

# Effect of Artemether Treatment on Plasma Lipid Profile in Malaria

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## Abstract

This study was undertaken to assess the effect of artemether treatment on plasma lipid profile in malaria infection. While the importance of lipid to plasmodial infective processes and metabolism is being increasingly appreciated, little is known about the attendant effect of chemotherapy on plasma lipid profile. Thirty patients with uncomplicated malaria were chosen from two secondary health-care facilities in Yobe State, Nigeria with informed consents and ethical clearance. Based on predetermined inclusion criteria patients were given 3.2 mg/kg of artemether with 1.6 mg/kg on subsequent days for a total of five days. This was done after the collection of urine and blood samples for urinalysis, malaria parasite density count and serum lipid analysis. A follow-up was planned seven (7) days from first dose during when clinical assessment and repeat malaria parasite density count and serum lipid analysis were done. Data were analyzed with statistical package for social scientist and Microsoft Excel spread sheet while level of significance at  $p \leq 0.05$  was calculated using paired t-test. Serum HDL cholesterol concentration recorded a significant decline of 0.13 mmol/L from a pre-treatment mean concentration of 1.17 mmol/L ( $p < 0.04$ ). Triglyceride, total cholesterol, LDL-cholesterol, VLDL-cholesterol showed increment or reductions that were not significant. The clinical cure rate was 50% and mean percentage reduction in parasitaemia was 52%. A possible explanation for this low cure rate could be resistance, unfavorable pharmacokinetic disposition or lack of full adherence. A trial with complete parasite clearance, possibly using artemisinin-based combinational therapy would provide a more compelling result.

## Keywords

Artemether, Plasma Lipid Profile, Malaria, Humans

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## 1. Introduction

Malaria is an acute febrile illness caused by haemoprotozoal organisms of the phylum Apicomplexa and genus *Plasmodium*. Its history is a fascinating story of mankind's struggle with a debilitating and devastating illness that at one time afflicted more than two thirds of the world's population and helped to shape the course of history [1]. Though as early as the Hippocratic era malaria was clearly identified with marshes, it was not until the late nineteenth century that Ross identified mosquito as the vector [2] and Charles Louis Alphonse Laveran showed plasmodium to be the pathogen [3]. Although numerous plasmodial species have been identified that naturally infect a variety of animals, only four are pathogenic to man. These are *Plasmodium falciparum* (*P. falciparum*)—the most pathogenic and the cause of most complications of malaria, *Plasmodium vivax* (*P. vivax*), *Plasmodium ovale* (*P. ovale*) and *Plasmodium malariae* (*P. malariae*). However, *P. knowlesi* which is evolutionary related to human forms has been implicated in naturally acquired symptomatic malaria in a 39-year-old Thai man [4].

It is a well established fact that the parasite induces in the host certain metabolic and biochemical changes observable both in the erythrocyte [5] [6] and in the serum [7]-[9]. These changes are not unrelated to the fact that, glycosylphosphatidyl inositol, the major component of malaria toxin is known to induce the production of inflammatory cytokines via interaction with CD14 on cells of the innate immune system with concomitant activation of toll-like receptors [10]. Part of these changes involves disorders in lipid transport and metabolism. Protein and lipid trafficking events are said to underlie host cell invagination during parasite entry that results in the parasitophorous vacuole, maintenance of the vacuole, development of antigenic and structural alterations in the cytoplasm and membrane of erythrocyte, new pathways of nutrient import and the machinery to sustain parasite protein export to the vacuolar and erythrocytic domains [11].

