JOURNAL OF CURRENT RESEARCH IN SCIENCE (ISSN 2322-5009)
CODEN (USA): JCRSDJ
2013, Vol. 1, No. 6, pp:526-532
Available at www.jcrs010.com

ORIGINAL ARTICLE

ARTESUNATE SUPPOSITORY FOR PRE-REFERRAL TREATMENT OF UNCOMPLICATED AND SEVERE *FALCIPARUM* MALARIA IN UNDER FIVE YEARS CHILDREN ATTENDING TWO HEALTH FACILITIES IN ABEOKUTA, NIGERIA

Agbeyangi OA[1], Sam-Wobo SO[1], Ekpo UF[1], Akinloye OA[2], Mafiana CF[3], Oduwole OA[4], Adediran OA[5], Dedeke IOF[5] and Oniwide TR[5]

1- Parasitology unit, Department of Biological Sc., University of Agriculture, Abeokuta Nigeria
2- Department of Biochemistry, University of Agriculture, Abeokuta Nigeria
3- Executive Secretary Office, National University Commission, Abuja, Nigeria
4- State General Hospital, Ijaye, Abeokuta Nigeria
5- Federal Medical Centre Idi-Aba, Abeokuta Nigeria

ABSTRACT: *Falciparum* malaria is an important cause of death and illness in children in southwestern Nigeria which is accompanied with vomiting and severe anaemia. Rectal artesunate suppository (Plasmotrim-50/200 mg Artesunate) was used for pre-referral treatment of uncomplicated, moderate and severe *falciparum* malaria in 264 under five years children attending two tertiary health facilities (Federal Medical Centre, Idi-Aba, Abeokuta (FMC) and State General Hospital Ijaye, (SGH)) in Abeokuta southwestern Nigeria that were selected systematically. Ethical approvals were obtained in addition to informed consent. Treatment were made at the point of selection based on WHO criteria for uncomplicated and severe malaria with blood sample collected at 0 hour and 24 hours for microscopic examination using giemsa staining technique. Analysis of data showed reduction in level of parasitaemia in all children at 24 hours of treatment with no parasite observed in some of the children with uncomplicated (60/78) and moderate *falciparum* malaria (21/32) in SGH, and uncomplicated (54/88) and moderate *falciparum* malaria (11/26) in FMC, while children with severe *falciparum* malaria have few parasites. There was considerable reduction in body temperature and few children with severe *falciparum* malaria persist body temperature between 38.0-38.9 ^{o}c. Children with uncomplicated and moderate *falciparum* malaria have fever while children with severe *falciparum* malaria showed symptoms such as vomiting, loss of appetite in addition to fever. Chloroquine is common drug of choice with few in combination with sulphadoxine-pyrimethemine and herbs. The use of artesunate suppository is effective in reducing level of parasitaemia thus effective when use as pre-referral therapy.

KEYWORDS: Treatment, Severe, Moderate, Uncomplicated, *Falciparum* Malaria, Rectal Artesunate, Children, Abeokuta, Nigeria.

INTRODUCTION

Malaria had been known as major cause of morbidity and mortality in endemic areas, especially in under five-year children in sub-Saharan Africa (UNICEF, 2010; WHO, 2011; Wong *et al.*, 2010; Murray, 2012). Distance to healthcare facilities is the main determinant of high mortality rate (CDC, 2009; Foster and Vilendrer, 2009; Gomes *et al.*, 2009). Mortality, currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to anti-malarial drugs (WHO, 2008; Hay *et al.*, 2010; Onwuka, 2012).

Malaria control requires an integrated approach comprising prevention including vector control and treatment with effective anti-malarial (Arrow *et al.*, 2005). The affordable and widely available anti-malarial chloroquine that was in the past a main-stay of malaria control is now ineffective in most *falciparum* malaria endemic areas, and also resistance to Sulfadoxine-pyrimethamine, Mefloquine and Amodiaquine is increasing rapidly (Sam-Wobo *et al.*, 2008; USAID, 2009).

