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Efficacy of Quinine versus Artemether in the Treatment of Severe Malaria

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ABSTRACT

Background: For centuries Quinine has been used as very effective antimalarial drug and with advent of Artemisinin and its derivative Artemether there stands a concern about the superiority among these drugs especially in case of severe malaria in paediatric population. This study compares these drugs to explore their effectiveness.

Methods: A randomized prospective study was conducted with a view to compare efficacy regarding fever clearance, parasitaemia clearance and coma resolution between Quinine (10 milligrams per kilogram per dose diluted in 100 ml of 10 % dextrose solution T.D.S for seven days) and Artemether (3.2 milligrams per kilogram per day I.M on the first day and 1.6 milligrams per kilogram per day from second to fifth day of treatment) among 138 children with severe malaria in Bolan Medical College, Quetta, Pakistan. Study was conducted from December 2009 to December 2011. Ethical clearance was taken from Ethical clearance committee, Bolan Medical College, Quetta, Pakistan.

Results: Parasitaemia clearance was better with Artemether than Quinine. Parasitaemia clearance was 68 (98.55%) and 69 (100%) on third and fifth day respectively in Artemether group while Quinine group had 64 (92.75%) and 67 (97.1%) on third and fifth day respectively [third day [RR=0.9412 (95%CI, 0.8759-1.0113) P=0.2084 and fifth day respectively [RR=0.9571 (95%CI 0.9109-1.0058) P=0.2446]. Between 24-72 hours the coma recovery rate for Quinine and Artemether were 49 (98%) and 41 (85.41%) respectively [RR=1.1473 (95%CI 1.0141-1.298) P=0.029203 but after 72 hours of treatment the coma recovery remained 49 (98%) for quinine while it was 42 (87.5%) for artemether; RR=1.12 (95%CI 0.9993-1.2553) P=0.0568. The rapid resolution of coma with Quinine within 24 to 72 hours and after 72 hours were statistically significant than Artemether.

Conclusions: In severe paediatric malaria intravenous Quinine or intramuscular Artemether therapy does not have any statistically significant difference in terms of fever clearance but Quinine has statistically significant shorter duration of coma resolution than with Artemether therapy after 24 hours of treatment.

Keywords: Artemether; Malaria; Quinine.

INTRODUCTION

It has been more than a century after the discovery of the malaria parasite but still there were estimated 216 million malarial episodes and 655,000 deaths due to malaria in 2010.[1] Approximately 86% of these malarial deaths worldwide were of children under 5 years of age,[1] which highlights its high case fatality rate in pediatric population.

Malaria is one of the major health and economic problems in South Asia with the Annual Parasite Incidence (API) being 1.9, 1.46 and 0.35 cases/1000 population of Pakistan,[2] India and Iran[3] respectively. In the same duration of time the *Plasmodium Falciparum* (Pf%) percentage out of total confirmed cases were 19%,

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52.12% and 19% in Pakistan,[2] India and Iran[3] respectively. Baluchistan stands out as one of the worst affected region of Pakistan where the API is 5.8 cases/1000 populations and Pf% is 32%.[2] The reasons of the current situation can be attributed to the widespread high chloroquine resistance,[4,5] and rapid increase of incidence of drug resistant *Plasmodium falciparum* malaria.[6,7] There are conflicting reports,[8,9] and no significant evidence of superiority in effectiveness of either artemether or quinine in the treatment of severe malaria. Despite these facts quinine is still used as the primary drug in many parts of Pakistan,[6,10] in both adult and pediatric population. Baluchistan being the least studied, heavily affected and largest province of Pakistan this study aims to detect difference in parasitaemia clearance, fever clearance and coma resolution between artemether and quinine treated children in case of severe malaria.

