

INTRAMUSCULAR ARTEMETHER VERSUS INTRAVENOUS QUININE IN TREATMENT OF CEREBRAL MALARIA IN PEDIATRIC PATIENTS

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ABSTRACT

Background: Cerebral malaria is one of the complications of malaria and carries high mortality if not treated timely and promptly. The current study was conducted in this regard to compare the role of intramuscular artemether with intravenous quinine in treatment of children with cerebral malaria.

Material & Methods: This was a hospital based randomized controlled trial conducted at the Pediatric unit A Department of Child Health, Khyber Teaching Hospital, Peshawar from May 2003 to April 2004. A total of 50 patients fulfilling of cerebral malaria were enrolled in the study. Each 25 patients were assigned randomly to receive either intravenous quinine or intramuscular artemether and response was documented. The results were compared with national and international studies.

Results: Majority of patients presented with altered consciousness (100%) and fever (96%). Out of 25 patients treated with Artemether, 22 (88%) recovered completely and three patients (12%) died. While in Quinine group 21 (84%) recovered completely and four (16%) died. No residual sequelae were detected in either group. Rate of resolution of coma, Parasitemia and fever was almost same in both groups. Deep coma and multi organ system involvement had poor prognosis. In quinine group hypoglycemia during treatment was observed in four patients (16%).

Conclusion: Artemether is as effective as quinine in the treatment of cerebral malaria.

KEY WORDS: Cerebral Malaria, Plasmodium Falciparum, Quinine, Artemether,

INTRODUCTION

Malaria is an Italian word means bad air as it is common in dumpy and marshy places¹. Malaria is caused by a protozoan named plasmodium (P). Four species of the plasmodium cause disease in human beings. These four species include Vivax, Falciparum, Ovale and Malaria².

Malaria is one of the oldest and biggest health issues affecting 40 % of the world's population. Malaria affects 300-500 million people and kills 1.5 to 2.7 million people annually². Malaria is one of the five major causes of under five years mortality in pediatric populations³. In Pakistan, Malaria is caused by two species of plasmodium vivax and falciparum⁴.

Plasmodium Falciparum causes malignant tertian malaria and can lead to complicated malaria like cerebral malaria and multi organ involvement. Plasmodium vivax causes benign tertian malaria and frequent relapses but rarely causes grave diseases⁵.

Plasmodium Falciparum is the serious most condition amongst all malaria species because of its severity at presentation and associated complications. Serious manifestations associated with falciparum malaria are cerebral malaria, acute renal failure, hypoglycemia, non cardiopulmonary edema and black water fever^{6,7}.

Plasmodium Falciparum is the most virulent of all malarial species because it infects erythrocyte of any stage leading to high grade Parasitemia⁸. The parasite multiplies so rapidly that the count reaches to 20 fold in a short period of 48 hours⁹. The asexual erythrocytic stage parasite density is having direct impact on clinical presentation i.e. higher is the parasite count more severe is the malaria and higher incidence of complications¹⁰.

Various diagnostic procedures are available for the diagnosis of malaria. These include stained blood films (thick and thin smear) can be performed only by experienced microscopists, PCR (polymerase chain reaction) based assay which is

extremely sensitive and specific method but costly procedure, and rapid diagnostic test including immunochromatographic dipstick assay. The rapid antigen detection tests include histidine-rich protein-2 (P falciparum specific), Plasmodium aldolase and Plasmodium lactate dehydrogenase¹¹.

Parenteral antimalarial are extremely important in treatment of severe malaria. Quinine was the mainstay of severe malaria treatment since 1630 till the deployment of parenteral chloroquine in the 1950s. But again quinine resumed its role in treatment of severe malaria when resistance appeared to chloroquine in South East Asia and Africa in late 1970s. The supremacy of quinine in treatment of severe malaria was unbeatable until introduction of artemisinin derivatives. Initial comparative studies were done with intramuscular artemether- a lipophilic derivative of dihydroartemisinin. Artemether proved safer and easier to use than quinine¹². Study conducted at Malawi reported that patients treated with artemether recovered more quickly from coma than patients with quinine¹³. All these studies have given the widespread but unproved belief that artemether may reduce mortality in cerebral malaria.

The current study was conducted in this context to compare the ability of the two medicine in reducing mortality and morbidity of cerebral malaria.

MATERIAL AND METHODS

This study was conducted at the department of Pediatrics Khyber Teaching Hospital Peshawar Khyber Pakhtoonkhwa. The study was randomized controlled trial conducted over a period of one year from May 2003 to April 2004.

Children presented with fever and altered consciousness with or without fits, MP positive on smear or patients with strong clinical suspicion of cerebral malaria who responded to antimalarial therapy were included in the study. Patients with encephalopathy due to other causes (like meningitis, encephalitis and poisoning) or patients receiving multiple therapies (like meningitis and encephalitis treatment) along with antimalarial were excluded from the study.

After taking informed consent all patients biodata including name, age, sex, address, date and time of admission were noted on proforma. History regarding fever, headache, altered consciousness and fits was also noted. General physical examination and neurological assessment was also done in all cases. Thick and thin smear for malarial parasite were prepared. Investigations like complete blood count with platelet count, blood urea, sugar creatinine electrolytes and urine analy-

sis were also carried out. Cerebrospinal fluid examination, CT brain, coagulation profile, liver function test and blood culture were performed where needed.

The patients were randomly assigned two groups A and B. Group A was given Artemether with initial dose of 3.2 mg /kg body weight on day one followed by a maintenance dose of 1.6 mg / kg for 4 days. Group B was given Intravenous quinine dihydrochloride diluted in 10 % dextrose water (1mg/dl) at an initial dose of 20 mg / kg stat as slow intravenous infusion over 2 hours followed by 10 mg/kg twice a day as slow intravenous infusion over 5 days.

