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Research Article

Artemether and Quinine are Safe and Effective in the Treatment of Severe Malaria in Nigerian Children

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Abstract
Severe malaria is a medical emergency. Parenteral artesunate is recommended over quinine for severe malaria. Artemether, is an alternative to parenteral artesunate in certain settings. The study compared the efficacy and safety of quinine with artemether. An open randomized trial conducted at the pediatric ward of a specialist care center. Thirty-two patients with severe malaria were randomly assigned to receive either artemether, 3.2mg/kg start and 1.6 mg/kg body weight intramuscularly daily for 4 days or quinine, 10mg/kg body weight in 5% dextrose/saline intravenously 8 hourly till recovery from coma or able to take oral dose. Patients were followed up for 14 days. Mean fever clearance time for quinine was significantly lower when compared with artemether, (46.5 ± 20.5 versus 72.00 ± 27.7 hours; P =0.006). The malaria parasite clearance time was however significantly lower with artemether than with quinine (31.5 ± 14.5 versus 46.5 ± 6.00 hours; P=0.001). Adverse events, including tinnitus and insomnia in quinine group were generally mild. There was no adverse effect observed with artemether. Quinine and artemether were both effective and safe in the treatment of severe malaria in children. Artemether was better tolerated, cleared parasite faster with earlier and sustained recovery from anaemia, jaundice and coma.

Key Words: Quinine, Artemether, Severe malaria, Antimalarial activity, Children

INTRODUCTION

Malaria remains an endemic disease in up to 40% of the world population. The WHO reported an incidence of 212 million cases in 2015, 90% in Africa, 7% in South East Asia, and 2% in Eastern Mediterranean (WHO, 2016). Approximately 2% of clinical attacks of malaria in African children are severe. About 303 000 deaths occur in young children (under 5 years) with a child dying every 2 minutes (WHO, 2016). However, adults are relatively semi immune (Ademowo *et al*., 1995). *Plasmodium falciparum* causes the most severe form of malaria and is also the most deadly. If not treated promptly could result in severe malaria, which includes cerebral malaria and severe anaemia (Olumese *et al*., 2002). Cerebral malaria can have a mortality rate of up to 25%, even with the best of treatment.

The rapidity by which malaria devastates children in Africa calls for urgent review of malaria therapy and management. Quinine, an antimalarial drug for severe malaria in children has complex dosing regimen, poor adherence and is poorly tolerated (Achan *et al*., 2011). There is need for reappraisal and search for effective and safer drugs for patients with severe malaria. It is on this basis that a comparative study of the efficacy of artemether and quinine in the treatment of severe malaria in children was designed. Artemether, a rapidly schizonticidal agent is combined with lumefantrine as a first line artemisinin-based combination therapy (ACT) for the treatment of uncomplicated *P. falciparum* malaria and administered intramuscularly is an alternative to parenteral artesunate for severe malaria (WHO, 2015). In Nigeria, malaria parasites were reported to be sensitive to quinine, hence reserved for initial treatment of severe and complicated *falciparum* malaria (Sowunmi and Salako, 1992; Olumese *et al*., 1999; Dondorp *et al*., 2010). However, quinine resistance has been reported (Adam *et al*., 2002; Pukrittayakamee *et al*., 2003). Alternatives to quinine are needed in view of the reported resistance, potential toxicity and intravenous route of administration, which may not be practical in rural areas (Karbwang *et al*., 1995). Parenteral artesunate has been advocated as the treatment of choice, in place quinine, for severe malaria globally (Dondorp *et al*., 2010). Artesunate is administered at a dose of 2.4mg/kg by slow intravenous injection over 5 minutes or IM, repeated at 12 and 24 hours, then once daily for up to 6 days if patient is unable to take orally; and mandatorily for 24 hours even if patient can take orally before 24 hours (Federal Ministry of Health, 2013). Intravenous administration and cumbersome method of preparation (Malaria Action Program for States, 2013) are also potential setback for parenteral artesunate.

This study was designed with the overall aim of determining the relative efficacy and safety of quinine and artemether in the treatment of severe malaria. The AQUAMAT study recommends intravenous artesunate over quinine in children less than 15 years of age (Dondorp *et al*., 2010).