METHODS

This prospective case control study was conducted in Pediatric unit I of Bolan Medical Complex Hospital from December 2009 to December 2011. Following patients were included in the study : Patients more than 1 year but less than 16 years age; patients with coma (GCS ≤ 9, lasting at least half hour after an episode of convulsion) and positive peripheral smear for asexual forms of *P. falciparum;* altered sensorium (GCS 10-15), convulsions and high grade fever with positive Malaria Parasite test (M.P); dark urine with positive M.P; decreased urinary output (<0.5milliliter per kilogram per hour) with positive M.P and patients with severe anemia (hemoglobin concentration <5.0 gram per deciliter) with positive M.P. Then the patients with the following features were excluded from this study: patients with coma along with positive cerebrospinal fluid (C.S.F) findings (increased protein, low glucose and pleocytosis) and negative M.P; C.T and CSF findings suggestive of meningitis/encephalitis; patients below 1year of age or above 16 years; patients already on malaria drug and/or antibiotics with antimalarial activity (azithromycin, tetracycline or chloramphenicol)[2,6,11] and patients with concomitant illness (sickle cell anemia, HIV, tuberculosis or other chronic disease). After the informed consent patients were subjected to detailed history, examination and laboratory tests and then a Performa was filled by attending physician. These patients were randomly allotted in one of the two groups- one which was treated with quinine hydrochloride (10 milligrams per kilogram per dose diluted in 100 ml of 10 % dextrose solution three times daily for seven days) and Artemether (3.2 milligrams per kilogram per day Intramuscular on the first day and 1.6 milligrams per kilogram per day from second to fifth day of treatment). Every patient went through thorough daily physical examination which mainly focused on the patient's Glasgow coma scale, pupil, and Core body temperature via tympanic membrane temperature, respiratory rate, pulse, blood pressure, fundoscopy and cranial nerves examination. Along with these physical examination the patients conditions were strictly monitored by the following laboratory tests: blood complete count, everyday quantitative parasite count of asexual forms (percentage of parasitized erythrocyte) was done until there were clearance of malaria parasite, serum creatinine in patients with low urine output (<0.5milliliter per kilogram per hour), chest X ray in patients developing respiratory distress, Computer Tomography scan of brain in patients with signs suggesting of increased intracranial pressure or focal signs. The patients were followed for 30 days post discharge to record any side effects of drugs or residual effects of disease. The primary end point of the study was death of the patient while the secondary end point was clearance of parasites or discharge. The patients who left against medical advice were not followed up. Ethical clearance was taken from the Ethical clearance committee, Bolan Medical College, Quetta, Pakistan.

The statistical analysis was done using SPSS for windows. We used Chi Square test to compare categorical data if all expected cell frequencies were ≥5 and fisher extract probability test for expected cell frequency <5). The value of 0.05 was used as the level of two tailed Significance. Intention-to-treat analysis was applied in this study.

RESULTS

Total 138 children were included in the study, 69 in each group. The age distribution between the two groups is shown in (Table 1). In the Quinine group there were 46 (66.66%) and in Artemether 44 (63.76%) boys whereas 23 (33.33%) and 25 (36.23%) were girls in Quinine and Artemether group respectively. The patients in this study came with the chief complains of fever, coma, convulsions, pallor, jaundice and oliguria. The most common presenting complaint was fever which was present in all the patients and the second most common presenting complaint was coma which was present in 50 (72.463%) and 48 (69.565%) patients in Quinine and Artemether groups respectively (Table 5). Only 10 (14.492%) patients in Quinine group presented with convulsions while it was 12 (17.391%) in Artemether group. Few patients also reported pallor 5 (7.246%) in Quinine and 6 (8.695%) in Artemether; jaundice 1 (1.44%) in Quinine and 2 (2.89%) in Artemether; oliguria 1 (1.44%) in Quinine and also 1 (1.44%) in Artemether, as their presenting complains. Patients with severe anemia (hemoglobin <6 grams per deciliter) were transfused.

Table 1. Age group frequency distribution table among Artemether and Quinine treated groups.

Age group	Artemether n (%)		Quinine n (%)	
0 -2	13 (18.84)		10 (14.5)	
3 -5	19 (27.54)		20 (29.0)	
6 -8	20 (28.99)	Mean age±SD	11 (15.9)	
9 -11	12 (17.39)		14 (20.3)	Mean age±SD
12 -14	3 (4.35)	6.04348 ± 3.54	11 (15.9)	
15 -17	2 (2.90)		3 (4.3)	7.231±4.274
total	69		69	

Table 2. Clinical features among the study groups.

