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A RANDOMIZED CLINICAL TRIAL REGARDING COMPARATIVE EFFICACY OF QUININE AND ARTESUNATE IN THE TREATMENT OF SEVERE MALARIA AMONG CHILDREN OF TRIPURA: A NORTH-EASTERN STATE OF INDIA

Paediatrics

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ABSTRACT

Background: Severe malaria is a medical emergency with high mortality in children. Recently, artesunate has replaced quinine as the first-line drug for severe malaria. Present study was undertaken to compare efficacy of quinine and artesunate in the treatment of severe malaria in children.
Methods: A randomized clinical trial was conducted among children aged up to 12 years, admitted in the medical college hospital with clinical features of severe malaria (WHO criteria). All the children admitted in Paediatrics ward were diagnosed as Malaria by slide method and QBC Assay and after satisfying WHO criteria for severe malaria. Finally, 60 children were included in the study (30 in the quinine group and 30 in the artesunate group).
Results: 60% children were aged 5 years or less and 40% children aged more than 5 years to 12 yrs. 90% children were afebrile within 48 hours after treated with artesunate as compared to 70% after treated with quinine. 90.33% children had parasites cleared within 48% hours with artesunate compared to 73.33% with quinine. 83.33% children were fully conscious within 24 hours in artesunate group compared to 33.33% with quinine for the same duration.Hypoglycaemia, nausea and vomiting (20% each) were the most common toxicities reported with quinine. 10% children complained of tinnitus. Neurotoxicity was reported in 6.66% children in both groups. Except 2 cases of neurotoxicity no other adverse reaction was reported with artesunate.**T**here were 3 deaths (10%) in quinine arm, all death occurred after 48 hours of treatment, compared to 2 deaths (6.66%) in artesunate arm, all death within 24 hours of admission. Overall mortality was 8.33%.
Conclusion: Artesunate is more effective than quinine in the treatment of severe malaria among children.

KEYWORDS

Artesunate, Children, Severe Malaria, Quinine

INTRODUCTION

Malaria is one of the major public health problemsin India. Around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Program (NVBDCP), of which 50% are due to Plasmodium falciparum. [1] About 95% population in the country resides in malaria endemic areas and 80% of malaria reported in the country is confined to areas where 20% of population resides in tribal, hilly, hard-to-reach or inaccessible areas.(1) Approximately 77% of malaria deaths globally are of children under 5 years of age.[2]

Tripura is adjacent to the Indo-Bangladesh border are mostly covered with thick forest and have poor communication and health infrastructure. The hilly and undulating terrain and the movement of people across the border have led to a persistence of malaria in the villages near the border.[3] Focal outbreaks of malaria are common in this region, which accounts for 8-12% of all reported malaria cases in India.

Plasmodium falciparum is a major malaria parasite in this region, causing 60-80% of malaria infections. The hot and humid climate prevailing in the region is ideal for the survival and multiplication of malaria vectors.[4] There is a possibility for multi-drug resistant falciparum malaria, prevalent in Myanmar and Thailand, entering India through the North-eastern states which warrants monitoring of status of drug resistant in this part of the country.[5]

In children severe malaria may rapidly become fatal unless treated promptly.[6] The standard treatment for severe malaria in children has been intravenous (IV) infusion (or intramuscular (IM) quinine.(6) However, quinine has a narrow therapeutic index meaning there is a small difference between therapeutic and toxic doses. [7] Hypoglycaemia is a serious adverse effect more prevalent if quinine infusion rates exceed 5mg/kg/hr [8], one reason why it is given as an IV infusion and not an IV bolus, and in pregnant women treated for malaria.[9]

Artesunate, an artemisinin derivative has recently replaced quinine as the first line drug for the management of severe malaria in children.[6] Artesunate can be given as an IV bolus dose with peak concentration reached within one hour of administration. Artesunate has however, been associated with neurological damage in animals exposed to the drug as part of toxicity testing.[10-12]However, studies have failed to show any evidence of neurotoxicity in human beings.[13, 14] South East Asian quinine artesunate malaria trial (SEAQAMMAT) Group has also concluded that artesunate should be the treatment of choice.[15]

OBJECTIVE:

To compare the efficacy of quinine and artesunate in the treatment of severe malaria among children with respect to fever clearance time, parasite clearance time, coma resolution time and mortality.