Since malaria is a serious public health problem in under five years children, and is accompanied with vomiting which make it difficult for oral drug administration, WHO upon research studies introduce rectal treatment of malaria through the use of suppositories (WHO, 2007; TDR, 2008; WHO, 2011).

Artesunate is the most versatile with its high water solubility facilitating the development of oral, intramuscular and rectal formulations. Artesunate suppositories have been identified by the World Health Organization (WHO) as

Corresponding Author: Agbeyangi OA, Parasitology unit, Department of Biological Sc., University of Agriculture, Abeokuta Nigeria. **E-mail:** oagbeyangi@yahoo.com

having great promise, especially for treatment of childhood malaria (WHO, 2012). They had been proved safe and efficacious for adults (Awad, 2003; Bar-Zeev, 2006), in children with non severe infections from Africa (Krishna, 2001), South East Asia (Sabchareon, 1998), South America (Gomez–Landires, 1996) and Papua New Guinea (Karunajeewa 2003; Karunajeewa, 2007).

Results from a variety of clinical studies have indicated that artesunate suppositories can be used for initial emergency and curative treatment in uncomplicated (Karunajeewa, 2007; Gomes *et al.*, 2008), moderate (Barnes, 2004), severe (Gomes *et al.*, 2009) and cerebral malaria (Aceng, 2005). However, WHO has recommended the sole used of an artermisinin derivatives for the treatment of patients with uncomplicated and severe *falciparum* malaria (WHO/UNICEF, 2003; WHO, 2007; WHO, 2011).

MATERIALS AND METHODS

2.1. Study Area, Health Facilities

The study was conducted in Abeokuta, Ogun State, Nigeria, between August 2008 to March 2009 in two health facilities namely: Federal Medical Centre, Idi-Aba, Abeokuta (FMC) and State General Hospital Ijaye, (SGH) all located in Abeokuta the capital city of Ogun State. Ogun State, Nigeria. Abeokuta is a tropical rain forest zone and lies approximately between Longitude $2^0 31''$ W and $4^0 31''$ E, Latitude $6^0 31''$ S and 8^0 N, its bounded in the south partly by the Atlantic ocean, and sharing common boundaries with Oyo and Ondo states.

2.2. Ethical Consent

The study objectives were discussed, and written consents was obtained from the State Ministry of Health Management and Medical Directors of the heath facilities used. Approvals to carry out the study were obtained from the ethical committees of each of the health facilities used with interactive sections with staff and parents of the children, only consented parents children were treated.

2.3. Research, Clinical Procedures

Children under five years (1-5 years) with clinical features of malaria (WHO, 2012) were eligible for recruitment. The treatment of malaria using rectal artesunate drugs (Plasmotrim-50/200mg Artesunate Anti-malarial, Rectocap, produced by Mepha Ltd Bausch-Basel Switzerland) was carried out by the Medical Doctors, Nurses and the research scientist. The first dose of rectal artesunate suppository (ies) drug(s) was given per rectum at a dose of 5 to 10mg/kg of body weight of thermostable suppositories. A combination of one or two 50mg or 200mg of the thermostable rectal artesunate drug (Plasmotrim 50mg, 200mg) were administered to the children. Each child was observed for 1hour after dosing and if suppository expelled, the same dose is re-administered and the observation continues.

Venous blood sample were collected using sterile needle and syringes from each child to determine the decrease in level of parasitaemia. All children were physically assessed after 24 hours for ability to tolerate oral medication, ability to eat, drinks, and move normally in addition to vital statistics. Both thick and thin film of each child blood was made on a microscope slide following Giemsa's staining Technique procedure of Carter and Lema (1993); Cheesbrough, (1998) and WHO, (2008). The numbers of parasites seen per field were counted against white blood cells in a thick blood film to give approximate number of parasites per mL of blood to determine parasite density (MPC/µl) and percentage parasitized red blood cells (PPRBCs) for both prior to administration of rectal artesunate (0 hour) and after treatment (24 hours). The presence of one or more of the following clinical/laboratory features and Signs and symptoms were used to classify the patient as suffering from uncomplicated malaria and severe malaria:

2.4. Uncomplicated Malaria

2.4.1. Signs And Symptoms

Fever or a history of fever within the preceding 2-3 days, Chills (feeling unusually cold), Rigors (shivering), Headache.