Supportive Treatment:

- (i) Vital record was taken in all cases including temperature, pulse, Blood Pressure, and convulsions
- (ii) Intake / output record was also taken
- (iii) Convulsions were treated with IV diazepam 0.3 mg/kg diluted. Children with refractory convulsions were given IV phenobarbitone 20mg/kg stat, followed by 5mg/kg once a day dose.
- (iv) Severe anemia was treated with packed cells
- (v) Fever was treated with cold sponging, per rectal and oral/through tube paracetamol

Response to treatment was recorded in the form of resolution of fever and unconsciousness; and clearance of malarial parasite on smear after using therapy.

RESULTS

In this hospital based study, a total of fifty cases were studied. Out of 50 cerebral malaria patients 29 were male and 21 were female with a male to female ratio of 1.5:1. Majority of the patients presented in age group 1 to 5 years followed by age group 5 to 10 years constituting 36% and 26 % of cases respectively. (Table 1)

Majority of cases were from FATA (Federally Administered Tribal Areas) with equal number of cases from Afghan Refugees i.e. 19 (38 %) cases each. Patients from settled areas of Khyber Pakhtoonkhwa constituted 24% of cases.

Altered consciousness was the presentation in 100 % of cases followed by fever in 96% of cases. Vomiting, headache and fits were found in 24%, 24% and 44% of cases respectively. Convulsions were present in five (10%) cases. Two patients presented with oliguria and generalized edema. Physical examination revealed that GCS (Glasgow Coma Scale) was < 11/15 in 28 (56%) cases while > 11/

15 in rest of the cases. Among fifty cases 25 i.e. 50 % had temperature of more than 102° F while in 46% of cases the temperature was high but less than 102° F. Jaundice was present in 10% of cases while splenomegaly in 40% of cases.

Malarial Parasite (MP) smear was prepared and examined from each patient before start on anti-malarial therapy. Results regarding the MP smear are given in Table 2.

Recovery was documented in the form of Resolution of fever, encephalopathy and parasite clearance. The time needed for axillary temperature to fall down below 99.6° F was 16 to 48 hours (with median of 32 hours) for Artemether group and 12-52 hours (with median of 32 hours) for quinine group with P-value =0.07. All 43 survivors recovered fully from encephalopathy. The median recovery time was 27 hours for artemether group

Table 1: Age wise distribution of cerebral malaria patients (n = 50).

Age in Years	Number of patients	Percentage
Less than 1 Year	12	24
1-5 Years	15	30
5-10 years	13	26
10-14 Years	7	14
Total	50	100 %

Table 2: Smear microscopy of cerebral malaria patients (n=50)

MP on SM	No of patients	Percentage
Tropozoite +	26	52
Tropozoite ++	8	16
Tropozoite+ Gametocyte	2	4
No MP on SM	14	28

Table 3: Response of Cerebral Malaria (Parasitemia clearance, resolution of Fever and Coma) to Artemether and Quinine (n=50).

Variables	Artemether Group Median & Range	Quinine Group Median & Range	P Value
Length of time in hours to bring temp d" 99.6 F°	32 (16 — 48)	35 (12 - 52)	0.07
Length of time (hours) to clear blood of MP	24 (12 — 30)	24 (12 – 32)	0.82
Length of time (hours) of recovery from coma	27 (15 — 48)	21 (12 – 43)	0.01

and 21 hours for quinine group (P value=0.1) while the parasite clearance time was equal (median 24 hours) for both groups. (Table 3)

Repeated convulsions were observed in four patients out of 25 patients treated with Artemether and one case in quinine group. Hypoglycemia was observed in 4 patients while hypotension and bradycardia was observed in two patients in Quinine group while these complications were not observed in Artemether group.

Mortality was 12% in Artemether group as compared to Quinine group where mortality was 16%.

DISCUSSION

Out of 50 cerebral malaria patients 29 were male and 21 were female with a male to female ratio of 1.5:1. Almost same was observed in study conducted by Memon S et al¹⁴. In our study majority of the patients presented in age group 1 to 5 years followed by age group 5 to 10 years constituting 36% and 26 % of cases respectively. In study conducted by Memon S et al the majority of patients were in the same age groups i.e. 1 to 10 years. MP (Malarial Parasite) smear was positive in 72 % of cases which was more as compared to Memon S et al who found smear positive in two third of the studied cases.

Recovery was documented in the form of Resolution of fever, encephalopathy and parasite clearance. Resolution of fever was comparatively more rapid in intramuscular artemether group as compared to intravenous quinine group. The same result was observed by other studies^{15, 16}. The time taken for complete clearance of malarial parasite from blood was almost the same i.e. 24 hours in either group. Different results were observed in various studies. In most studies artemether took shorter time to clear the parasite as compared to quinine. While in other few the result was vice versa like a study conducted by Olumese PE et al who found a rapid parasite clearance with intravenous quinine as compared to intramuscular artemether¹⁸. Though the parasite clearance was almost the same in our study yet the coma resolution was less in quinine group as compared to artemether

group. This showed that parasite clearance has no direct relation with symptoms resolution.

Repeated convulsions were observed in four patients out of 25 patients treated with Artemether and one case in quinine group. Hypoglycemia was observed in 4 patients while hypotension and bradycardia was observed in two patients in Quinine group while these complications were not observed in Artemether group. Hypoglycemia has also been observed by other studies^{19,20}.

In this study we found overall mortality of 28%. Mortality was 12% in artemether group while 16% in quinine group. High mortality associated with cerebral malaria has been observed in other studies as well¹⁹. There was no significant difference in overall mortality in either group in study conducted by Tayler TE et al¹⁵.

CONCLUSION

Artemether is as effective as quinine in the treatment of cerebral malaria.

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