World Journal of Medical Sciences 6 (2): 42-45, 2011
ISSN 1817-3055

Comparison of Coma Resolution Time in the Course of Treating Children with Severe Falciparum Malaria with Quinine and Artemether

[1]*O.A. Osonuga,* [2]*A.A. Osonuga,* [3]*I.O. Osonuga and* [4]*A. Osonuga*

[1]School of Medical Sciences, University of Cape coast, Cape coast, Ghana and
Department of Pharmacology, Olabisi Onabanjo University, Remo Campus, Nigeria
[2]Department of Nursing, University of Cape coast, Cape coast, Ghana
[3]Department of Physiology, Olabisi Onabanjo University, Remo Campus, Ikenne Remo, Nigeria
[4]School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana

Abstract: Two treatment regimens are currently widely used in treating severe Falciparum malaria in children. Efforts in this study seek to compare the coma resolution time in the course of treating severe malaria with Quinine and Artemether. Thirty two patients who met the inclusion criteria for the study, were randomly assigned into two groups of sixteen each. Patients in the Quinine group (Q) received quinine (Evans) 10mg/kg in 5% dextrose-saline infusion at 8hrs intervals but changed to oral quinine of same dosage for 7days. The patients in the artemether group (A) received 1.6mg/kg artemether twice daily on day 0 and then 1.6mg/kg artemether for four days via intramuscular route. The patients were followed up for 14days. Coma resolution time in Quinine group and Artemether group was 9.00 ± 24.59 and 4.50 ± 13.05 respectively. The results showed that Artemether relative to Quinine has faster coma resolution time in patients with severe malaria.

Key words:

INTRODUCTION

Malaria continues to be a major global health problem, with over 40% of the world's population (more than 2400 million people) exposed to varying degrees of malaria risk in some 100 countries in Africa, Asia, central America, Oceania and south America.

It causes more than one million deaths worldwide each year and over 90% of them occur in Africa. Severe malaria is caused by *Plasmodium falciparum* infection and usually occurs as a result of delay in treating an uncomplicated attack of falciparum malaria. In children, it could however develop rapidly [1-4].

Severe Malaria is approximately 2% of clinical attacks of malaria in African children. About 1-2million deaths occur, most of them in young children (under 5 years) with a child dying every 30seconds. Hence it is a medical emergency [4, 5].

Severe malaria is defined by the presence of one or more pernicious signs and symptoms including fever about 37.5°C and above (this may be irregular or continuous), irritability, prostration, jaundice, convulsion, hypoglycemia (blood glucose <40mg/dL), anemia (Hemoglobin <5g/dL) and at times unconsciousness.

There may be renal failure, hemolysis, hepatomegaly, splenomegaly, respiratory distress, circulatory collapse and bleeding diathesis.

The most common complication of severe malaria is cerebral malaria, defined as unrousable coma not attributable to any other cause. It is reported that even with correct treatment, the lethality rate among children with cerebral malaria approaches 20% [3, 6, 7].

The presentation is usually intense in severe cases, among children under 5 years, non immunes and pregnant women and may require hospitalization with intensive care facilities. In the course of treating severe malarial patients, there is need for experienced and committed medical personnel, supportive care monitors and facilities because of it's high morbidity and mortality [4].

Corresponding Author: O.A. Osonuga, School of Medical Sciences, University of Cape Coast, Ghana and
Department of Pharmacology and Therapeutics, Olabisi Onabanjo University, Remo Campus, Nigeria.
E-mail:overcomers2007@yahoo.com.

Many antimalarial medications are currently in use, of such is quinine (a relatively older drug) the standard treatment of severe malaria in children and Artemether (a derivative of Artemisia and a newer drug), thought to be much safer [8].

Since cerebral malaria is the most common complication of severe malaria and it is characterized by coma[4], efforts in this study seek to compare coma resolution time in the use of these widely accepted antimalarial drugs in the treatment of children with severe malaria.

MATERIALS AND METHODS

Patients and Methods: Patients were recruited in Ikenne local Government area of Ogun State at Overcomers Specialist hospital, Ilishan and General hospital Ikenne. The hospitals have facilities for resuscitating and handling emergency.