The parasite is critically dependent on macromolecules derived from host plasma and erythrocyte membrane. Grellier *et al.* [12] demonstrated that parasite growth was complete using serum-free medium supplemented only with a human high density lipoprotein (HDL) fraction. Development was incomplete with the low density lipoprotein fraction (LDL) and did not occur at all with the very low density lipoprotein (VLDL) fraction. Specific fatty acid combinations presumably derived from the HDL fraction and free fatty acids were said to provide optimum growth environment [13]. Of particular importance is erythrocyte membrane cholesterol and sphingolipid to parasite entry and continued existence in the intravacuolar environment. Lipid raft cholesterol is said to be absolutely needed for raft protein association and depletion of membrane cholesterol by methyl  $\beta$ -cyclodextrin (MBCD) is said to lead to abrogation of infection and expulsion of the parasite from the erythrocyte [14]. Inhibition of parasite sphingomyelin synthase by dl-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol (PPMP) leads to arrest of tubovesicular network formation, a transport organelle extending from the parasitophorous vacuole membrane to the periphery of the erythrocyte and is used for nutrient import [15]. Because of these profound effect of malaria infection on blood lipids and unique pathways of lipid metabolism in plasmodium [16], targeting of lipid metabolism has been considered attractive for rational antimalarial chemotherapeutic drug design and development. In furtherance of the research on lipid and malaria, artemether was chosen. It is now used as one of the artemisinin backbones in combinational therapy (ACT) of malaria in areas of the world where multidrug resistant *Plasmodium falciparum* malaria is prevalent [17] [18]. As a rapidly acting blood schizontocide, earlier studies with artemether monotherapy revealed fever clearance time and parasitological cure rate of 30 hours and >90% respectively [45] [46]. Due to its lipid solubility we therefore set out to examine the concomitant changes in plasma lipid profile in malaria in response to artemether chemotherapy.

## 2. Materials and Methods

### 2.1. Study Design

The study was a single-blind, self-controlled experimental model.

### 2.2. Subjects

Thirty patients with clinically mild and moderate malaria were chosen by stratified sampling method. They were chosen predominantly from General Hospitals, Potiskum and Buni-Yadi, both located in Yobe State, in the sudan savannah belt of Nigeria where annual temperature and rainfall average 37°C and 16.7 cm respectively: as a result of this, malaria transmission can be described as relatively stable. Potiskum and Buni-Yadi are 100 kilo-

meters east and 55 kilometers south respectively of Damaturu (Location: 11.75°N, 11.96°E), the state capital and, majority of the population are subsistent farmers and herdsman. Informed consents and ethical clearance were obtained from the patients (or their guardians) and the Principal Medical officer in-charge of the hospitals respectively.

### 2.3. Selection of Subjects

Patients were selected based on certain inclusion and exclusion criteria. Sample size,  $n = 30$  was calculated from the formula:

$$\frac{(u + v)^2 (\delta_1^2 + \delta_2^2)}{(\mu_1 - \mu_2)^2} \quad [19]$$

where:

$u$  = one-sided percentage point of the normal distribution corresponding to 100%—the power (power of the study was fixed at 90%, so  $u = 1.28$ );

$v$  = Percentage point of the normal distribution corresponding to the (two-sided) significance level (this was 1.96 for 5 percentage point);

$(\delta_1, \delta_2)$  = Standard deviations of pre-treatment and post-treatment groups respectively (0.4, 0.4); and

$(\mu_1 - \mu_2)$  = The required difference between the mean of pre-treatment and post-treatment groups (0.25).

This resulted in a sample size of 32.8 for each group and, was approximated to 30. Patients were co-opted into the study according to predetermined inclusion and exclusion criteria.

### 2.4. Treatment and Intervention

A patient who was deemed fit and was co-opted into the study was placed in a recumbent position and reassured. A full explanation of what the study entailed was made to the patient or parents and consent obtained. Five (5) millilitres of blood were drawn from the antecubital vein using universal safety precautions: 3 millilitres were immediately transferred into a plain sterile bottle, centrifuged and the serum stored and transported on ice packs for serum lipid assay within 48 hours. A drop of blood was immediately transferred onto a clean glass slide for thick smear for malaria parasite density estimation. The remaining volume of blood was transferred into a heparinised bottle for haemoglobin concentration estimation. On-the-spot urine sample was also collected from the patient to test for glycosuria and proteinuria and for pregnancy (in women of child-bearing age); all specimen containers were code-labelled.