METHODOLOGY

Study area: Present study was carried out at Agartala Govt. Medical College, Tripura, India, a multi-speciality hospital that receives cases from eight districts of the state. Ethical clearance for the study was obtained from Institutional Human Ethical Committee.

Study design: This was an open-label, randomized, clinical trial carried out for the duration of one and half years (January 2013 to June 2014). Subjects included in the study were all cases up to 12 years of age (irrespective of gender) admitted to the paediatrics unit of the medical collegewith clinical feature of severe malaria (WHO Criteria) having malaria parasites in the peripheral smear.

Inclusion criteria: All the admitted patient in paediatrics unit dignosed as malaria by slide method and QBC Assay and staisfing WHO criteria for severe malaria were included.

Exclusion criteria: i. ECG with QTc interval >0.45 sec, ii. Known case of G6PD deficiency,iii. Previous treatment with antimalarils for more than 24 hours, iv.Patients with contraindicatin to any of the above two drugs, and V. Patients whose parents has not given consent for the study.

Sample size: All consecutive malaria cases satisfying WHO criteria

for severe malaria admitted during the study period were considered and finally 60 patients were included in the study.

Parents written informed consent were taken before allocating one of the regimens. Patients received either quinine or artesunate by systematic random sample, every EVEN number received quinine and every ODD number artesunate. All patients invariably received at least 24 hours of intravenous therapy and a complete 7 days course. Oral therapy was substituted as soon as patients were able to tolerate.On admission, all patients were weighed, a detailed history including residence, travel history, previous treatment, drug history, vaccination etc were taken.A through clinical examination was done and findings were recorded. Axillary temperature and other vitals were recorded 4 hourly. Systemic and fundus examination was done on daily basis.The CNS examination was repeated at the time of regaining consciousness. All the cases were subjected to the following investigations at the time of admission (Day 0): Simultaneous thin and thick blood slides were prepared for species identification and parasite count, complete blood count, Hb% (urgent), ECG and Random Blood Sugarbefore, during and after the antimalarial doses, blood urea and creatinine level, serum bilirubin - total and direct, Lumber puncture and CSF analysis for pressure, cells , sugar, proteins and culture and sensitivity in cases of cerebral malaria, chest X-ray, liver function test, urine analysis for sugar, albumin, RBCs, pus cells and benzidine test for haemoglobinuria. All the above haematological test was repeated on day 3 and 7.Blood for malaria parasites were send on day 0,1,2,3 and day 7.The main stay of diagnosis and monitoring was blood slides and serial QBC assay.All patients were screened for: 1. Hypoglycaemia (RBS <40 mg/dl)and 2. ECG abnormalities.

Treatment was started immediately and all other aspect of supportive treatment, based on guidelines, were unaffected by the study. If assigned, artesunate2.4 mg/kg body weight was given IV on admission, then at 12 h, 24 h, and thereafter once daily until oral medication could be taken reliably. When the patient had recovered sufficient to take tablets, we administered oral age-specific ACT-AL for 3 days.Alternatively, quinine dihydrochloride was given in a 20 mg/kg loading dose infused over 4 h followed by 10mg/kg infused over 2-4 h three times a day until starting oral therapy. When the patient had recovered sufficiently to take tablets, we administered oral quinine 10 mg/kg every 8h to provide a total quinine course of 7 days. We recommended both regimens with inj Clindamycin 10 mg/kg/dose IV 8 hourly followed by 30 mg/kg/day 8 hourly for 7 days once the patient could take oral medication.Primaquine 0.75 mg/kg on day 2 were given as per latest National drug policy of India. our primary endpoint was death from severe malaria - i.e., in-hospital mortality and secondary outcome measures were fever clearance time, parasite clearance time, coma resolution time (times to eat, speak, sit and discharge), and development of severe complications.