Patients who satisfied inclusion criteria (see below) were admitted for treatment in the ward. The children were randomly allocated into 2 treatments groups; treatment Q and A for quinine and artemether respectively. On enrolment, a brief history was obtained from accompanying adult (which may be the parent or guardian) and a clinical examination was performed. Body weight, oral and rectal temperature were recorded and monitored every four hours. The following were also documented -- presence or absence of pallor, jaundice, respiratory distress, drowsiness for each patient. Before administration of any drug, laboratory tests were done.

The patients in the quinine group received quinine (Evans) 10mg/kg in 5% dextrose/saline infusion, which was administered to the patients through intravenous canula for 4 hours. This served as the loading dose. Maintenance dose was given as 10mg/kg dose and then repeated 8hourly. The quinine infusion was later changed to oral medication when patient's clinical condition allowed for this. An oral dose of 10mg/kg was given 8 hourly [9]. The duration of treatment was 7days. The patients were monitored for toxic reactions i.e. hemolysis, convulsions, restlessness, disturbed vision.

The patients in the artemether group received 1.6mg/kg artemether twice on day 0 and then 1.6mg/kg daily for the next four days through deep intramuscular route [9]. The patients were only discharged after their clinical conditions became stable and good response to treatment attained. This happened usually after the third day.

The clinical examination and observation made were recorded daily for 8days (0-7) and on day 14. At each visit, patient (in case of older children) or parents/guardian were questioned, examined and documented for the presence of any adverse reactions to the administered drugs.

Ethical and parental approval for the study was obtained from Olabisi Onabanjo University Teaching Hospital, Nigeria, joint ethical review committee and informed consent from the parents or guardians.

Coma resolution time was defined as time according to attain a Blantyre scale value of 5 for at least 24 hours from treatment initiation.

Inclusion Criteria:

- Children from either sex with age ranging from 1year to 12years.
- Fever with temperature greater than 37.5°C within the last 24hours.
- Presence of convulsion, vomiting, hypoglycemia, anemia and headache.
- Informed consent obtained from the parents and guardians.
- Assurance that patients will be resident within catchments of study for follow-up.
- Absence of concomitant illness such as bronchopneumonia, typhoid, meningitis, urinary tract infection.
- Absent history of administration of antipyrexia.
- The Blantyre Coma Score of <3.

Exclusion Criteria:

- History of blood transfusion in the last two months.
- Presence of concomitant illness.
- History of previous allergy to quinine and artemether.
- Lack of informed consent.

Withdrawal Criteria:

- If any concomitant illness developed during the study.
- If informed consent is withdrawn by parents or guardian.
- If patient (or parents/guardian) is unwilling to continue in the study.
- Failure to comply with protocol [10].

Any adverse effect in the course of treatment were documented and compared in the two groups. The intensity of adverse experience was classified as;

Mild: An adverse experience that can be tolerated by the patient, causing minimal discomfort without interfering with everyday activities.

Moderate: An adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An adverse experience which prevents normal everyday activities.

Therapy was considered safe when adverse effect were mild and moderate.

Statistical Analysis: Data was analyzed using Epi-info version 6 (11), proportions were compared by calculating chi-square with Yates's correction. Normally distributed data for example, weight and temperature were compared by student's t-test. Mean value was given in the text (and tables).

Standard deviation and p-value less than 0.05 were taken as statistically significant.

RESULTS

Thirty-four patients who met the inclusion criteria were enrolled into the study. Two patients were withdrawn as a result of default in follow-up within 7 days. The 32 patients studied were randomly allocated to quinine or artemether study group. They were made up of 22 (68.7%) male and 12 (31.3 %) female. Their age ranged from 1 to 12 years, mean was 7 ± 3.63 and weight ranged from 7kg to 35kg, mean 19.83 ± 8.22.

The clinical features at presentation in the two groups are shown in Table 1. These features were similar in the two groups as the p-values were not statistically significant. The commonest presenting features were fever (84%), poor appetite (96.9%), pallor (96.9%) and jaundice (50.0%).