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MATERIALS AND METHODS

Patients were recruited from the Overcomers Specialist Hospital, Ilisan and General Hospital Ikenne, Ogun State, Nigeria. Ethical approval for the study was obtained from the Olabisi Onabanjo University/Olabisi Onabanjo University Teaching Hospital joint ethical review committee. Inclusion criteria included children with either sex, age ranging from 1 to 12 years, Fever (temperature >37.5%) within the last 24 hours, microscopically proven malaria parasitaemia, presence of convulsion, hypoglycaemia and anaemia. Informed consent was obtained from the parents or guardians with the assurance that patients will be resident within catchments area of the study for follow-up. Exclusion criteria included presence of concomitant illness such as bronchopneumonia, typhoid, meningitis and urinary tract infection, history of blood transfusion in the last two months, history of previous allergy to quinine or artemether, and lack of informed consent. Withdrawal criteria included development of any concomitant illness during the study, withdrawal of informed consent by parent or guardian, unwillingness to continue in the study and failure to comply with protocol.

Patients who satisfied the criteria above were admitted for treatment in the ward. The children were randomly allocated into 2 treatment groups; for quinine and artemether respectively. On enrolment, a detailed history and clinical examination was carried out. The following were documented for each patient, body weight, body temperature, presence or absence of pallor, drowsiness, respiratory distress, convulsion, jaundice, coma, dehydration, urine retention, abnormal chest signs and liver or spleen enlargement. Before administration of drug, blood sample was collected for the following tests: thick and thin blood films for malaria parasite identification and quantification, random blood glucose, packed cell volume and full blood count. Urine was also collected for urinalysis, which was done using Combi 9 Clinitext for albumin, glucose and haemoglobinuria.

Patients in the quinine group received quinine (Evans) 10 mg/kg in 5% dextrose/saline infusion, which was administered to the patients through intravenous cannula for 4 hours. This served as the loading dose. Maintenance dose was given as 10 mg/kg dose, and then repeated 8 hourly. The quinine infusion was later changed to oral medication when patient's clinical condition allowed for this. An oral dose of 10 mg/kg was then given 8 hourly. The duration of treatment was 7 days. The patients were monitored for toxic reactions such as vertigo, tinnitus, disturbed vision, haemolysis, convulsion, restlessness and syncope. Patients in the artemether group received 3.2 mg/kg artemether on day 0 and then 1.6 mg/kg daily for the next four days through deep intramuscular route. Each patient was monitored for adverse reactions, which were documented. The patients were only discharged after their clinical conditions became stable and good response to treatment attained. This happened usually after the third day. Treatment outcome of all patients in the 2 groups was assessed in terms of clinical and parasitological response. Parasite clearance time was defined as the time from drug administration until there was no patent peripheral parasitaemia for at least 48 hours. Fever clearance time was defined as the time from drug administration until the axillary temperature drops below 37.5ºC and remained so for at least 72 hours. Symptoms clearance time was defined as the time between initiation of drug administration and the disappearance of all presenting symptoms of malaria.

Adverse effects were compared in the two groups. The intensity of adverse experience was classified as follows:

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 that prevented normal daily activities, prolonged hospitalization or resulted in death.

Therapy was considered safe when adverse event was mild or moderate.

Treatment success if parasite count on day 3 was <25% of pre-treatment count, and there was no parasitaemia on days 7 and 14.

Statistical Analysis:

Data was analyzed using Epi-info version 6. Proportions were compared by calculating chi-square with Yate's correction. Normally distributed data for example, weight and temperature were compared by student's t-test. Kruskal – Wallis test was used to compare data not conforming to normal distribution e.g. parasite density. Values are given in the text and tables as mean ± standard deviation. P-values less than 0.05 were taken as statistically significant.

RESULTS

Thirty-four patients who met the inclusion criteria were enrolled into the study. Thirty-two patients with 16 in each group successfully completed the study. Their age ranged from 1 to 12 years (mean 7.0 ± 3.6) and weight ranged from 7.0 to 35.0 kg (mean 19.8 ± 8.2) (Table I).

The presenting symptoms in the patients were poor appetite, fever, vomiting, chill/rigor, drowsiness, dark urine, body aches, cough and convulsion. The presenting clinical features of the patients are shown on Table 1. There were no significant differences in the features between those in the quinine and artemether treatment groups.

