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COMPARATIVE STUDY OF INTRAVENOUS QUININE VERSUS INTRAMUSCULAR ARTEMETHER IN THE CEREBRAL MALARIA TREATMENT AMONG CHILDREN

Dr Iqra Rahim[1], Dr Haroon Rafique[2], Dr Iqtaza Arif[3]

[1] Islamic International Medical College, Rawalpindi

[2] Demonstrator Forensic Medicine Mohi ud Din Islamic Medical College Mirpur AJK

[3] Medical Officer at Holy family Hospital Rawalpindi

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Abstract:

Aim: *To compare the effectiveness of intramuscular artemether with intravenous quinine sulphate infusion in cases of cerebral malaria.*

Study design: *A randomized clinical trial.*

Place and Duration: *In the Pediatric department of Benazir Bhutto Hospital, Rawalpindi for one year duration from March 2019 to March 2020.*

Methods: *The study cases were divided in to two groups. Group A and B patients were treated with intramuscular artemether and intravenous quinine respectively to compare the effectiveness of the two drugs in cerebral malaria.*

Results: *There were 34 patients with cerebral malaria in each group. In group A there were 20 (58.82%) men and 14 (41.18%) women. In group B there were 21 (61.76%) men and 13 (38.24%) women. (P = 1.0000). The ratio of men to women in groups A and B was 1.42: 1 and 1.61: 1. The average age of patients in groups A and B was 7.6 years + 4.2 SD and 7.0 years + 4.3, respectively SD (p = 0.5625). The average recovery time for patients with cerebral malaria in groups A and B was 24.8 hours + 9.3 SD and 30.5 hours + 9.1 SD, respectively (p = 0.0130). Mortality in groups A and B was 4 (11.76%) and 5 (14.71%) cases, respectively (p = 1.0000).*

Conclusion: *Intramuscular artemeter was more effective than intravenous quinine infusion in cerebral malaria.*

Key words: *cerebral malaria, coma, intramuscular artery, intravenous quinine.*

Corresponding author:

Dr. Iqra Rahim,

Islamic International Medical College, Rawalpindi

QR code

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INTRODUCTION:

Malaria is a parasitic infection caused by intracellular plasma protozoa. There are 4 types of Plasmodium that infect humans: P. falciparum, P. vivax, P. ovale and P. malaria. Among them, P. falciparum causes the most serious disease. It is the only species that can cause deadly disease if left untreated. Patients without an immune system may die from the first symptoms within a few days. P vivax usually does not affect vital organs, but is responsible for increased morbidity[1-2]. It played an important role in human history, and with an estimated 300-500 million cases and over 01 million deaths each year, he did more harm to people than infectious diseases. Malaria Plasmodium falciparum is one of the most common life-threatening infections in the world, with a high frequency in India, Nepal, Bangladesh and Pakistan. This is an important public health problem in Pakistan. Malaria Plasmodium falciparum is one of the most common life-threatening infections in the world, with a high frequency in India, Nepal, Bangladesh and Pakistan. This is an important public health problem in Pakistan[3-4].

