participants were all children aged ≤ 17 yrs and who were positive for malaria parasite, either on PBF examination or MP card test and exclusion criteria were met.

All cases with proven malaria (103 patients) were admitted and included in the study. Three patients dropped out from the study as they went home against medical advice for personal and family reasons. A total of 100 cases completed the study.

In every enrolled patient routine haematological investigation like haemoglobin, total and differential white cell count and platelets

count were performed on the day of admission. Liver function tests including serum bilirubin (total and direct), SGPT and renal function tests namely blood urea and serum creatinine were estimated on the same day. Blood sugar was done to rule out hypoglycemia.

The cases were classified according to their clinical severity into complicated malaria and uncomplicated malaria according to recent WHO guidelines.

Clinical features

i. Impaired consciousness or unarousable coma.

ii. Prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance.

iii. Failure to feed.

iv. Multiple convulsions – more than two episodes in 24 h.

v. Deep breathing, respiratory distress (acidotic breathing).

vi. Circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children.

vii. Clinical jaundice plus evidence of other vital organ dysfunction.

viii. Haemoglobinuria.

ix. Abnormal spontaneous bleeding.

x. Pulmonary oedema (radiological).

Laboratory findings

I. Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl).

II. Metabolic acidosis (plasma bicarbonate < 15 mmol/l).

III. Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%).

IV. Haemoglobinuria.

V. Hyper-parasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5%/250 000/µl in areas of high stable malaria transmission intensity).

VI. Hyperlactataemia (lactate > 5 mmol/l).

VII. Renal impairment (serum creatinine > 265 µmol/l).

In order to study the effect of Quinine versus artesunate in patients of complicated malaria, a sample size was calculated at 95% confidence interval assuming from our previous hospital data that 7.2 out of 10 patients admitted in our hospital ailing with malaria had complicated malaria with permissible error of ± 10% in estimating the sample size.

Sample size

$N = Z^2 \times P \times Q \div E^2$

N = required sample size

Z = confidence level at 95% (standard value of 1.96)

P = proportion of success in population

Q = 1- P

E = permissible error

From the above calculation, sample size comes out to be 77. Therefore we had taken 77 patients of complicated malaria as our sample size.

Patients with uncomplicated malaria were 23 in number and this is how the total number of patients studied was 100.

Patients with uncomplicated malaria were given oral chloroquine in cases of *P. vivax* malaria and combination of lumefantrine and artemether orally in cases of *P. Falciparum* and mixed malaria. Primaquine was given to all patients of *P. vivax* malaria for radical cure according to the WHO guidelines.

Cases with complicated malaria were assigned into two groups and were given quinine and artesunate according to random table. In 77 complicated malaria group, 37 patients received quinine and rest were treated with artesunate (Figure 1). Patients of complicated malaria were given adjunctive treatments for the management of complications according to WHO guidelines.[6,7] The outcome after giving trial of antimalarial was measured on the basis of splenic regression, fever defervescence, duration of stay, mean blood requirement, and final outcome. They were assessed clinically on a daily basis.

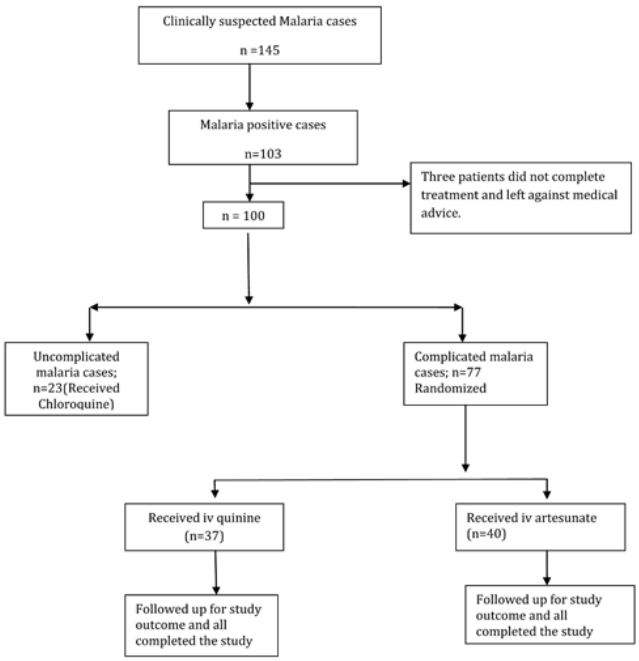

Figure 1 Showing flow diagram of the study population.