The physical findings were similar in the two groups. The findings at presentation are shown in Table 1.

A total of 5 out of 32 patients were in coma during enrollment for the study, 2 out of 16 (6.3%) in quinine group and 3 out 16 (9.4%) in artemether group (Table 2).

The coma clearance time for quinine was 9.00 ±24.59 hours while that of artemether was 4.50 ± 13.05 hours.

Table 1: Pattern of Clinical Presentations at Recruitment

Clinical presentation	Quinine	Artemether	P-value	Total
Age (Years)	8.24±3.44	6.00±3.71		7.00±3.65
Weight (kg)	20.78±7.80	18.88±8.72	19.83±8.22	
Fever	13(48%)	14(52%)		27(96%)
Vomiting	14(43.8%)	10(31.2%)	0.10	24(75%)
Poor appetite	15(46.9%)	16(50%)	0.31	31(96.9%)
Nausea	2(6.3%)	3(9.4%)	0.63	5(15.7%)
Body aches	8(25.0%)	5(15.6%)	0.28	13(40.6%)
Yellow eyes	5(15.6%)	3(9.4%)	0.41	8(25.0%)
Grunting	5(15.6%)	5(15.6%)	1.00	10(31.2%)
Diarrhea	2(6.3%)	1(3.1%)	0.54	3(9.4%)
Cough	8(25.0%)	10(31.3%)	0.48	18(56.3%)
Jaundice	8(25.0%)	8(25%)	1.00	16(50%)
Pallor	15(46.9%)	16(50%)	0.31	31(96.9%)
Respiratory distress	9(28.1%)	11(34.4%)	0.47	20(62.5%)
Convulsion	10(31.3%)	13(40.6%)	0.24	23(71.9%)
Coma	2(6.3%)	3(9.4%)	0.63	5(15.7%)
Dehydration	16(50.0%)	16(50.0%)		32(100%)
Temperature (°C)	14(50%)	14(50%)		28(100%)
Drowsing	10(31.3%)	12(37.5%)	0.45	22(68.8%)

*Values are significantly lower at $p < 0.05$

Table 2: Coma resolution time (Hours)

Drugs	Clearance Time (Hours)
Quinine	9.00±24.59
Artemether	4.50±13.05
P value	0.523

*Values are significantly lower at $p < 0.05$

DISSCUSION

The presenting features of the 32 patients are shown in Table 1 above. The clinical severity were similar in both groups (Artemether and Quinine) and hence not statistically significant.

The commonest presenting symptoms were poor appetite, fever, cough, vomiting and pallor and are in agreement with the findings of Sowunmi *et a.* [11], Shazia *et al.* [7] and WHO [3,4]. Vomiting was the commonest gastrointestinal manifestation of severe malaria in the children, thus suggesting the reason for perenteral route of drug administration [3]. The reasons why this is so (i.e. vomiting) are not clearly understood but Sowunmi et al suggested that it may be due to preferential sequestration of parasites in gastric vascular beds [11].

Coma is thought to be due to massive sequestration in the brain [12] and it's related to convulsion [3].

There were no deaths in both groups during the study. This may suggest artemether is as effective as quinine in controlling mortality in children with severe malaria or if any difference, it is not significant as seen in previous studies [3, 4, 13].

From the initiation of treatment, the time it took for the child to regain consciousness was the Coma recovery time. It shorter in the Artemether group (4.50 ± 13.05) than the quinine group (9.00 ± 24.59). This is similar with findings by Shazia *et al.* [7], PrayGod *et al.* [13], Ojuawo *et al.* [14], Huda *et al.* [15] and Taylor *et al.* [16].

Shorter recovery time was observed in some studies with quinine than with artemether [17, 18].

In Africa and by extension Nigeria, there are insufficient evidences to place superiority of one antimalaria therapy over the other in children, Quinine still remains the most widely used medication in treating severe malaria [3, 19]. However, Artemether is an equally effective alternative especially with resistance to quinine observed in Africa [13].

This study shows that artemether relative to quinine has a faster coma resolution time. Knowledge of this could help in reducing hospital admission time or planning of best suiting treatment regimen for patient with severe malaria in terms of cost and logistics, since both therapies are effective.