2.4.2. Clinical Manifestations

Generalized body and joint pain, Nausea with or without vomiting, Loss of appetite, Sweating, Abdominal Pain (especially in children), Bitterness in the mouth, Irritability and refusal to feed (in infants) (Karrunnajewa *et al.*, 2004).

2.5. Severe Malaria

2.5.1. Clinical Manifestations

Prostration, impaired consciousness, respiratory distress (acidotic breathing), Multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, or haemoglobinuria.

2.5.2. Laboratory Tests

Severe anaemia Hb < 5g/dL or PCV< 15%., hypoglycaemia, acidosis, renal impairment, hyperlactataemia or hyperparasitaemia.

2.5.3. Signs And Symptoms

Fever plus at least one of the following: prostration, altered consciousness, lethargy or coma; respiratory distress; severe anaemia; convulsions; inability to swallow; persistent vomiting (WHO, 2006)

2.6. Data Analysis

The data from the questionnaires were entered and analyzed using Epi info (CDC, Atlanta, GA) version 6.0 into percentiles. The data from blood sample analysis prior to administration of artesunate suppository (0 h) and after administration (24 h) for parasite density and reduction of parasitemia after treatment were obtained. Analyses of the relationship between the variables and for significance were done using SPSS for windows (SPSS, Inc., Chicago, IL) version 16.0. All significance are reported at $P<0.05$.

RESULTS

Two hundred and sixty four under five years' children were assessed in two tertiary health facilities (136 persons in State Hospital Ijaye, Abeokuta, Ogun State (SGH) and 128 persons in Federal Medical Centre Idi-Aba, Abeokuta, Ogun State (FMC) as shown in Table 1. With nature of malaria diseases, SHA had 78 uncomplicated, 32 moderate, and 26 severe *falciparum* malaria diseases while FMC had 88 uncomplicated, 26 moderate, and 14 severe *falciparum* malaria diseases.

3.1. Parasitaemia Before Treatment (0 Hours) With Rectal Artesunate Suppository

Malaria parasite count (MPC) before treatment (0 hour) of group 1-5 is higher among the children with uncomplicated *falciparum* malaria while MPC >20 is high among children with severe *falciparum* malaria in both health facilities (Table 1).

Malaria parasite count per microlitres (MPC/µl) before treatment (0 hour) of group1-500 is higher among the children with uncomplicated *falciparum* malaria while MPC/µl group 1001-1500 is higher among children with severe *falciparum* malaria in both health facilities. Result on percentage parasitized red blood cells (PPRBCs) before treatment (0 hour) showed that children with uncomplicated *falciparum* malaria were more among group 1-5 while PPRBC >15 is higher among children with severe *falciparum* malaria in both health facilities (Table 1).

Body temperature before treatment (0 hour) >39^{o}c is common among children with severe *falciparum* malaria while between 37.0-37.9^{o}c is common among the children with uncomplicated *falciparum* malaria (Table 1).