The statistical analysis was performed by using student's "t" test and Chi square test to find out the significance of difference in mean between two variables. In present study, p value < 0.05, <0.01 and <0.001 was considered as significant, very significant and highly significant respectively.

Results

This is the secondary analysis of the study and primary outcomes of the study have already been published.[8] Out of 100 patients, 58% were males and 42% were females, with male to female ratio of 1.4: 1. Majority of patient (39.1%) were in the age group of 1-5yr. In the study group of 100 patients; 45 patients were positive for *Plasmodium vivax*, 38 patients were positive for *Plasmodium falciparum* and 17 patients had mixed malaria (Table 1).

There was decreasing trend in mean duration of fever in quinine group (37.29±21.33 hrs) in comparison to artesunate group (39±18.53 hrs) though the difference was not statistically significant (p >0.05) (Table 2).

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The mean duration of stay was less for quinine (6.93±2.18) as compared to artesunate (7.83± 3.21) though the difference was not statistically significant (p >0.05) (Table 3).

The mean time for complete splenic regression was comparable between both groups with duration being 7.28±1.33 and 7.11±1.23 days in quinine and artesunate group respectively. Spleen was not palpable in 2 cases in quinine group. The difference was statistically not significant (p >0.05) (Table 4).

The mean volume of blood required was less in quinine (14.43±10.30) ml/kg as compared to artesunate (15.83±10.83) ml/kg. The difference was not statistically significant (p >0.05) (Table 5).

3 patients expired in the quinine group, while there was no mortality in the artesunate group. The difference was statistically not significant (p>0.05) (Table 6).

Table 1 Age and sex distribution in the study group

Age	Males (%)	Females (%)	Total (%)
<1year	04 (4%)	03(3%)	07(07%)
1-5 years	25(25%)	13 (13%)	38 (38%)
5- 10 years	15(15%)	16 (16%)	31 (31%)
>10 years	14(14%)	10(10%)	24(24%)
Total	58(58%)	42(42%)	100(100%)

Table 2 Therapeutic Response of Antimalarial in the form of Fever Defervescence Time

Day	Quinine (n=37) (%)	(Mean±SD)	Artesunate (n=40) (%)	(Mean±SD)
<48 hours	27(72.97%)	26.29±9.24	20(50%)	24±10.73
≥ 48hrs	10(27.03%)	66±16.59	20(50%)	54±10.03
Total	37(100%)	37.29±21.33	40(100%)	39±18.53

Table 3 Therapeutic response of antimalarial on duration of stay in complicated malaria

Duration of stay	Quinine n=37(%)	Artesunate n=40(%)
< 7 days	14(40.55%)	13(32.5%)
> 7 days	23(59.45%)	27(67.5%)
Mean ± SD (days)	6.93±2.18	7.83± 3.21

Table 4 Therapeutic response to Antimalarial in the form of Splenic Regression time in complicated malaria

Day	Quinine (n=37)(%)	Artesunate (n=40) (%)	Significance
< 7 days	15(40.5%)	17(42.5%)	χ 2 = 0.01 P value >0.9
> 7 days	22(59.5%)	7(57.5%)	
Mean ± SD (days)	7.28±1.33	7.11±1.23	

Table 5 Therapeutic response to antimalarial in the form of blood transfusion requirement in complicated malaria

No of BT (ml/kg)	Quinine n=37(%)	Artesunate n=40(%)
None	8(21.65%)	7(17.5%)
10 ml/kg	8(21.65%)	13(32.5%)
20 ml/kg	12(32.4%)	10(25%)
30 ml/kg	7(18.9%)	10(25%)
>30 ml/kg	2(5.4%)	0
Mean ±SD(ml/kg)	14.43±10.30	15.83±10.83

Table 6 Response of Anti-Malarial on the Outcome in complicated malaria

Outcome	Quinine n=37(%)	Artesunate n=40(%)	Total (%)
Discharged	34(91.9%)	40 (100%)	χ 2 = 0.57 P value > 0.5
Expired	3 (8.1%)	0	

Discussion

We studied and evaluated the effect of intravenous quinine and intravenous artesunate in complicated malaria patients. We used these two drugs on the basis of randomisation and compared their effect in management of complicated malaria patients.