Patients co-opted into the study were then given 3.2 mg per kilogram body-weight of artemether, administered in the hospital orally or intramuscularly. 1.6 mg per kilogram body-weight was repeated on subsequent days for the remaining four days (in the hospital for those allotted to receive artemether intramuscularly). For those receiving oral drugs, the remaining doses were completed at home. No analgesic or haematinic was administered. ARTEM branch of artemether, purchased from the Sales Representative of Nigeria-German Chemicals at Jos, North-Central Nigeria was used.

Subjects were reassessed one week later by clinical and laboratory methods. Resolution or persistence of initial clinical features of malaria earlier recorded was noted. Also noted were signs and symptoms that could have been attributed to artemether toxicity. A numerical score was accorded patient according to clinical response as follows.

Clinical Response	Score
Complete resolution of symptoms	2
Resolution of symptoms within 48 hr but with resurgence as at follow-up	1
No clinical response at inception of treatment	0

Percentage changes in malaria parasite density were calculated as follows:

$$\frac{\text{Pre-treatment MP density} - \text{Post-treatment MP density} \times 100}{\text{Pre-treatment MP density}}$$

Accordingly, a positive sign to a change denotes decrease in MP density after treatment while a negative sign denotes an increase.

Statistical analysis was done with Microsoft Excel spreadsheet (2003 version) and Statistical Package for Social Sciences (SPSS) version 10.0. Paired t-test was used for significance testing, considering 0.05 to be significant.

## 2.5. Estimation of Serum Lipid Profile

Serum lipid profile: triglyceride, total cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol were assayed by a combination of enzymatic and spectrophotometric methods. Methods and calculations used for estimation of serum triglyceride and cholesterol are as outlined in Triglyceride-GPO Reagent Set by TECO Diagnostics, USA (2003).

Very Low-Density Lipoprotein Cholesterol was estimated using the formula below.

Friedewald Formula [20] was used in calculating this. It is given by:

$$\text{VLDL - cholesterol (mmol/L)} = \frac{\text{triglyceride (mmol/L)}}{2.2}$$

Low-Density Lipoprotein Cholesterol was estimated using Friedewald Formula [20] as shown below.

$$\text{LDL - cholesterol} = \text{Total cholesterol} - (\text{HDL - cholesterol} + \text{VLDL - cholesterol})$$

## 2.6. Estimation of Malaria Parasite Density

A drop of blood from a plastic pipette was transferred from a freshly drawn blood to the centre of a clean glass slide. The tip of the pipette was used in dispersing the blood in a circular fashion, applying care not to cause rouleaux formation. This was left to dry in the air. The freshly prepared Giemsa stain was poured gently on the film and left to stain for 30 minutes in a horizontal position after which excess stain was washed off with clean water and left to dry again before reading. With a drop of cedar oil, 40× magnification lens was used to ascertain areas of the film with the most evenly distributed white blood cells (WBC). With 100× magnification lens, 200 WBC were counted together with the associated malaria parasites. The density of malaria parasite was calculated using an estimated WBC count of 8000/ml as follows.

$$\frac{\text{Malaria Parasite Density}}{\text{(per } \mu\text{L of blood)}} = \frac{8000 \times \text{parasites counted against 200 WBC}}{200}$$

The method and calculation used in this section is as recommended [21].

## 2.7. Screening Test

Measurement of urinary glucose and urinary protein were screening tests used for patients' eligibility before being co-opted into the research program [22] [23].

## 3. Results

The total number of patients used for the study was 30 (n = 30), with 13 males and 17 females and, mean and median ages of patients were 27 and 25 years respectively with a standard deviation of 12 years. The age range was 54 years. **Table 1** captures patients' biodata, clinical responses, and absolute and percentage changes in malaria parasite density and serum lipid estimations.

- Percentage changes in serum lipid profile were calculated as follows:

$$\frac{\text{Pr-treatment value (mmol/L)} - \text{Post-treatment value (mmol/L)}}{\text{Pre-treatment value (mmol/L)}} \times 100$$

Therefore, positive sign to a percentage change denotes decrease of post-treatment value from pre-treatment value and a negative sign denotes an increase from the pre-treatment value.