Malaria Falciparum is one of the main causes of ill health, neuro disability and death in tropical countries. About 40% of the world's population is at risk. There are over 500 million clinical cases each year. One percent of symptomatic infections can be complicated and become severe malaria. Severe malaria can occur as anemia, hypoglycaemia, metabolic acidosis, recurrent seizures, coma or multiple organ failure and is estimated to cause over a million deaths per year. Brain malaria (CM) is the most serious neurological symptom of malaria. Cerebral malaria is defined by the World Health Organization as a clinical syndrome characterized by coma at least 1 hour after the end of the seizure or hypoglycemic correction, the formation of asexual Plasmodium falciparum and nothing else in the spread of peripheral blood[5-6]. The reason for explaining the coma. The mortality rate is high, and some survivors suffer from brain damage that occurs in the form of long-term neurocognitive deficiencies. Cerebral malaria is the most common cause of non-traumatic encephalopathy in the world[7]. The basis of treatment is quinine or artemia, which are effective antimalarial drugs. The clinical picture of cerebral malaria may persist or worsen, although the parasites are removed from the blood. Even with effective anti-malarial drugs in tertiary hospitals, mortality is unacceptably high. Mortality increases with multiorgan failure (renal failure, jaundice, respiratory failure, severe anemia, lactic acidosis). The pathogenesis of cerebral malaria is multifactorial and includes obstruction, sequestration and rosette formation, cytokine release, cerebral edema and increased intracranial hypertension. The classic pathological feature of human CM is the sequestration of infected and uninfected red blood cells in the veins and capillaries of the brain. On the blood side, the blood brain barrier (BBB) parasite red blood cells (pRBC) are attracted to the sticky regions of pRBC by activating endothelial cells, monocytes and platelets, which leads to hypoxia and ischemia of local tissues. Endothelial activation is also associated with the release of proinflammatory cytokines such as TNF-α. It has also been suggested that excess TNF-α may lead to exaggerated disease behavior and "closure" of local activity in the affected areas of the brain[8-9]. Other cytokines are also associated with the pathogenesis of CM and coma. Although sequestration has a pathological, characteristic feature of MC, it is an important element of MC pathogenesis, although sequestration alone is unlikely to lead to a coma. The clinical picture of MC probably results from the effects of sequestration, metabolic changes such as hypoglycemia and metabolic acidosis, and the effects of pro-inflammatory cytokine production from the central nervous system (CNS) and systemic.

The first-line treatment for cerebral malaria is intravenous quinine infusion, but it causes hypoglycaemia, hypotension and arrhythmias. It is given as a long-term intravenous infusion and requires close monitoring. For this reason, it is very difficult to use it in peripheral hospitals, which can cause delays at the beginning of treatment, which can be one of the causes of high mortality and morbidity due to cerebral malaria. Intramuscular artemeter is easy to apply, has fewer side effects (reversible cardiac conduction defects, hemolysis and high dose neurotoxicity) and there is no need for monitoring[10].

TOOLS AND METHODS:

This is a randomized clinical study was held at the Pediatric department of Benazir Bhutto Hospital, Rawalpindi for one year duration from March 2019 to March 2020.

The patients were divided into two groups; Group A and B who received intramuscular Artemether and intravenous Quinine respectively. There were 34 patients in each group. This sample size was calculated using average duration of recovery from coma by artemether 34.8hrs + 8.2SD12,average duration of recovery from coma by quinine 40.8hrs + 8.2SD12, 95% confidence level and 90% power of test under open-epi software.

Criteria included: children of both sexes from 6 months to 12 years of age with a fever above 101 ° F, less than 11 Glasgow Coma Scores (GCS) results and peripheral blood showing trophozoite rings or plasma falciparum smears.

Exclusion criteria:
1. Shown in the analysis of suspected meningitis (septic, tuberculosis or viral) and cerebrospinal fluid (CSF).
2. Children receiving quinine / artemeter 24 hours before serving.

Data collection procedure: After approval by the hospital's ethics committee, all children who met our inclusion criteria were accepted. Written informed consent was obtained from parents / guardians. A detailed medical history and physical examination were carried out. Routine tests such as FBC, urea, sugar, electrolytes, creatinine, malaria parasite smears and PT / aPPTT were performed. If necessary, brain computed tomography and CSF tests were performed. Patients were randomly divided into two groups using the lottery method. Group A patients received intramuscular (I / M) artemether 3.2 mg / kg stat than 1.6 mg / kg daily for 5 days, and patients from group B received intravenous (I / V) infusion of quinine sulfate in 10% water dextrose 20 mg / kg than 10 mg / kg every 8 hours for 5-7 days. All patients were followed up to day 3 of treatment to see improvement in GCS. Patients were changed to 2 live medications if there was no improvement. All the above-mentioned information has been recorded in the proforma. Strict exclusion and inclusion criteria were used to control errors and bias in the study results.

Data analysis procedure: All data was entered into SPSS version 17 and analyzed. Frequencies and percentages were calculated for categorical variables such as gender and effectiveness. The mean and standard deviation were calculated for continuous variables such as age and recovery time. A T test was performed to compare the recovery time of both drugs. A p value of <0.05 was considered significant. Recovery time was examined for age and sex using the chi-square test to see treatment regulators.