Clinical features	Quinine n (%)	Artemether n (%)
Fever	69 (100)	69 (100)
Coma	50 (72.46)	48 (69.56)
Convulsions	10 (14.49)	12 (17.39)
Severe Anaemia	5 (7.25)	6 (8.7)
Jaundice	1 (1.45)	2 (2.9)
Oliguria	1 (1.45)	1 (1.45)

After the commencement of treatment fever clearance time was noted. On the third day of the treatment 62 (89.855%) patients under the quinine treatment experienced decline of temperature to norm but only 61 (88.405%) resolved fever in Artemether group; RR=1.0164 (95% CI 0.9046-1.1421) P=0.791337. By the fifth day, 69 (100%) and 66 (95.652%) patients had no fever in quinine and Artemether groups respectively; RR=1.0455 (95% CI 0.9942-1.0994) P=0.24452. Seventh day fever clearance was 69 (100%) for both of the study groups (Table 3).

Unlike the fever clearance, artemether had very rapid parasitaemia clearance in comparison to Quinine. Parasitaemia clearance was seen in 68 (98.55%) with the use of artemether but was only 64 (92.753%) with quinine on the third day; RR=0.9412 (95%CI 0.8759-1.0113) P=0.2084. While on the fifth day parasitaemia clearance was 69 (100%) for Artemether and 67 (97.101%) with Quinine; RR=0.9571(95% CI 0.9109-1.0058) P=0.2446. Similar to fever clearance, parasitaemia clearance was also 69 (100%) with both drugs on the seventh day of the therapy.

Coma was one of the prominent presenting complain which resolved rapidly with quinine therapy than artemether. Forty three (86%) out of 50 patients recovered from coma in less than 24 hours after the initiation of the quinine therapy but only 39 out of 48 (81.25%) comatose patients recovered with artemether during the same time duration; RR=1.0585 (95% CI 0.8876-1.2622) P=0.527089. Between 25 to 72 hours after initiation of therapy 49 (98%) and 41 (85.41%) were out from coma with Quinine and Artemether respectively, RR=1.1473 (95% CI 1.0141-1.298) P=0.029203. After 72 hours of treatment Quinine group had 49 (98%) while Artemether had only 42 (87.5%) recoveries; RR=1.12 (95%CI 0.9993-1.2553) P=0.0568. (Table 5)

Table 3. comparison of fever clearance in Quinine and Artemether treated groups.

Fever Clearance	Quinine (N=69) n (%)	Artemether (N=69) n (%)	P- value	Risk ratio	95% confidence interval
Day 3	62 (89.85)	61 (88.40)	0.791337	1.0164	0.9046-1.1421
Day 5	69 (100)	66 (95.65)	0.24452	1.0455	0.9942-1.0994

Table 4. Comparision of parasitaemia clearance between the Quinine and Artemether study groups.

Parasitaemia Clearance	Quinine (N=69) n (%)	Artemether (N=69) n (%)	P- value	Risk ratio	95% confidence interval
Day 3	64 (92.753)	68 (98.550)	0.2084	0.9412	0.8759-1.0113
Day 5	67 (97.101)	69 (100)	0.2446	0.9571	0.9109-1.0058

Table 5. Comparison of Coma resolution between the Quinine and Artemether treated groups.

Coma resolution in hours	Quinine (N=50) n (%)	Artemether (N=48) n (%)	P- value	Risk ratio	95% confidence interval
<24	43 (86)	39 (81.25)	0.527089	1.0585	0.8876-1.2622
25-72	49 (98)	41(85.41)	0.029203	1.1473	1.0141-1.298
>72	49 (98)	42 (87.5)	0.0568	1.12	0.9993-1.2553

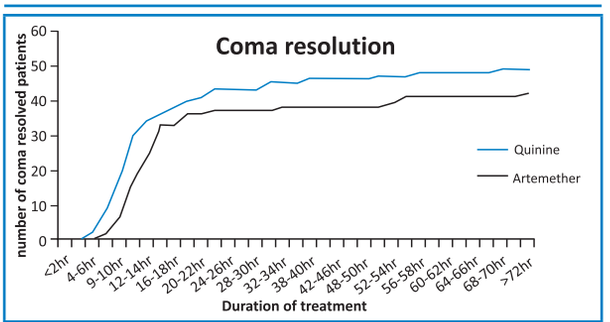

Figure 1. Comparison of coma resolution between the Quinine and Artemether groups.