Table 1: Parasitaemia before treatment (0 hours) with Rectal Artesunate suppository

Parameters	Health Facilities					
	SHA (136)			FMC (128)		
	Uncomplicated(78)	Moderate(32)	Severe(26)	Uncomplicated(88)	Moderate(26)	Severe(14)
MPC						
0	4	0	0	3	0	0
1-5	45	16	0	42	9	0
6-10	27	10	1	33	8	0
11-20	2	4	14	10	5	4
>20 MPC/µl	0	2	11	0	10	14
0	1	0	0	1	0	0
1-500	72	27	14	80	17	3
501-1000	5	5	6	7	8	6
1001-1500	0	0	6	0	1	5
PPRBC						
0	10	1	0	1	0	0
1-5.0	37	12	1	57	10	2
5.1-10.0	34	9	3	24	7	2
10.1-15.0	5	6	10	4	6	4
>15.0	1	5	12	0	3	8
TEMPERATURE ^{o}c						
36.0-36.9	3	0	0	0	0	0
37.0-37.9	29	5	3	8	5	1
38.0-38.9	46	17	6	62	12	3
>39.0	4	6	17	18	9	10

3.2. Effect Of Rectal Artesunate Suppository After Treatment (24 Hours) In Parasitaemia

Reduction in level of parasitaemia was observed in all children attending both health facilities at 24 hours of treatment with no parasite observed in some of the children with uncomplicated (60/78) and moderate *falciparum* malaria (21/32) in SHA, and uncomplicated (54/88) and

moderate *falciparum* malaria (11/26) in FMC. With children with severe *falciparum* malaria, majority were founded in MPC group 1-5 in both health facilities (Table 2).

Children showed a higher reduction in (MPC/µl) at 24 hours of treatment among the children with uncomplicated and moderate *falciparum* malaria and majority of the children with severe *falciparum* malaria felt in group1-500 MPC/µl. There is a considerable reduction in PPRBC at 24 hours of treatment, majority of children with uncomplicated (74/78) and moderate *falciparum* malaria (28/32) in SHA, and uncomplicated (78/88) and moderate *falciparum* malaria (16/26) in FMC felled in PPRBC group 0. With children with severe *falciparum* malaria, majority were founded in MPC group 1-5.0 in both health facilities (Table 2).

Table 2: Effect of Rectal Artesunate suppository after treatment (24 hours) in Parasitaemia

Parameters	Health Facilities					
	SHA (136)			FMC (128)		
	Uncomplicated(78)	Moderate(32)	Severe(26)	Uncomplicated(88)	Moderate(26)	Severe(14)
MPC						
0	60	21	0	54	11	0
1-5	17	10	21	25	10	3
6-10	1	1	4	5	3	7
11-20	0	0	1	4	2	4
>20 MPC/µl	0	0	0	0	0	0
0	75	27	0	79	15	0
1-500	3	5	26	9	10	12
501-1000	0	0	0	0	1	2
1001-1500	0	0	0	0	0	0
PPRBC						
0	74	28	0	78	16	0
1-5.0	3	2	20	10	9	8
5.1-10.0	1	2	5	0	1	2
10.1-15.0	0	0	1	0	0	3
>15.0	0	0	0	0	0	1
TEMPERATURE °c						
36.0-36.9	32	12	0	20	4	0
37.0-37.9	46	16	17	68	20	7
38.0-38.9	0	4	9	0	2	7
>39.0	0	0	0	0	0	0

The use of rectal artesunate resulted in reduction in body temperature due to reduction in level of parasitaemia in majority of the children with uncomplicated and moderate *falciparum* malaria felled between body temperatures 37.0-37.9 °c and few children with severe *falciparum* malaria still have body temperature between 38.0-38.9 °c, with no children having body temperature >39 °c (Table 2).

3.3. Nature Of Malaria Diseases And Symptoms Observed

Majority of the children with uncomplicated and moderate *falciparum* malaria have fever and in combination with cough, catarrh and abdominal discomfort while children with severe *falciparum* malaria showed symptoms such as vomiting, loss of appetite and convulsion together with fever (Table 3).