RESULTS:

There were 34 patients in each group. The total hospital stay was 5-7 days. In group A there were 20 (58.82%) males and 14 (41.18%) women. In group B there were 21 (61.76%) men and 13 (38.24%) women (group P = 1.00). The male-female ratio in groups A and B was 1.42: 1 and 1.61: 1. The age groups of children with cerebral malaria are shown in Table 1.

TABLE-1: Age Distribution of Cases

Age in years	Group A n (%)	Group B n (%)	P value
> 1	04 (11.76)	02 (5.88)	0.6728
1-5	07 (20.59)	09 (26.47)	0.7757
6-10	13 (38.24)	14 (41.18)	1.0000
11-14	10 (29.41)	09 (26.47)	1.0000
Total	**34 (100.00)**	**34 (100.00)**	-

TABLE 2: Mean Age of Patients

Group	Age in years (Mean + SD)			P value
	Male	Female	Total	
A	6.3±4.4	9.4±3.3	7.6±4.2	0.5625
B	6.1±4.4	8.6±3.8	7.0±4.3	

The average recovery time for patients with cerebral malaria in groups A and B was 24.8 hours + 9.3 SD and 30.5 hours + 9.1 SD, respectively. The p value was 0.0130; This was statistically significant. Mortality in groups A and B was 11.76% and 14.71%, respectively. The P value is equal to 1.0000, which is considered statistically insignificant.

DISCUSSION:

The mean age of patients in the artemether group were 7.6 years + 4.2 SD and in quinine group was 7.0 years + 4.3 SD. The mean age in our study is more than another study which showed mean ages in artemether and quinine groups as 6.6 years ± 3.5 SD and 5.8 years ±2.4 SD years respectively. Majority of patients in our study were between 6 and

14 years of age[10-11]. From 6 to 10 years of age were 13 (38.24%) in artemether group and 14 (41.18%) in quinine group and from 11 to 14 years, there were 10 (29.41%) in Artemether group and 9 (26.47%) in quinine group. According to Memon S et al, most cases were in 5-10 years age group (56.5%) with 32.6% in the 1-5 years age group. In our study the coma resolution time in artemether group was significantly shorter when compared to coma resolution time in quinine group (p value 0.0130)[12]. It was 24.8 hours + 9.3SD in artemether group and 30. 5hours + 9.1SD in quinine group. This result is in agreement with the local study conducted by Memon et al15 in which the coma resolution time in artemether group was 34.8 ± 8.2 and 40.8 ± 7.0 in quinine group with p value <0.050. Another local study conducted by Mehdi et al showed good response in patients treated with artemether than quinine. The responders in case of quinine were 34.8% while in case of artemether the frequency of responders was 65.2%. On the other hand a local study conducted by Khan et al17, mean time for regaining full consciousness from coma with orientation in time space and person and no neurological deficit was 36 hours in both groups of artemether and quinine but he has reported early clearance of plasmodium parasite from blood in artemether group[13-14]. The mean disappearance time of Plasmodium from the blood was 36 hours in quinine group and 24 hours in artemether group thus showing the effectiveness of artemether. Olumese reported median recovery time of 24 h and 33 h in artemether and quinine groups respectively. Huda et al from India compared the artemether and quinine in cerebral malaria patients. According to his study, fever clearance time in artemether and quinine group was 44.5 and 45.9 hours respectively (P >0.05). Parasite clearance time was significantly shorter in artemether group (40.9 vs. 51.9 hours; P<0.001). Recovery from coma was shorter in artemether group (34.8 vs. 38.1 hours; P<0.05)[15]. The overall mortality rate was 23.9% with no significant difference between the two groups.

CONCLUSION:

According to the results of this study: Intramuscular artemeter takes less time resolution of coma in patients with cerebral malaria than intra venous quinine so it is clinically most effective. It is an effective alternative drug for the treatment of cerebral malaria in Pakistani regions with minimal medical facilities.

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