- Percentage changes in malaria parasite density were calculated as follows.

**Table 1.** Biodata, clinical response, changes in MP density and serum lipid profile.

Serial no.	Age	Sex	Clinical Response	% Reduction in Parasitaemia	Route of Administration I.M/P.O	Serum Lipid Profile Change									
						TG		T.Chol		HDL-C		LDL-C		VLDL-C	
						Abs Change (mmol/L)	% Change	Abs Change (mmol/L)	% Change	Abs Change (mmol/L)	% Change	Abs Change (mmol/L)	% Change	Abs Change (mmol/L)	% Change
1	39	F	2+	86%	IM	+0.1	8%	+0.3	9%	-0.1	11%	+1.8	95%	-0.1	17%
2	3	M	1+	50%	PO	+0.5	45%	+1.6	59%	0	0%	+1.4	93%	+0.2	40%
3	38	M	2+	60%	IM	+0.7	54%	-0	0%	-0.3	25%	0	0%	+0.3	50%
4	25	M	0	9%	IM	+0.3	30%	+0.2	4%	-0.5	38%	+0.6	19%	+0.1	20%
5	44	F	1+	58%	IM	-0.1	8%	+0.3	6%	-0.3	27%	+0.7	23%	-0.1	17%
6	3	M	1+	52%	PO	+0.3	23%	+0.1	3%	-0.3	30%	+0.3	17%	+0.1	17%
7	44	M	1+	60%	IM	+0.5	36%	+0.8	15%	0	0%	+0.5	14%	+0.3	50%
8	38	M	2+	82%	IM	+0.4	40%	-0.5	11%	+0.1	10%	-0.7	22%	+0.1	20%
9	14	F	1+	57%	PO	+0.1	9%	-0.6	16%	+0.1	14%	-0.7	28%	0	0%
10	22	F	2+	86%	IM	+0.5	28%	-0.9	15%	-0.2	14%	-0.9	24%	+0.2	25%
11	15	F	1+	50%	IM	-0.4	24%	-0.2	5%	+0.2	20%	-0.2	8%	-0.2	25%
12	22	F	2+	60%	IM	+0.1	6%	-0.3	5%	+0.1	8%	-0.5	14%	+0.1	13%
13	30	F	0	20%	PO	+0.8	89%	-0.4	8%	+0.1	8%	-0.9	25%	+0.4	100%
14	38	M	1+	50%	IM	-0.3	17%	+0.2	5%	+0.2	17%	+0.1	5%	-0.1	13%
15	40	F	0	33%	IM	+0.3	21%	-0.3	6%	+0.3	30%	-0.8	26%	+0.2	33%
16	25	F	2+	82%	IM	-0.3	20%	+0.8	19%	-0.1	10%	+1.1	44%	-0.2	29%
17	25	F	2+	60%	PO	-1.4	58%	-1.3	26%	-0.2	17%	-0.5	19%	-0.6	55%
18	30	F	2+	84%	PO	+0.1	6%	+2.1	42%	-0.2	10%	+2.2	100%	+0.1	13%
19	57	M	2+	60%	IM	-1.3	57%	-1.4	22%	-0.5	33%	-0.4	10%	-0.5	50%
20	26	F	0	-24%	PO	-0.7	41%	-0.6	12%	-1.3	59%	+1	50%	-0.3	38%
21	19	F	1+	45%	PO	+1	111%	-0.4	8%	+0.1	8%	-1	28%	+0.5	125%
22	20	M	0	-11%	IM	+0.4	25%	+0.9	24%	-0.4	33%	+1.1	61%	+0.2	29%
23	4	M	1+	-50%	IM	+0.5	56%	+1.3	35%	+0.2	20%	+0.9	39%	+0.2	50%
24	22	F	2+	86%	PO	-0.2	15%	+0.2	5%	0	0%	+0.3	12%	-0.1	17%
25	30	F	1+	57%	IM	+0.3	38%	-0.4	8%	0	0%	-0.5	14%	+0.1	25%
26	27	M	2+	60%	PO	-0.2	13%	-0.8	15%	-0.1	10%	-0.6	16%	-0.1	14%
27	35	F	2+	78%	IM	+0.1	10%	+0.5	14%	-0.1	10%	+0.6	27%	0	0%
28	22	M	2+	80%	IM	+0.2	18%	-0.4	9%	-0.1	9%	-0.4	14%	+0.1	20%
29	22	F	2+	82%	PO	+0.2	15%	-0.5	10%	+0.1	9%	-0.7	23%	+0.1	17%
30	30	M	2+	60%	PO	-1.5	52%	-0.5	10%	-0.6	38%	+0.8	42%	-0.7	54%