Table 3: Symptoms of malaria-Nature of malaria among the study group

Parameters	Health Facilities					
	SHA (136)			FMC (128)		
	Uncomplicated(78)	Moderate(32)	Severe(26)	Uncomplicated(88)	Moderate(26)	Severe(14)
Symptoms of malaria						
FV	42	7	0	10	2	0
FV+CG	10	5	1	11	1	0
FV+BT	7	6	0	36	1	0
FV+VM	4	1	10	8	4	1
FV+MJ	4	2	0	2	0	0
FV+CV	0	0	1	0	0	0
FV+LA	3	2	1	3	1	0
FV+AD	3	1	0	2	0	0
FV+CC	2	3	0	2	0	0
FV+CT	3	0	0	4	0	0
VM+LA	0	2	5	5	8	3
FV+VM+BT	0	3	8	0	9	10

FV-Fever, VM-Vomiting, BT-Body temperature, CG-Cough, MJ-Muscles and Joint aches, CV-Convulsion, LA-Loss of appetite, AD-Abdominal discomfort, CC-Chill/Cold, CT-Catarrh.

3.4. Nature Of Malaria And Anti-Malaria Used

Data obtained on anti-malaria drugs used by the children under study showed that majority of children with uncomplicated *falciparum* malaria used chloroquine as common drug of choice with few in combination with sulphadoxine-pyrimethemine and herbs. The use of artesunate derivatives is low especially rectal artesunate suppository (Table 4).

Table 4: Anti-malaria used - Nature of malaria among the study group

Parameters	Health Facilities					
	SHA (136)			FMC (128)		
	Uncomplicated(78)	Moderate(32)	Severe(26)	Uncomplicated(88)	Moderate(26)	Severe(14)
Anti-malaria used						
CQ	47	15	14	25	5	4
CQ+ SP	8	5	9	29	6	2
CQ+SP+ ART	1	1	0	5	4	2
CQ+SP+ART+ HB	1	0	0	4	2	1
CQ+SP+ HB	0	0	0	7	3	1
CQ+ART	2	1	0	5	0	1
CQ+ART+ HB	1	0	0	1	0	0
CQ+ HB	2	1	1	7	2	2
SP	10	5	1	1	2	1
SP+ ART	4	2	0	3	0	0
SP+HB	0	1	0	0	1	0
ART	1	0	0	0	1	0
HB	1	1	1	1	0	0

HB- Herbs, CQ- Chloroquine, SP- Sulfadoxine-Pyrimethamine, ART- Artesunate

DISCUSSION

Results revealed that majority of the children under study have uncomplicated and moderate *falciparum* malaria in both two health facilities which is an indication of low frequency of infection of malaria diseases in an urban settlement of Abeokuta, this result is in line with result obtained by Ojo and Mafiana (2005) and Sam-Wobo *et al.,* (2012). Majority of children with uncomplicated and moderate *falciparum* malaria that felled between MPC group 1-5 is an indication of mild infection rate and is in line with results obtained by Karunajeewa *et al.,* (2007) and Gomes *et al.,* (2009) while children with severe *falciparum malaria* that felled between MPC group >20 is an indication of severe infection rate and this conform with results obtained by Karunajeewa *et al.,* (2003). Data obtained on the use of rectal artesunate that showed great reduction in the level of parasitaemia in the children under study after 24 hours of treatment especially among uncomplicated and moderate *falciparum* malaria is an indication of effectiveness of the drug, and is in line with result obtained treatment of uncomplicated and moderate *falciparum* malaria with rectal artesunate by Agbenyega (2008). The great reduction in infection levels with respect to MPC/lL and PPRBCs and the drop in temperature showed that rectal artesunate is effective in the management and treatment of malaria infection in children less than 5 years because of reduction in parasitaemia within 24 hours of treatment. The results confirm observations by Awad *et al.,* (2003); Gomez *et al.,* (2003); Karunnajeewa *et al.,* (2003); Barnes *et al.,* (2004); Bar-Zeev and White, (2006); Krishna, (2006); Agbenyega, (2008); Gomes *et al.,* (2008); and TDR, (2008) on the effectiveness of rectal artesunate in children. Majority of the parent does not use effective anti-malaria drugs for treating uncomplicated, moderate and severe *falciparum* malariadiseases. Resistance to Chloroquine and sulphadoxine-pyrimethemine that were used by the parent of the children has been reported in Nigeria (Lege-Oguntoye *et al.,* (1989).

