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Original Research Article

Artemether-Lumefantrine Vs Quinine in Cerebral Malaria A Comparative Study among Tribal Community of Hill Tracts in Bangladesh

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ABSTRACT

Objective: The aim of this study was to compare oral Artemether-Lumefantrine to intravenous Quinine by exploring its effectiveness in cerebral malaria in hospitalized patients.
Materials and Methods: A randomized prospective study was conducted among 64 hospitalized cases of cerebral malaria. One group of patients was treated with intravenous Quinine and another group was treated with oral Artemether-Lumefantrine. Response in clinical, laboratory parameters and outcome of treatment were noted every eight hours.
Results: Oral Artemether-Lumefantrine showed almost similar response in clinical and laboratory parameters with median temperature (101º F), pulse rate (102 b/m), systolic BP (110mmHg), GCS (12), hemoglobin (9.8 g/dl), WBC (9000/µl), platelet (130000/µl), B. glucose (101 mg/dl), S. creatinine (1.8 mg/dl), ALT (32 U/L), mean disappearance time of parasite from blood (40 hours), and mean time for regaining full consciousness (30 hours). Final outcome was also similar in both drugs with only 1 death (3.1%) reported in each group.
Conclusion: In cerebral malaria intravenous Quinine or oral Artemether-Lumefantrine therapy does not have any statistically significant difference in terms of clinical parameter, laboratory parameter and final outcome.

Keywords: Cerebral malaria, Artemether-Lumefantrine, Quinine.

INTRODUCTION

An estimated five hundred million people contract malaria each year worldwide, resulting in almost two million deaths yearly. [1] The Plasmodium falciparum parasite is responsible for almost all the neurological complications associated with malaria. In 2002, an estimated 2.2 billion individuals were exposed to Plasmodium falciparum in malaria endemic areas, with 515 million clinical episodes and over 1 million deaths. [2] The most fatal manifestation of Falciparum Malaria is cerebral malaria. Cerebral malaria if not treated, has a very high mortality and morbidity. By the widespread drug resistance the situation is further complicated, which is quickly emerging to even the new drugs. [3] The strict definition of cerebral malaria requires the presence of Plasmodium falciparum parasitemia with a Glasgow Coma Scale score of 9 or less, and other causes ruled out. [4]

Quinine has its primary role in the treatment of severe malaria. But,

intravenous Quinine has a narrow therapeutic window. Parental Quinine administration needs a constant rate infusion with dosing three times a day. Administration in intramuscular route is painful, and can cause sterile abscesses and predispose to lethal tetanus. [5] Although blindness and deafness may follow self poisoning, these adverse effects are rare in cerebral malaria; however, hypoglycaemia is a serious problem during patient management when Quinine is infused, especially in children and pregnant women. [6] In remote areas of developing countries there are not enough qualified healthcare personnel to manage the cerebral malaria in early stage of disease with intravenous access. Mortality increases due to delayed start of treatment. With appropriate and easy treatment protocol the mortality of cerebral malaria can be reduced. Oral Quinine is not a good option in cerebral malaria because of its delayed absorption and less parasite clearance rate within 48 hours which causes high mortality rate. [6] This study was conducted to compare the efficacy of intravenous quinine and oral Artemether-Lumefantrine, the two most frequently used drugs for cerebral malaria and to find out the outcome of oral Artemether-Lumefantrine as an effective oral emergency drug.

MATERIALS AND METHODS

This is a descriptive prospective hospital based cross sectional study done for one year (January 2014 to December 2014) in Rangamati Sadar Hospital Bangladesh among tribal. A full detailed history with proper systemic and neurological examination was performed by the authors. The diagnosis was confirmed with microscopic blood film examination (both thick and thin film) and rapid diagnostic test (RDT). Routine necessary laboratory tests were done to exclude other alternate diagnosis. History, clinical examination and laboratory investigations were recorded on standard forms on admission and then every four hourly.