The parasite density in the study group ranged from 71,500 to 140,024/µl of blood (mean 95,122.63 ±16,044). The quinine group had a range of 71,500 to 108,400/µl (mean 89,425/µl ±12,481) while the artemether group had a range of 72,500 to 140,024/µl (mean 100,820/µl ±17,520). Both groups were comparable, (P >0.05). Parasitaemia reduced progressively over time in the course of treatment. Parasite cleared in all patients by day 3 in both quinine and artemether groups except in one patient in the artemether group in whom parasitaemia only cleared by day 7 (Fig 1). The mean parasite clearance time was significantly reduced in artemether group (31.5 ± 14.5 hr) compared with quinine (46.5 ± 6.0 hr; P = 0.001). A total of 28 out of the 32 patients enrolled into the study had fever (temperature ≥37.5ºC) at day 0, with 14 in each of the two groups. At day 3, seven of the patients in artemether group but only 1 of the patients in quinine group still had fever. By day 7, no fever was seen in quinine group while 2 of the patients in artemether group still had fever. However, by day 14, fever had cleared in all patients. The fever clearance time for quinine (46.5 ± 20.5 hours) was significantly reduced relative to artemether, which was 72.0 ± 27.7 hours (*p*-value =0.006) (Fig. 2).

Table 1:
Pattern of Clinical Presentation at Recruitment

Clinical Presentation	Quinine	Artemether	Total	P value
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	0.64
Fever	13 (48%)	14(52%)	27 (100%)	0.71
Vomiting	14 (43.8%)	10(31.2%)	24 (75%)	0.10
Poor appetite	15 (46.9%)	16(50%)	31 (96.9%)	0.31
Chill/rigor	11 (34.4%)	9(28.1%)	20 (62.5%)	0.46
Nausea	2(6.3%)	3(9.4%)	5 (15.7%)	0.63
Dark urine	7 (21.9%)	9(28.1%)	16 (50.0%)	0.48
Body aches	8 (25.0%)	5(15.6%)	13 (40.6%)	0.28
Grunting	5 (15.6%)	5(15.6%)	10 (31.2%)	1.00
Could not sit	5 (15.6%)	7(21.9%)	12 (37.5%)	0.46
Diarrhoea	2 (6.3%)	1(3.1%)	3 (9.4%)	0.54
Cough	8 (25.0%)	10(31.3%)	18 (56.3%)	0.48
Jaundice	8 (25.0%)	8(25.0%)	16 (50.0%)	1.00
Pallor	15 (46.9%)	16(50.0%)	31 (96.9%)	0.31
Respiratory distress	9 (28.1%)	11(34.4%)	20 (62.5%)	0.47
Convulsion	10 (31.3%)	13(40.6%)	23 (71.9%)	0.24
Coma	2 (6.3%)	3(9.4%)	5(15.7%)	0.63
Liver enlargement	15 (46.9%)	15(46.9%)	30 (93.8%)	1.00
Spleen enlargement	14 (43%)	15(46.9%)	29 (89.9%)	0.54
Anaemia (pcv <30.0%)	10 (31.3%)	13(40.6%)	23 (71.9%)	0.24
Hypoglycemia (glucose< 45mg%)	8 (25.0%)	7(21.9%)	15 (46.9%)	0.72
Haemoglobinuria	8 (25%)	8(25%)	16(50%)	1.00