CONCLUSION

The great reduction in infection levels (parasitaemia) and the drop in temperature within 24 hours of treatment showed that rectal artesunate is effective in the management and treatment of malaria disease in children under 5 years and can be use as pre-referral therapy. However, there is need for health education by government health institutions and development partners for the general public to be aware of the use of rectal artesunate for managing childhood malaria and reducing mortality.

ACKNOWLEDGMENT

The authors appreciate the support of management and staff of the hospitals and the cooperation of parents, guardians, and the children during the study.

REFERENCES

Aceng JR, Byarugaba JS, Tumwine JK. Rectal artemether versus randomized clinical trial. British Medical Journal 2005;330(7487):334-340.

Agbenyega T. Efficacy and safety of rectal artesunate in paediatric patients– a randomized controlled study (Ghana). TDR Annual Report 2008.

Arrow KJ, Gelband H, Jamison DT. Making antimalarial agents available in Africa. N Engl J Med 2005;353(4):333–5.

Awad MI, Alkadru AMY, Behrens RH, Baraka OZ, Eltayeb IB. Descriptive study on the efficacy and safety of artesunate suppository in combination with other anti-malarias in the treatment of severe malaria in Sudan. Am J Trop Med Hyg 2003;63:153–158.

Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M, Molyneux ME. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomized study. Lancet 2004;363:1598–1605.

Bar-Zeev N, White NJ. Evidence behind the WHO guidelines: hospital cares for children: efficacy and safety of artemisinin derivatives in children with malaria. J Trop Pediatr 2006;52:78–82.

Carter JY, Lema OE. Practical Laboratory Manual for Health Centers in Eastern African. Nairobi, Kenya: African Medical and Research Foundation 1993:87:143.

Centre for Disease Control and Prevention (CDC). CDC Activities in Tanzania. Atlanta, GA: Annual Report 2009.

Cheesbrough M. District Laboratory Practice in Tropical Countries (Part 1). United Kingdom: Cambridge, UK: Cambridge University Press 1998;pp:454.

Foster D, Vilendrer S. Two treatments, one disease: childhood malaria management in Tanga, Tanzania. Malar J 2009;8:1475-2875-1188-1240.

Gomes M, Ribeiro I, Warsame M, Karunajeewa H, Max P. Rectal artemisinins for malaria: A review of efficacy and safety from individual patient data in clinical studies. BMC Infect Dis 2008;8:39.

Gomes MF, Faiz MA, Gyapong GO. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009;373:557–566.

Gomez L, Jurado MH, Cambon N. Randomised efficacy and safety study of two 3-day artesunate rectal capsule/mefloquine regimens versus artesunate alone for uncomplicated malaria in Ecuadorian children. Acta Tropical 2003;89:47–53.

Gomez–Landires EA. Efficacy of artesunate suppository followed by oral meflofloquine in the treatment of severe falciparum malaria in endemic areas where resistance to chloroquine exists in Ecuador. Japanese Journal of Tropical Medicine and Hygiene 1996;24:14-24.

Hay SI, Gething PW, Snow RW. India's invisible malaria burden. Lancet 2010;376(9754):1716-1717.

Karunajeewa HA, Kemiki A, Alpers MP, Lorry K, Batty KT, Ilett KF, Davis TM. Safety and therapeutic efficacy of artesunate suppositories for treatment of malaria in children in Papua New Guinea. Pediat Infect Dis 2003;22:251–256.

Karunajeewa HA, Ilett KF, Dufall K, Kemiki A, Bockarie M, Alpers MP, Barrett PH, Vicini P, Davis TM. Disposition of artesunate and dihydroartemisinin after administration of artesunate suppositories in children from Papua New Guinea with uncomplicated malaria. Antimicrobial Agent of Chemotherapy 2004;48:2966-2972.