Patients were assigned two groups of 32 patients in each group. These were named Quinine Group and Artemether-Lumefantrine Group. Quinine Group patients were treated with Quinine dihydrochloride infusion (Inj. Jasoquine 300mg/5ml amp) in the dosage of 600mg in 500ml of 10% Dextrose water every 8 hours for at least seven days. Artemether-Lumefantrine Group patients were treated with Artemether-Lumefantrine (Tab. Coartem, Artemether 20mg, Lumefantrine 120mg) by oral or nasogastric tube (semiconscious or unconscious patient) in the dosage of 4 tablets at initial diagnosis and the after 8, 24 and 48 hours. Clinical parameters (temperature, pulse, systolic blood pressure, Glasgow coma scale), laboratory parameters (hemoglobin, WBC, Platelet, B. Glucose, S. Creatinine, ALT), mean disappearance time of plasmodium from blood and mean time for regaining full consciousness was noted every four hours. Side effects of drugs were also noted.

Statistical analysis: Statistical analysis was made using the chi-square test for categorical variables. A value of $p<0.05$ was considered statistically significant. The Statistical Package for Social Sciences, SPSS (version 16.0) was used to analyze data.

Ethical considerations: Institutional Review Board (IRB) approval was obtained from ethical committee of Chittagong Medical College and Hospital. Before administering the survey, investigators explained the purpose of the study to all patients and patient's attendants if patient is unconscious. The voluntary nature of participation and the anonymous and confidential nature of the interview schedules were strongly emphasized. Verbal informed consent was obtained.

RESULTS

Total 64 patients were diagnosed with cerebral malaria and treated as intravenous Quinine group (32 patients) and oral Artemether-Lumefantrine group (32 patients). Age group 20-40 were more

vulnerable to cerebral malaria (n=40). Male gender showed increased vulnerability (n=39). (Table 1)

Table 1: Age and gender group treated with quinine and Artemether-Lumefantrine

Age Group:	Quinine	Artemether-Lumefantrine
<20	4	1
20-40	19	21
>40	9	10
Gender:		
Male	21	18
Female	11	14

Our study revealed that there was no significant difference (p >0.05) in response to clinical parameters with Quinine and Artemether-Lumefantrine, Temperature, pulse rate, blood pressure and Glasgow coma scale showed improved response with oral Artemether-Lumefantrine which was almost similar to intravenous Quinine sulphate (Table 2).

Table 2: Clinical parameter response after 48 hours

Clinical parameter	Quinine	Artemether-Lumefantrine
Temperature (ºF)	100.5 (100-101)	101 (100.5-101.5)
Pulse rate (beats/mi)	98 (94-102)	102 (90-114)
Blood pressure (Systolic) mm Hg	120 (110-130)	110 (90-130)
Glasgow coma scale	12 (11-13)	12 (11-13)

*median (IQR) estimated. (p>0.05)

Table 3: Laboratory parameter response at 48 hours

Lab parameters:	Quinine	Artemether-Lumefantrine
Hemoglobin	10.5 (8.4-11.3)	9.8 (8.7-11.2)
WBC Total count	8500 (7450-9150)	9000 (5250-11500)
Platelet	127500 (75750-190250)	130000 (90000-200000)
Blood Glucose	111.50 (80-140)	101 (82.5-133)
S. Creatinine	1.4 (1.03-3.25)	1.8 (0.9-3.4)
ALT	65 (38.75-125)	60 (37-105)

*median (IQR) estimated. (p>0.05)

We also found similarity in the laboratory parameters between quinine and Artemether-Lumefantrine which was recorded at 48 hours after treatment. Hemoglobin, WBC total count, platelet, blood glucose (to assess hypoglycemia), serum creatinine (kidney function) and ALT (liver enzyme) all showed improved response with oral Artemether-Lumefantrine which was similar to intravenous Quinine. (Table 3)

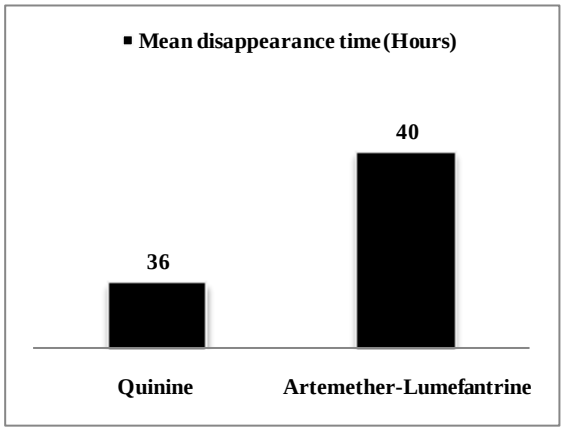

Figure 1: Mean disappearance time of plasmodium from blood.