Follow up of the patients:
All the patients were monitored for full 7 days during the hospital stay. After recovery they were discharged with advice to review on day 14 and day 28 in the paediatrics dept.Relevant haematological and biochemical test were repeated on follow-up visits.Neurological examination performed to assess any residual neurological sequelae and other complications.

Data analysis: The data analysis was by SPSS 16.0 and Epi info.

RESULTS

A total of 60 patients fulfilling the criteria of severe *P. falciparum* malaria were treated in the study. Of these, 60% patients were from 5 years or less age group, and 40% patients were from more than 5 yrs to 12 yrs age group. Rural-urban distributions of patients were 90% and 10% respectively. 90% patients were from indigenous populations and only 10% were from other communities. [Table1]

In the present study, most of the patients presented with overlapping features of severe malaria. 85% (51 cases) of cases presented with splenomegaly. Most common presentation was severe anemia (Hb<5gm/dl). 33 cases (55%) had severe anemia. Cerebral malaria was the second most common presentation. There were 12 cases (20%) presented with coma. There were 3 cases (5%) presented with jaundice and 2 cases (3%) with renal failure requiring repeated dialysis. 12 patients had generalized convulsions at the time of admission or shortly after. [Table 2]

Fever clearance time with quinine and artesunate shows that 90% of patients were afebrile within 48 hours in artesunate treated group, compared to 70% in quinine treated patient. 90.33% patients had parasites cleared within 48% hours with artesunate, whereas it was 73.33% with quinine. Results also shows faster coma clearance with artesunate. 83.33% patients were fully conscious within 24 hours in artesunate group, compared to 33.33% with quinine for the same duration. [Table 3]

Hypoglycaemia and nausea and vomiting (20% each) were the most common toxicities reported with quinine. 10% patient had tinnitus. Neurotoxicity was reported in 6.66% cases in both groups. Except 2 cases of neurotoxicity no other adverse reaction were reported with artesunate. [Table 4]

3 death (10%) were recorded in quinine arm, all death occurred after 48 hours of treatment. On the other hand, there were 2 deaths (6.66%) in artesunate arm, the deathswere within 24 hours of admission. Overall mortality was 8.33%. [Table 5 and 6]

DISCUSSION

Fever clearance time is defined as the period of time in hours from administration of the first dose of the anti-malarial drug till the axillary temperature remained at or below 37 degree for 72 hours. In the present study we found fever clearance time was not significantly different. But proportion of patients getting afebrile was greater in artesunate arm. 90% of patients were afebrile by 72 hours after administration of first dose; whereas, it was 70% in quinine group. Mohanty et al [16] found fever clearance time with artesunate to be 43.55±20hrs and 62.23±16.99 hrs with quinine. Cao et al [17] found no difference in fever clearance time in Vietnamese children in 2007. Eltahir et al [18], also in 2010 found no significant difference in fever clearance time.

Parasite clearance time is defined as time in hours, taken from administration of first dose till parasites were undetectable in patients peripheral blood films and remained so for 7 days. We found that within 48hrs time all the patients cleared 100% of parasites with artesunate. Whereas, only 73% of patients did so with quinine therapy. Data from study by Cao et. al. [17] suggest that artesunate is superior to quinine in the clearance of parasites with a mean difference of 50 hrs in favour of artesunate (95% CI 73.55 to 26.79 hrs). Data from study by Eltahir et. al. [18] contrasts this and suggests no difference between the two treatment groups with mean parasites clearance time of 20.8 hrs. Mohanty et al [16] found significantly less time to clear all parasites with artesunate than quinine (41.67 ±16.68 hrs with artesunate and 52.42±12.69 hrs with quinine).