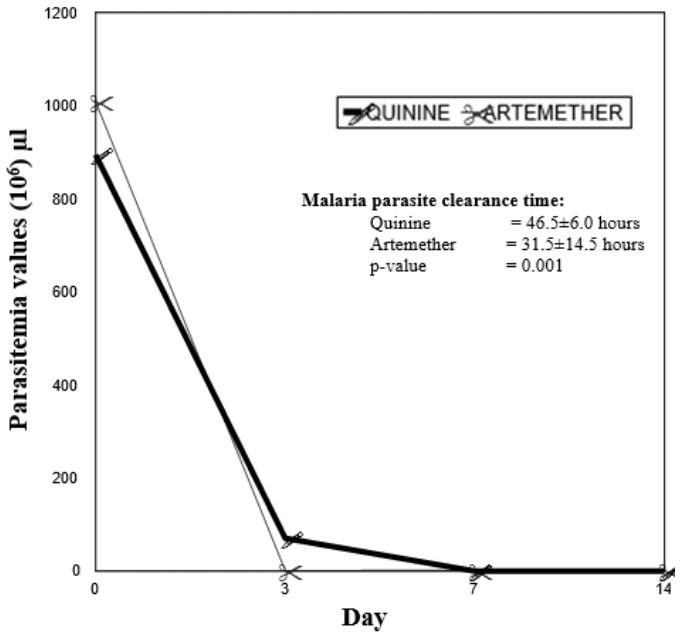

Figure 1
Pattern of malaria parasites clearance in patients treated with Quinine and Artemether.

Jaundice was observed in 16 patients (50%) at enrolment with 8 patients in each treatment group. By day 3, only 2 and 4 patients had cleared jaundice in quinine and artemether groups respectively. However, by day 7, jaundice had cleared in all the patients in both groups. No patient developed jaundice in the course of treatment. Thirty patients had enlarged liver at day 0 with 15 from each treatment group. At day 3, no patient in quinine group and only one in the artemether group had resolved liver enlargement. However, by day 7, all the patients in artemether and only one in quinine group no longer had enlarged liver. All the remaining 14 patients in the quinine group resolved liver enlargement by day 14.

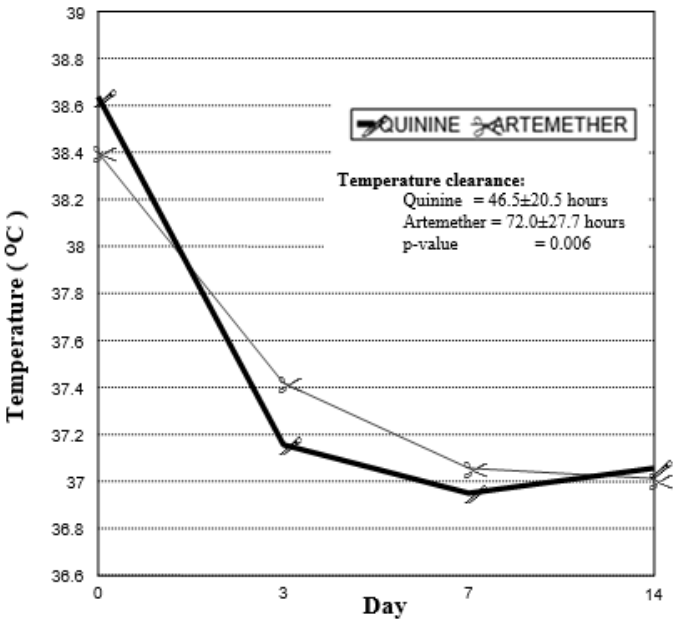

Figure 2
Pattern of temperature changes in patients treated with Quinine and Artemether

Of the 29 patients with enlarged spleen, 14 were in quinine group while 15 were in artemether group. By day 7, the spleen enlargement in all the 14 patients in both the quinine and artemether groups had resolved. At day 0, 23 patients (71.9%) had convulsion, with 13 (40.6%) from artemether group and

10 (31.3%) from quinine group. No other patient convulsed in the course of treatment. Five (15.6%) patients presented with coma at day 0 with 2 in quinine and 3 in artemether group. No patient developed coma in the course of treatment. At day 0, 31 of the 32 patients (97%) presented with anorexia. By day 3, only 4 of the 16 (25%) in the artemether group and 7 of the 15 (46.7%) in the quinine group were found to be anorexic. The remaining anorexic patients got better at day 7 for quinine and day 5 for artemether.

No adverse effect of note was observed in the course of treatment with artemether, while 7 (43.8%) patients treated with quinine complained of ringing in the ear and 6 (37.5%) had insomnia.