Fever duration was less than 48hrs in 72.3% cases in quinine treated group and it was 50% in artesunate group. The mean duration of fever was 37.29 ± 21.33 hrs in quinine group and 39.0 ± 18.53 hrs in artesunate group. The χ2 value was 2.35 which was statistically (P >0.2) not significant. Karbwang et al.,[9] found mean fever defervescence time to be 79 hrs and 84 hrs in artemisinin derivative and quinine treated patients respectively.

Therapeutic response in the form of splenic regression time showed complete regression of spleen in less than 7 days in 38.46% cases in quinine group and 41.66% cases in artesunate group. The mean time for complete splenic regression was 7.28±1.33 and 7.11±1.23 days in quinine and artesunate group respectively. Spleen was not palpable in 2 cases in quinine group. The χ2 value was 0.01 which was statistically (P >0.05) not significant.

Duration of hospital stay was less than 7 days in 36.92% cases in quinine treated group and it was 33.33% in artesunate group. The mean duration of stay was less for quinine (6.93±2.18) as compared to artesunate (7.83± 3.21). However, the difference between them was statistically not significant (p >0.05). Similarly Cao XT et al.,[10] in a study on comparison of quinine and artesunate in complicated malaria concluded that there was no significant difference in fever clearance time, and length of hospital stay.

Mean blood volume requirement was less in quinine treated group (14.43±10.30) as compared to artesunate group (15.83±10.83). The difference was statistically not significant (p >0.05). Since the mean haemoglobin was more in quinine treated group than artesunate group so mean blood volume requirement was more in artesunate treated group.

In complicated malaria 3 patients expired in the quinine group, while there was no mortality in the artesunate group. The χ2 value was 0.57 which was statistically (P>0.2) not significant. Other authors have also reported a slightly higher mortality in the quinine group. Newton and Dondorp A[11] reported that mortality was 12% with artesunate and 22% with quinine and the difference was not statistically significant (p=0.22). Cao XT et al.,[10] in Vietnam reported that mortality was 4.5% with quinine and 3.7% in artesunate group.

We observed in our study that although the mortality was slightly higher in the quinine group but that was because of the larger number of patients in this group and on statistical analysis, the increase was not statistically significant. The splenic regression time was less for artesunate as compared to quinine but the fever defervescence time, mean duration of hospital stay, and mean blood volume requirement was less for quinine as compared to artesunate. Therefore quinine stills seems to be as effective as artesunate in management of complicated malaria in western Rajasthan.

Conclusion

There is no significant resistance to artesunate and it was found effective in the management of severe complicated malaria in this region. Although there were less deaths in the artesunate treated group but a larger study would be required to justify its use as a drug of first choice in the management of complicated malaria. It would be worthwhile to preserve the sensitivity of artesunate. It should be

reserved for use in cases of complicated malaria, in admitted patients, by parenteral route and under strict supervision of competent doctors. It should not be allowed to be marketed as a monotherapy orally.

On comparing quinine with artesunate in the treatment of complicated malaria, both drugs had a good efficacy. The splenic regression time was less for artesunate as compared to quinine but the fever defervescence time, mean duration of hospital stay, and mean blood volume requirement was less for quinine as compared to artesunate. Therefore quinine stills seems to be as effective as artesunate in management of complicated malaria in Western Rajasthan.

Limitation of the study

As this study had small sample size so it is difficult to extrapolate these results to large populations. The spectrum of resistance of malaria parasite differs in various region of the world so these results can be applied to the area where study was conducted.

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None.

Conflicts of interest

None.

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