DISCUSSION

There was difference between the ages of the two groups, the first group being slightly older, but this difference was not found to be statistically significant. This age was slightly different from other studies conducted in Asia,[12] but it may be because of the late presentation of patients in this province. There were more boys (Quinine: 66.66%; Artemether: 63.76%) in the study then girls (Quinine: 33.33%; 36.23%) in both groups. That may be because of gender bias as boys are brought early to medical attention in our culture.

Fever was universally found in both groups and it is consistent with international data.[13,14] It is the most common complaint with which the patients are brought to hospital and similar finding was reported in Africa.[13] The presence of coma was found to be significantly more than reported internationally.[15,16] This may be due to uninterrupted malarial transmission in this region or late presentation of our patients. However the presence of coma in the two groups was not statistically significant. Our percentage of patients with coma was similar to South Sudan,[17] perhaps representing the late presentation in both areas. As far as convulsions were concerned there was no statistically no difference between the two groups, but they were less than reported in adults in India.[18] This may represent a pathophysiological difference between the two age groups or it may be the genetic variation. Some studies have documented the presence of severe anemia as the dominant presenting feature of severe malaria,[12, 19] but in our study the severely anemic constituted the minority in both groups. Our study showed the paucity of Jaundice in both groups, this is in sharp contrast to some Indian workers who found the increasing prevalence of jaundice in the last decade.[20] This may relate to the absence of severe anemia as the presenting feature in this study. Similarly renal failure was not the presenting feature of our patients in sharp contrast to other international studies.[12,15,20,21]

The fever clearance seems to be better in the Quinine group but it was not statistically significant as compared to artemether on both third [RR=1.0164 (95% CI 0.9046-1.1421) P=0.791337] and fifth [RR=1.0455 (95% CI 0.9942-1.0994) P=0.24452] days. This is consistent with other international studies,[14,22] as some studies show that there is no clear difference between the two drugs in this regard.[23] The little difference found could be due to the fact that we were using intra muscular Artemether rather than intravenous Artesunate.[24] The parasite clearance time was also not statistically significant between both drugs [Third day: RR=0.9412 (95% CI 0.8759-1.0113); fifth day: RR=0.9571 (95% CI 0.9109-1.0058) P=0.2446] this is again is congruous to other studies,[14,22] although there are studies by Indian authors that support other finding.[25] There is no clear relation between the fever clearance time and parasite clearance time.

In our study the coma resolution time was shorter for quinine group than artemether group, but again it was not statistically significant in <24 hours but it was statistically significant between 24-72 hours and after 72 hours of treatment. Less than 24hours: RR=1.0585 (95% CI 0.8876-1.2622) P=0.527089; 24-72hours: RR=1.1473 (95% CI, 1.0141-1.298) P=0.029203; >72hours: RR=1.12 (95% CI 0.9993-1.2553) P=0.0568. The coma clearance time in this study was more related to fever clearance time than parasite clearance time. Workers from Sudan have found that the coma resolution time was shorter with Artemether,[25-27] this difference is probably due to genetic factors.

This study showed the presence of renal failure as the most common complication occurring in two patients while cerebral complications, both short term and long term were not seen. The presence of renal failure was independent of whether the patients were treated with Quinine or Artemether. Workers have found the presence of renal failure in <1% of cases,[28] although ours was a little higher.

CONCLUSIONS

There is no statistically significant difference between intravenous Quinine and intramuscular Artemether therapy in the treatment of severe paediatric malaria except for the rapid coma resolution with Quinine therapy after 24 hours of treatment.

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CONFLICT OF INTERESTS

The Authors have no competing interests.

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