DISCUSSION

We present data on a comparative study on the efficacy and safety of artemether and quinine in the treatment of severe malaria. Patients who were allocated into the two treatment groups had similar presenting features. Vomiting was the commonest gastrointestinal manifestation of severe malaria in children, the reason why this is so are not clearly known, but it has been suggested that it may be due to preferential sequestration of parasites in gastric vascular beds (Sowunmi *et al*., 2000; Buffet *et al*., 2011). Cough was observed in 56.3% of the patients and may be due to increased sequestration of parasites in the pulmonary vascular bed or viral respiratory infection. Sequestration, increased parasite biomass and cytoadherence in small vessels by parasitized erythrocytes cause microcirculatory obstruction, reduce vascular lumen thereby reducing blood flow (Dondorp *et al*., 2000; Simpson *et al*., 2002). due to cytoadherence of parasitized erythrocytes. Recently, it was posited that endothelial protein C receptor is the host receptor responsible for sequestration of infected erythrocytes in the brain and other organs in cerebral malaria (Azasi *et al*., 2018). Parasite adhesion binds endothelial proterin C receptor.

Diarrhoea was the least common of the presenting features in severe malaria as the symptom occurred in only 9.4% of the children. The finding of cough, vomiting and diarrhea in severe malaria is consistent with previous reports (Anumudu *et al*., 2004; Sodeinde *et al*., 1996). Fever as expected was very common as it occurred in 87.5% of the patients.

Abdominal organ enlargement was found to be common in this study. Hepatomegaly was found in 93.8% and splenomegaly in 90.6%. It has been suggested that hepatomegaly and splenomegaly may be used as malariometric indices (Sowunmi, 1996a). The liver resolution time was faster with artemether than quinine as it took 7 and 14 days respectively. Both drugs resolved enlarged spleen during the course of treatment such that by day 7, all enlarged spleens were resolved in both treatment groups. The spleen is involved in preferential withdrawal of infected erythrocytes from circulation and often undergoes reactive hyperplasia in fulfilling this role (Buffet *et al*., 2011). This has led to the suggestion that a failure of splenic clearance may be a factor in the development of severe malaria (Bach *et al*., 2005).

Although the mean malaria parasite density was higher in the artemether treatment group than the quinine group, however, the parasite clearance time of 31.5 hr for artemether was markedly shorter than 46.5 hr for quinine. Artemether has been reported to have a faster malaria clearance time than quinine (Huda *et al*., 2003). There was no reappearance of malaria parasite after clearance among the patients in both groups except one in whom parasite reappeared by day 7 in artemether group. Recrudescence occurs when artemether is given in short monotherapy. The only patient with recrudescence of malaria parasites had artemether treatment extended by additional five days, which led to full parasite clearance. Coma recovery was faster in the artemether group unlike the finding in Nepal which recorded a faster coma resolution with quinine compared to artemether (Rehman *et al*., 2013). Fever clearance time of 46.5±20.5 hr with quinine was faster relative to artemether, which was 72.0 ± 27.7 hr.

The fever clearance time with quinine is consistent with the findings of (Huda *et al*.,2003; Salako *et al*.,1994). This suggests the anti-inflammatory property of quinine. Similarly the fever clearance time for artemether in this study is comparable with the finding in Thailand (Karbwang *et al*., 1995). Artemether, also known as dihydroartenisinin methyl ether is lipid soluble, and may administered as oral, rectal, intramuscular but not intravenous. Artemether may be preferred to artesunate in certain situations of unavailability of artesunate or difficulty with the preparation. Artesunate which is water soluble may be administered as oral, rectal, intramuscular and intravenous at a dose of 2.4 mg/kg. However, the intravenous and intramuscular preparation as well as administration may be challenging, involving patient's accurate weight and the determination of the number of 60 mg vials required based on the patient's weight. For parenteral use, artesunate is reconstituted with 1 ml of 5% sodium bicarbonate and must be shaken until the solution is clear, usually takes 2-4minutes. The reconstituted solution is diluted with normal saline, 2 mls for IM and 5 mls for IV. Dose has to be recalculated to ascertain the required dose to be withdrawn for the predetermined route of administration (Malaria Action Program for States, 2013). Any left-over reconstituted injection has to be discarded because the drug will re-crystallize within 1 hour and will be unsuitable for administration due to the potential of crystallization within the vessels and possible gangrene.