REFERENCES

1. WHO, 2009. Malaria Case Management operations manual (ONLINE) 2009. Available from: URL: whqlibdoc.who.int/publications//9789241598088_eng.pdf.
2. Roll Back Malaria Partners set ambitious financial targets for 19 African countries fighting malaria. Geneva: World Health Organization. (Online) 2007. Available from: URL: http:// www.rollbackmalaria.org/ amd2007/ pr/ pr_ rbm AMD2007-e.pdf.
3. WHO, 2010. Guidelines for the treatment of Malaria. 2nd edition, 2010. Available online from: URL: http://www.who.int/malaria/docs/TreatmentGuidelines.pdf.
4. WHO, 2000. Management of Severe Malaria, A Practical Handbook 2nd Edition.
5. Greenwood, B.M., A.K. Bradley, A.M. Greenwood, *et al*., 1987. Mortality and Morbidity from Malaria among children in rural area of Gambia, West Africa. Tran R Soc Trop Med. Hyg., 81: 478-486.
6. Srivicha, K., W. Polrat, V. Suparp, *et al*., 2003. Clinical Experience with intravenous Quinine and Intramuscular Artemether for the treatment of Severe Malaria in Thialand Southeast Asian J. Trop. Med. Public Health, 42(1): 54-61.
7. Shazia, M., S. Salma and M.A. Nizamani, 2007. A comparative clinical study of artemether and quinine in children with severe malaria. World Appl. Sci. J., 2(3): 163-167.
8. Jones, K.L., S. Donegan and D.G. Lalloo, 2010. Artesunate Versus Quinine for Treating Severe Malaria (Review). The Cochrane Collaboration Issue 1, John Wiley & Sons, Ltd.
9. Osonuga *et al*., 0000.
10. Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010. (Online) 2010. Available online from: URL: http// www.whqlibdoc.who.int/ publications/2010/9789241500470_eng.pdf.
11. Sowunmi, A. and O.A. Ogundahunsi, *et al*., 2000. Gastrointestinal manifestations of acute falciparium malaria in children. Acta Tropical., 74(1): 73-6.
12. Qijun Chen, M. Schlichtherle and M. Wahlgren, 2000. Molecular Aspects of Severe Malaria. Clinical Microbiology Reviews, 13(3): 439-450.
13. PrayGod, G., A. Frey and M. Eisenhut, 0000. Artemisin derivatives versus Quinine in treating severe malaria in children: a systematic review……???? where is the J. Name and Full Pages.
14. Ojuawo, A., A.R. Adegboye and O. Oyewalo, 1998. Clinical response and parasite clearance in childhood cerebral malaria: A comparison between intramuscular artemeter and intravenous quinine. East. Afr. Med. J., 75: 450-452.
15. Huda, S.N., T. Shahab, S.M. Ali, K. Afzal and H.M. Khan, 2003. A comparative clinical trial of artemether and quinine in children with severe malaria. Indian Pediatr, 40(10): 939-945.
16. Taylor, T.E., B.A. Wills, P. Kazembe *et al*., 1993. Rapid coma resolution with artemether in Malawian children with cerebral malaria. Lancet, 341: 661-662.
17. Aceng, J.R., J.S. Byarugaba and J.K. Tumwine, 2005. Rectal artemether versus intravenous quinine for the treatment of cerebral malaria in children in Uganda:randomised clinical trial. BMJ, 330: 334. doi:10.1136/bmj.330.7487.334 PMID:15705690.
18. Aguwa, C.N., C.V. Ukwe and M.O. Adibe, 2010.A Comparative Study of Quinine and Artemether in the Treatment of Severe Malaria in Nigerian Children. Tropical J. Pharmaceutical Res., 9(1): 11-17.
19. Olumese, P., 2010. Updates: WHO Guidelines for the Treatment of Malaria. 4th RBM Case Management Working Group Meeting. (Online). Available from: URL: http:// www.rbm.who.int/ partnership/ wg/ wg_management/ppt/4cmwg/3POlumese.pdf.