On examining the blood slide (both thick and thin blood film) every 4 hourly, we found mean disappearance time of parasite plasmodium falciperum at 36 hours and 40 hours with Quinine and Artemether-Lumefantrine respectively. (Figure 1)

Mean time for regaining consciousness was also measured to assess the treatment response. The patient was clinically examined with continuous follow up. Intravenous Quinine sulphate showed almost similar response (28 hours) in comparison to oral Artemether-Lumefantrine (30 hours). (Figure 2)

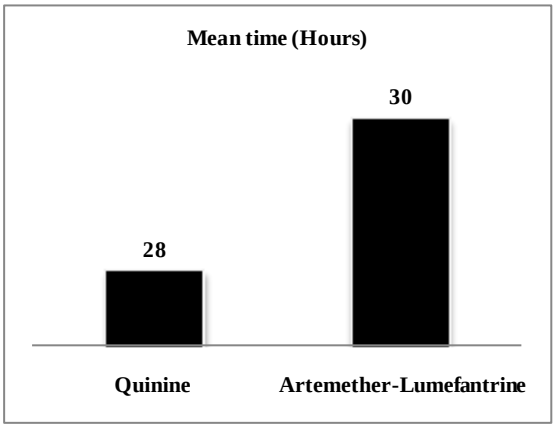

Figure 2: Mean time for regaining full consciousness.

After completion of treatment the outcome was measured. Full recovery rate was very good with both drugs. The only complication found after treatment was severe weakness with both the drugs (n=3). Mortality rate was very low in both Quinine (n=1) and Artemether-Lumefantrine (n=1). Hypoglycemia and vomiting are the two side effects found in only 2 patients treated with Quinine infusion. (Table 4)

Table 4: Final outcome with quinine and Artemether-Lumefantrine

Final outcome	Quinine n (%)	Artemether-Lumefantrine n (%)
Fully Recovered	30 (93.8)	29 (90.6)
Recovered with complications	1 (3.1)	2 (6.3)
Death	1 (3.1)	1 (3.1)
Side effects of drugs	2 (6.3)	0 (0.0)

DISCUSSION

Quinine is the standard drug used for the treatment of cerebral malaria. Artemether- Lumefantrine combination is a new product and claimed to be more effective in cerebral malaria. Both drugs showed comparable results in this study and is consistent with others published reports and further studies confirmed these results. [7,8] Our study is comparable and almost equivalent to the study conducted earlier in China. [9] Mean disappearance time of plasmodium from blood and the mean time for regaining full consciousness with Artemether- Lumefantrine showed similar result with the study done in China. [9] This life-saving benefit of Artemether-Lumefantrine compared with Quinine in severe malaria has to derive from its greater intrinsic parasiticidal activity. The principal pharmacodynamic advantage of Artemether-Lumefantrine is that it has a much broader stage-specificity of action than does quinine. It kills circulating ring-stage parasites before they can mature, which reduces sequestration of infected erythrocytes in the venules and capillaries of vital organs and thereby prevents potentially lethal microvascular obstruction. [10] The large and consistent reduction in mortality associated with Artemether-Lumefantrine and the consistent finding that mortality reduction is greatest in hyperparasitemia, lends support to the central quantitative role of parasitised erythrocyte sequestration in the pathology of malaria. [11] Any delay in treating severe infection will increase mortality. The ease and safety of oral Artemether-Lumefantrine is important practical advantages. Artemether-Lumefantrine is more expensive to buy, but quinine is more expensive to administer.

Cerebral malaria treatment is considered equivalent to Quinine therapy and probably this concept has not changed over the years. When resistance to Chloroquine was reported from almost every part of the world a devastating situation was created. At that time the only option left was quinine for cerebral malaria. Unfortunately intravenous Quinine is not available due to the lack of trained healthcare personnel in remote areas of developing and underdeveloped countries. Delay in hospital admission and starting treatment increases mortality. The only option left then is early start of treatment with oral administration. With early oral administration of Artemether- Lumefantrine both mortality and morbidity can be reduced by almost equal response to intravenous quinine in clinical and laboratory result.

CONCLUSION

Oral Artemether-Lumefantrine is an excellent drug when administered early in patients with cerebral malaria. In comparison with intravenous Quinine it showed almost same outcome in clinical and laboratory parameters with less side effects. So, oral Artemether-Lumefantrine can be considered as a second line treatment option in cerebral malaria when intravenous Quinine is not available.

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