Jaundice clearance was better with artemether than quinine, as by day 3, 50% of jaundiced patients were clinically cleared in artemether as against 25% in quinine treatment group. By day 7, all the patients with jaundice were clinically cleared. The jaundice in malaria has been reported to have haemolytic, hepatic and cholestatic component (Molyneux *et al*., 1989). The fact that quinine is known to cause haemolysis may perhaps be responsible for its slower jaundice clearance. Proteinuria and haemoglobinuria occurred in 50% of the patients at presentation. This is similar to 20-50% and 44.4% reported from early studies in children with *Plasmodium falciparum* malaria at enrolment (Sowunmi, 1996b). Proteinuria is a common feature of febrile illnesses, while haemoglobinuria is usually due to massive erythrocyte destruction in severe malaria cases. Both proteinuria and haemoglobinuria got cleared in the course of treatment by both drugs. There was no evidence of adverse local, gastro-intestinal, cardiovascular, and neurological or other systemic toxic effect. The adverse reaction observed with quinine such as tinnitus and insomnia were mild and disappeared on stoppage of treatment. This is in consonance with earlier reported observation (White *et al*., 1982). In the treatment of severe malaria, parenteral artesunate or artemether for a minimum of 24 hours or when patient recovers from coma and

can tolerate orally should be followed by a course of artemisinin combination therapy (ACT).

In conclusion, the study has demonstrated that quinine and artemether are effective and safe in the treatment of severe malaria. Quinine however has a shorter fever clearance time than artemether, which may be attributed to the antipyretic properties of quinine. However, artemether relative to quinine has (i) better tolerance and safety (ii) more rapid malaria parasite clearance time and coma recovery time (iii) a faster jaundice resolution time and (iv) better liver enlargement resolution time.

REFERENCES

Achan, J., Talisuna, A.O., Erhart, A., Yeka, A., Tibenderana, J.K., Baliraine, F.N., Rosenthal, P.J., D'Alessandro, U. 2011. Quinine, an old Antimalarial drug in a modern world: role in the treatment of malaria. Malaria Journal 10:144. Doi:10.1186/1475-2875-10-144.

Adam, I., Idris, H.M., Mohamed-Ali, A.A., Aelbasit, I.A., and M.I. Elbashir. 2002. Comparison of intramuscular artemether and intravenous quinine in the treatment of Sudanese children with severe falciparum malaria. East Afr Med J. 79(12):621-5.

Ademowo, O.G., Falusi, A.G., and O. O. Mewoyeka. 1995. Prevalence of asymptomatic parasitaemia in an urban and rural community in South Western Nigeria. Central African Journal of Medicine 41(1): 18-21.

Anumudu, C.I., Okafor, C.M., Ngwumohaike, V., Afolabi, K.A., Nwuba, R.I., and M. Nwagwu. 2004. Clinical manifestations and immune response to MSP1(19) in severe paediatric malaria in Adeoyo State maternity hospital, Ibadan. Afr J Med med Sci 33(1): 57-63.

Azasi, Y., Lindergard, G., Ghumra, A., Mu, J., Miller, L.H., Rowe, J.A. 2018. Infected erythrocytes expressing DC13 PfEMP1 differ from recombinant proteins in EPCR-binding function. Proc Natl Acad Sci USA 115(5):1063-1068. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC 5798336/pdf/pnas.201712879.pdf

Bach, O., Baier, M., Pullwitt, A., Fosiko, N., Chagaluka, G., Kalima, M., Pfister, W., Straube, E., and M. Molyneux. 2005. Falciparum malaria after splenectomy: a prospective controlled study of 33 previously splenectomized Malawian adults. Trans. R Soc Trop Med Hyg 99: 861-867

Buffet, P.A., Safeukui, I., Deplaine, G., Brousse, V., Prendki, V., Thellier, M., Turner, G.D., Mercereau-Puijalon, O. 2011. The pathogenesis of Plasmodium falciparum malaria in humans: insight from splenic physiology. Blood 117(2):381-392. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3031473.

Dondorp, A.M., Fanello, C.I., Hendriksen, I.C.E., Gomes, E., Seni, A., Chhanganlal, K.D., Bojang, K., Olaosebikan, R., Annumobi, N., *et al*., for the AQUAMAT group. 2010. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomized trial. Lancet 376:1647-1657.