$$\frac{\text{Pre-treatment MP density} - \text{Post-treatment MP density} \times 100}{\text{Pre-treatment MP density} \times 100}$$

Accordingly, a positive sign to a change denotes decrease in MP density after treatment while a negative sign denotes an increase.

The mean pre-treatment concentration for serum triglyceride was  $1.44 \pm 0.48$  mmol/L and that for post-treatment concentrations was  $1.47 \pm 0.35$  mmol/L. The standard errors were 0.09 mmol/L and 0.06 mmol/L for pre-treatment and post-treatment concentrations respectively. Comparison of pre-treatment and post-treatment mean concentrations showed yielded a t-value of 0.3 with a df of 29 and P-value of 0.77. This was not considered significant. These data are presented in **Table 2** below.

Values for serum total cholesterol were as follows: mean of  $64 \pm 0.86$  mmol/L and  $4.63 \pm 0.81$  mmol/L for pre-treatment and post-treatment concentration respectively. Comparison of these two means showed a t-value of 0.05, with 29 degrees of freedom, and a p-value of 0.96; this was not considered significant. Serum HDL-cholesterol concentrations estimation showed a pre-treatment mean value of  $1.17 \pm 0.32$  mmol/L and a post-treatment mean value of  $1.04 \pm 0.24$  mmol/L. Standard errors of 0.06 mmol/L and 0.04 mmol/L for pre-treatment and post-treatment concentrations respectively were calculated. Comparison of the two mean showed  $t = 2.18$ ,  $df = 29$ ,  $p = 0.04$ . This was considered significant. The mean value for pre-treatment concentrations of serum LDL-cholesterol was  $2.82 \pm 0.76$  mmol/L and that for post-treatment concentrations was  $2.97 \pm 0.68$  mmol/L. The standard errors were 0.14 mmol/L and 0.12 mmol/L for pre-treatment and post-treatment concentrations respectively. Comparison of pre-treatment and post-treatment means showed  $t = 0.96$ ,  $df = 29$  degrees,  $p = 0.34$ . This was not significant. Serum VLDL-Cholesterol concentrations had a pre-treatment and a post-treatment mean value of  $0.66 \pm 0.21$  mmol/L and  $0.67 \pm 0.16$  respectively. Standard errors of 0.04 mmol/L and 0.03 mmol/L for pre-treatment and post-treatment concentrations respectively were calculated. Comparison of the two mean showed  $t = 0.2$ ,  $df = 29$ ,  $p = 0.84$ . This was not significant. These are presented in **Table 2** above.

**Table 3** below shows the mean pre-treatment malaria parasite density for all patients (4352/ $\mu$ L), the mean post-treatment malaria parasite density (1927/ $\mu$ L) and the mean percentage reduction in malaria parasite density (52%). None of the 30 patients had complete parasite clearance. In fact, 3 actually recorded an increase in parasitaemia, 2 of which belonged to the group that received intra-muscular artemether. For those patients who received oral artemether (12; 40%), the mean percentage reduction in parasitaemia was 53% as against 47% for those who received intra-muscular artemether (18; 60%).

The clinical cure rate was fifty percent (50%) while the number of patients that had initial clinical response but with recurrence of symptoms at follow-up was ten (33%). Five patients (17%) showed no response at all after treatment with artemether. The mean haemoglobin concentration prior to treatment with artemether was 11.5 g/dL as compared to 11.4 g/dL after treatment with artemether. The difference was not significant.