Karunajeewa HA, Manninig L, Mueller I, Ilett KF, Davis TME. Rectal administration of artemisinin derivatives for the treatment of malaria. JAMA 2007;297:2381–2390.

Krishna S. Reevaluation of how artemisinin work in light of in vitro evidence for emerging resistance. Trends Molec Med 2006;12:200–205.

Krishna S, Planche T, Agbenyega T, Woodrow C, Agranoff D, Bedu-Addo G, Owusu-Ofori A, Appiah J, Ramanathan S, Mansor S, Navaratnam V. Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. Antimicrobial Agents Chemotherapy 2001;45:509–516.

Lege-Oguntoye L, Abua JU, Werblinska B, Ogada WN, Blotbooma B, Olurinola PF. Chloquine resistance Plasmodium falciparum in semi-immune children in Zaria, northern Nigeria. Transaction of the Royal Society of Tropical Medicine and Hygiene 1989;pp:509-601.

Murray CJL. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2012;379:413-431.

Ojo DA, Mafiana CF. Seasonal pattern of malaria fever among children in Abeokuta, Ogun State, South-West, Nigeria. Pak J Soc Sci 2005;3:572–576.

Onwuka A. Saving Nigeria from a mass Killer. Punch Viewpoint. Tuesday November 2012;13:21.

Sabchareon A, Attanath P, Chanthavanich P, Phamaksool P, Prarinyanupharb V, Poonpanich Y, Mookmanee D, Teja-Isavadharm P, Heppner DG, Brewert J, Chongsuphajaisidhi T. Comparative clinical trial of artesunate suppositories and oral artesunate in combination with mefloquine in the treatment of children with acute falciparum malaria. American Journal of Tropical Medicine and Hygiene 1998;58:11-16.

Sam-Wobo SO, Agbeyangi OA, Ekpo UF, Akinloye OA, Mafiana CF, Adeleke MA. Rectal artesunate, their utilization and parental perception in the management of malaria in children from Abeokuta, South-western Nigeria. Journal of Vector-Borne and Zoonotic Diseases 2012;12(2):151-155.

Sam-Wobo SO, Akinboroye T, Anosike JC, Adewale B. Knowledge and practices of pregnant women in semi-urban communities on malaria treatment measures, Abeokuta, Nigeria. Tanzan J Health Res 2008;10:226–231.

TDR. Efficacy and Safety of Rectal Artesunate as Emergency Treatment in Children with Severe Malaria Who Are Unable to Take Oral Medication, and Development of Appropriate Strategies for Its Use. Annual Report, 2008.

UNICEF. World Malaria Day 2010: Africa Update, Roll Back Malaria Progress & Impact Series No. 2, April, UNICEF on behalf of the Roll Back Malaria (RBM) Partnership, Geneva 2010.

USAID. USAID Malaria Program: Infectious Diseases, Malaria, Technical Areas and Treatment and Drug Resistance. Health Technical Report 2009.

WHO. Consideration of mass drug administration for the containment of artemisinin-resistant malaria in the Greater Mekong subregion. Geneva, World Health Organization, 2012.

WHO. World Malaria Report 2008. Geneva, Switzerland: WHO, 2008.

WHO/UNICEF. The Africa Malaria Report, 2003 Geneva.

WHO: World Malaria report, Global malaria programme. Geneva: World Health Organization Publication; 2011.

Wong PS, Tan CH, Lee V, Li MZ. Molecular epidemiological investigation of Plasmodium knowlesi in humans and macaques in Singapore. Vector-Borne Zoonot Dis 2011;11:131–135.

World Health Organization (WHO). Artemisinin-Based Suppositories in the Management of Severe Malaria (Rectal Artemisinin). Global malaria programme,WHO/H.T.M/MAL. 2007;1118:1–16.

World Health Organization (WHO). Briefing on Malaria Treatment Guidelines and Artemisinin Monotherapies. Geneva 2006;pp:1–28.