Dondorp, A.M., Kager, P.A., Vreeken, J., White, N.J. 2000. Abnormal blood flow and red cell deformability in severe falciparum malaria. Parasitol Today 16:228-232.

Federal Ministry of Health. National Malaria Control Programme Abuja, Nigeria. 2011. National Guidelines for diagnosis and treatment of malaria. nmcpnigeria.org.

Federal Ministry of Health. National Malaria Control Programme Abuja, Nigeria. Training Manuals on Malaria. Case management of malaria in the hospital. Trainers content.

Federal Ministry of Health, Malaria Action Program for States. 2013. Treatment of severe malaria with injectable artesunate. Training workbook, Nigeria.

Huda, S.N., Shahab, T., Ali, S.M., Afzal, K., and H.M. Khan. 2003. A comparative clinical trial of artemether and quinine in children with severe malaria. Indian Pediatr. 40(10): 939-45.

Karbwang, J., NorBangchang, K., Thanavibal, A., Ditta, M., and T. Harinasuta. 1995. A comparative clinical trial of two different regimens of artemether plus mefloquinine in multidrug resistant falciparum malaria. Trans R Soc Trop Med Hyg 89;269-270.

Molyneux, M.E., Taylor, T.E., Wirima, J.J., and A. Borgstein. 1989. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Q J Med; 71: 441-459.

Olumese, P.E., Amodu, O.K., Bjorkman, A., Adeyemo, A.A., Gbadegesin, R.A., and O. Walker. 2002. Chloroquine resistance of P.falciparum is associated with severity of disease in Nigerian children. Trans R Soc Trop Med Hyg 96: 418-420

Olumese, P.E., Bjorkman, A., Gbadegesin, R.A., Adeyemo, A.A., and O. Walker. 1999. Comparative efficacy of intramuscular artemether and intravenous quinine in Nigerian children with cerebral malaria. Acta Trop 73:231-236.

Pukrittayakamee, S., Wanwimolruk, S., Stepniewska, K., Jantra, A., Huyakorn, S., Looareesuwan, S., and N.J. White. 2003. Quinine pharmacokinetic-pharmacodynamic relationships in uncomplicated falciparum malaria. Antimicrob Agents Chemother. 47(11): 3458-63.

Rehman, M.U., Shrestha, B., Zehri, T., and S. Thapa. 2013. Efficacy of quinine versus artemether in the treatment of severe malaria. J Nepal Health Res Counc 11(23):17-21.

Simpson, J.A., Aarons, L., Collins, W.E., Jeffery, G.M., White, N.J. 2002. Population dynamics of untreated Plasmodium falciparum malaria within adult human host during the expansion phase of the infection. Parasitology 124(Pt 3):247-263.

Sodeinde, O., Adeyemo, A.A., Gbadegesin, R.A., Olaleye, B.O., Ajayi-Obe, K.E., and O.G. Ademowo. 1996. Interaction between acute diarrhea and falciparum malaria in Nigerian children. J Diarrhoea Disease Research Dec 14(4): 369- 373.

Sowunmi, A. 1996a. Hepatomegaly in acute falciparum malaria in children. Trans R Soc Trop Med. Hyg 90: 540- 542.

Sowunmi, A. 1996b. Renal function in acute falciparum. Arch Dis child 76: 293-298.

Sowunmi, A., Ogundahunsi, O.A.T., Falade, C.O., Gbotosho, G.O., and A. M. J. Oduola. 2000. Gastro intestinal manifestations of acute falciparum in children. Acta Tropica 5; 74(1): 73-6

Sowunmi, A. and L. A. Salako. 1992. Evaluation of the relative efficacy of various antimalarial drugs in Nigeria children under 5 years of age suffering from acute uncomplicated falciparum malaria. Ann Trop Med Parasitol 86: 1-8.

White, N.J., Looareesuwan, S., and D.A. Warrell. 1982. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. Am J Med 73: 564-572.

World Health Organisation. 2015. Guidelines for the treatment of malaria, 3rd edition. WHO, Geneva, Switzerland. www.who.int.

World Health Organisation. 2016. World malaria report. http://www.who.int/malaria/publications/world-malaria-report-2016/report/en. Accessed on October 3, 2017