We found that coma resolution time is faster with artesunate treatment. 80% patients were fully conscious within 48 hrs of starting artesunate. Only 53% of patients did so with quinine therapy. Mohanty et al [16] found that this was significantly faster with artesunate than quinine (50.4±31.49 hrs with artesunate and 70.15±17.56 hrs with quinine). We also observed that those who receiving quinine developed more adverse reactions in comparison to those receiving artesunate. The most common adverse reaction reported was nausea, vomiting and hypoglycaemia. Rolling T et al [19] found that adverse effect in patients treated with artesunate were limited to delayed haemolysis and temporary deterioration in renal function, that too only in 60% of the patients, while those treated with quinine it was 71%.

There were 3 death in quinine group and 2 death in artesunate group. All deaths were within 24 hours of admission in artesunate group. Data from SEAQUAMAT [17] group suggests that mortality in artesunate recipients was 15% (107 of 730), compared with 22% (164 of 731) in quinine recipient; an absolute reduction of 34.7% (95% CI 18.5-47.6%, P = 0.0002). In AQUAMAT study [20], involving 5425 African children it was found that 230 (8.5%) patients assigned to artesunate treatment died, compared with 297 (10.9%) assigned to quinine treatment (OR stratified for study site 0.75, 95% CI0.63- 0.90; relative reduction 22.5%, 95% CI 8.1-36.9; P= 0.0022).

CONCLUSION

Artesunate is a good alternative to quinine in severe malaria among children with better efficacy and coma clearance than quinine. Artesunate is easy to administer in rural infrastructure poor set-up, safe, continuous monitoring is not required, with minimal side effect.

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Conflicts of Interest: There are no conflicts of interest.

Table 1: Distribution of study subjects according to age, gender and residence (n = 60)

Gender	≤ 5 Years	5-12 Years	Total
Male	15	14	29
Female	21	10	31
Total	36 (60%)	24(40%)	60(100%)
Ethnicity	**Rural**	**Urban**	**Total**
Indigenous population	52	2	54
Others	2	4	6
Total	54 (90%)	6 (%)	60(100%)

Table 2: Clinical and laboratory characteristics of patients on admission(n = 60)

Characteristics	Total	%
Temperature (F)>1010F	60	100
Splenomegaly	51	85
Severe anemia (Hb% <5gm/dl)	33	55
Parasite burden (100000/µl)	15	25
Repeated generalized convulsion	12	20
Blood sugar (<40mg/dl)	11	18.33
Glasgow Coma Scale Score<7	6	10
Blantyre coma scale score <3	6	10
Respiratory distress	5	8.33
Microscopic haemoglobinuria	3	5
Jaundice (>3mg/dl)	3	5
Renal failure	2	3.33

Table 3: Fever, parasite and coma clearance time in patients treated with quinine and artesunate

Time (in hrs)	Quinine (n=30)		Artesunate (n=30)	
	N	%	N	%
Fever clearance time				
Within 24 hrs	6	20	9	30
24-48 hrs	15	50	18	60
48-72 hrs	6	20	1	3.33
Parasite clearance time				
Within 24 hrs	10	33.33	18	60
24-48 hrs	12	40	10	33.33
48-72 hrs	05	16.66	0	-
Coma clearance time				
Within 24 hrs	2	33.33	5	83.33
24-48 hrs	3	50	1	16.66
48-72 hrs	1	16.66	0	-

Table 4: Drug toxicity with quinine and artesunate

Toxicity	Quinine		Artesunate	
	Number	%	Number	%
Hypoglycaemia	6	20	0	-
Nausea and vomiting	6	20	0	-
Intolerance	3	10	0	-
Tinnitus	3	10	0	-
Neurotoxicity (psychosis)	2	6.66	2	6.66
Local pain reaction, necrosis	1	3.33	0	-

Table 5: Number of deathsin quinine and artesunate treated group

Intervention	Number	Percentage
Quinine	3	10
Artesunate	2	6.66
Total	5	8.33

Table 6. Time interval between admission and death

Time	Quinine		Artesunate	
	Number	%	Number	%
Within 24 hrs	0	-	2	6.66
24-48 hrs	0	-	0	-
48-72 hrs	3	10	0	-

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