**Table 2.** Concentration of serum lipid fractions.

Substance estimated in Serum (mmol/L)	Pre-treatment concentration Mean $\pm$ SD (mmol/L)	Post-treatment concentration Mean $\pm$ SD (mmol/L)	p-Value
Triglyceride	$1.44 \pm 0.48$	$1.47 \pm 0.35$	0.77
Total cholesterol	$4.64 \pm 0.86$	$4.63 \pm 0.81$	0.96
HDL-cholesterol	$1.17 \pm 0.32$	$1.04 \pm 0.24$	0.04
LDL-cholesterol	$2.82 \pm 0.76$	$2.97 \pm 0.68$	0.34
VLDL-cholesterol	$0.66 \pm 0.21$	$0.67 \pm 0.16$	0.84

A p-value of  $\leq 0.05$  was considered significant.

**Table 3.** Malaria parasite density (per  $\mu$ L).

	Pre-treatment	Post-treatment	Mean % reduction in parasitaemia
MP density	4352	1927	52%

## 4. Discussion

Malaria is an acute febrile illness caused by hemoprotozoal organisms of the genus *Plasmodium*. It affects predominantly the tropical and semi-tropical regions of the world and is transmitted through the bite of female anopheline mosquito in which the sexual half of its dual life-cycle occurs and has further contributed to the economic predicament of this region [24]. The severity of the 'malaria burden' became all the more pronounced as the parasite developed resistance to almost all available antimalarials—chloroquine, sulfadoxine-pyrimethamine and mefloquine from the 1960s to 80s [25]–[29]. This created room for more research which led to the isolation and purification of artemisinin with clinical efficacy [30]–[32]. But this experimental breakthrough was characterised by a particular limitation—the poor solubility of artemisinin in water and oil which led to the birth of other artemisinin derivatives [33]–[37]. Artemether is one of the oil soluble artemisinin derivatives that is clinically used for the treatment of malaria. Its clinical efficacy has been proven in various clinical studies [38] [39]. Despite its reported efficacy clinical reports demonstrated that treatment of mild to moderate cases of malaria with artemether carries with it an alteration in plasma lipid profile. However, out of the five commonly measured plasma lipid parameters, it was only the change in the serum high density lipoprotein-cholesterol (HDL-C) that was significant. Comparison of pre-treatment mean concentration ( $1.17 \pm 0.32$  mmol/L) and post-treatment mean concentration ( $1.04 \pm 0.24$  mmol/L) revealed a decrease of 0.13 mmol/L that was significant at a p-value of 0.04 with 29 degree of freedom. The other serum lipid fractions—triglyceride, total cholesterol, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol also showed changes after treatment. However, the changes recorded in these fractions were not significant: an increase of 0.03/L was recorded for serum triglyceride from a pre-treatment mean concentration of 0.44 mmol/L; this was not significant at a p-value of 0.77 with 29 degree of freedom. Serum low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol mean concentrations also were on the increase after treatment. LDL-C increased by about 0.15 mmol/L and VLDL-C by about 0.01 mmol/L; these were not significant at p-values of 0.34 and 0.84 respectively, and 29 degree of freedom. A reduction of 0.01 mmol/L was recorded in the serum total cholesterol concentration and was also not significant.

Research into plasma lipid profile with respect to malaria parasitaemia and after treatment is a relatively new field and as such, there is paucity of findings for comparison. However, accessible research literature with regards to lipid and malaria attest to the fact that malaria parasitaemia induces in the serum varied and profound changes most especially in triglyceride and cholesterol portions. Chrisna *et al.* [40] reported increases in serum triglyceride, total cholesterol and LDL-cholesterol concentrations in malaria patients though distinction was not made with regards to the severity of malaria. Serum HDL-cholesterol concentration was notably reduced in the same study. Nwobodo *et al.* [41] obtained the same pattern of plasma lipid changes in malaria. In a similar design to study the effect of malaria on common plasma lipid parameters, a previous study demonstrated a reverse of the immediately preceding studies. Triglycerides concentration was significantly lower in malaria patients than in uninfected controls while total cholesterol, LDL-cholesterol and HDL-cholesterol concentrations were significantly higher among malaria patients than in controls and these differences were said to be correlated with the severity of malaria. In a malaria treatment and prophylaxis study (with similar design as this work) where sustained parasite clearance was obtained [42], the mean serum concentrations of triglycerides and LDL-cholesterol were significantly reduced from the baseline pre-treatment values after complete parasite clearance while the serum total cholesterol and HDL-cholesterol concentrations were significantly increased. These changes are completely opposite to the results obtained in this study. Though the authors of this work could not access other works of similar design to arbitrate between these divergent results, the inability to obtain complete parasite clearance and reliance on only uncomplicated malaria may lie at the heart of these differences. Within the context of this study, it could safely be said that, the treatment of mild to moderate (uncomplicated malaria) induces a reduction in serum HDL-cholesterol concentrations.

Artemether is an excellent antimalarial agent and belongs to a group reputed to be the most rapidly acting schizontocidal agents [43] reducing parasite burden by a factor of  $10^4$ /cycle of schizogony [44]. Clinical cure rates of ninety percent (90%) and above have been recorded in previous studies with artemether monotherapy. In this study, we obtained a clinical cure of only 50% of patients and a mean parasite reduction of 52% of pre-treatment values. This contrasts sharply with previous studies [45] [46]. A possible explanation may be the phenomenon of recrudescence which plagues the artemisinin group of antimalarial agents when used as monotherapy or, an incipient form of resistance [47]–[50]. Additionally, the absorption of intramuscular artemether is documented as erratic and incomplete [51] [52]. This may have contributed to poor plasma concentration of ar-

temether and consequently, poor clinical and parasitological outcome of the study. Since most of the patients (60%) received intramuscular injections of artemether it is reasonable to implicate low plasma concentration of artemether and its more active metabolite, dihydroartemisinin in this low therapeutic outcome. Another, reason is the possibility that, for those patients who took oral medication, the initial clinical response could have prompted a false sense of recovery thereby leading to cessation of drug administration. This second reason is made plausible by the fact that ten patients (33%) had initial response but had recurrence of symptom at follow-up.

A very positive note in clinical outcome was the safety of artemether. Follow-up assessment revealed no symptom referable to any organ-system. Even in the group that showed no clinical response ab initio, there were no additional complaints that could be traced to artemether. This is in keeping with the well documented clinical safety profile of artemisinin compounds [53]-[56], toxicity in animals studies notwithstanding [57]-[59]. An additional high-point of this study was the rapidity with which symptoms resolved: among those patients that had clinical response, follow-up assessment revealed resolution of fever, headache and joint pain (the commonest presenting symptoms in this study) before 48 hours from the commencement of treatment. This is in consonance with the well documented rapidity of action of artemether—44.5 and 40.9 hours for fever clearance and parasite clearance time respectively [60].

## 5. Conclusion

In drawing a conclusion, this study has demonstrated that treatment of mild and moderate cases of malaria with artemether causes a significant reduction in serum HDL-cholesterol concentration. Because of the lack of total parasite clearance, any statement on the fate of the other lipid fractions would be scientifically unsound. This should await further studies with an artemisinin-based combinational agent, which is documented to have superior clinical efficacy to artemisinin derivatives alone.

## 6. Limitation

The limitation inherent in this work is with regards to the time frame of clinical and parasitological assessment of patients. Because of lack of financial support the malaria parasite assessment could not be done at a more frequent interval.

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## Abbreviations

TG: Triglyceride;  
T.Chol: Total Cholesterol;  
HDL-C: High Density Lipoprotein Cholesterol;  
LDL-C: Low Density Lipoprotein Cholesterol;  
VLDL-C: Very Low Density Lipoprotein Cholesterol;  
MBCD: Methyl  $\beta$ -Cyclodextrin;  
MP: Malaria Parasite;  
WBC: White Blood Cells;  
I.M: Intramuscular;  
P.O: Per Oral;  
ACT: Artemisinin Combination Therapy.