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Clinical Study

Therapeutic Efficacy of Artemether-Lumefantrine for the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Northern Ethiopia

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Introduction. Multidrug resistance of *Plasmodium falciparum* is spreading throughout Africa. This has posed major challenges to malaria control in sub-Saharan Africa. *Objective*. The aim of the study was to evaluate the efficacy of artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in North Ethiopia. *Methods*. This prospective study was undertaken during August–November 2009 on 71 malaria patients that fulfilled the inclusion criteria set by the WHO. Patients were followed up for 28 days. Thick and thin blood films were prepared by Giemsa stain for microscopy to determine parasite density. A standard six-dose regimen of artemether-lumefantrine was administered over three days and was followed up with clinical and parasitological evaluations over 28 days. *Results*. The cure rate (ACPR) was found to be high (97.2%) in this study. The parasite and fever clearance time was also rapid. Artemether-lumefantrine for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in the study area showed 97.2% cure rate and only 2.8% failure rate. *Conclusion*. The result showed that the drug could continue as first line for the treatment of uncomplicated *Plasmodium falciparum* malaria in the study area. The efficacy of artemether-lumefantrine needs to be carefully monitored periodically in sentinel sites representing different areas of the country.

1. Introduction

Malaria is one of the major public health problems worldwide causing more than one million deaths each year. It is widespread in hot humid regions of Africa, Asia, and South and Central America [1]. According to world health organization (WHO) estimation, about 300–500 million people are infected with malaria every year. More than 90% of all malaria cases are in sub-Saharan Africa. Nearly 85% of malaria is caused by *Plasmodium falciparum* and is responsible for about 90% of the deaths from malaria [2]. Malaria has been consistently reported as one of the three leading causes of morbidity and mortality in Ethiopia. Areas below 2000 meters above sea level are considered to be potentially malarious [3]. Malaria-related morbidity and mortality has been increasing in sub-Saharan Africa, primarily as a result of increased resistance to the common first line drugs—chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) [4, 5]. Accordingly, the WHO recommends that treatment policies for *falciparum* malaria in all countries experiencing resistance to monotherapy should be combination therapies containing artemisinin derivatives. Artemisinin antimalarial drugs decrease parasite density more rapidly than other antimalarial drug when used alone. The short half-life of the artemisinin derivatives minimizes the period of parasite exposure to subtherapeutic blood levels. Artemether reduces parasitaemia, and lumefantrine eliminates residual parasites. As the parasites are never exposed to artemether alone,

this is thought to minimize the development of resistance [6]. However, the wide spread use of artemisinin-based combination therapies (ACTs) could have a major impact on the treatment of malaria [7]. Widespread resistance of malaria parasites to commonly available anti-malarial drugs has necessitated countries to review and deploy new anti-malarial drug policies to ensure effective case management [8]. Thus, this study aimed to evaluate the clinical and parasitological therapeutic efficacy of artemether-lumefantrine (AL) or Coartem against uncomplicated *P. falciparum* malaria in Alamata district, North Ethiopia.

2. Patients and Methods

2.1. Study Design and Population. A prospective study was conducted in Alamata district, Tigrai regional state, North Ethiopia, during August–November 2009. The sample size was determined based on WHO standard protocol assuming the anticipated population proportion of clinical failure of 20%, with 95% confidence interval (PI), 10% precision, and 20% dropout, 73 patients were enrolled. Study subjects were selected using convenient method as outlined in standard protocol procedure [9]. Patients above 6 months of age, slide confirmed infection with *P. falciparum*, initial density of 1000–100,000 asexual parasite/μL, and temperature $\geq$37.5°C were included. Patients with pregnancy, mixed infection, infections other than malaria, history of allergy to drugs tested, presence of severe malnutrition, danger signs, and history of hypersensitivity reactions to the drug were excluded. *P. falciparum* positive cases were treated with 6 doses of AL scaled by age/weight as outlined in the monogram of the producer. AL was given as a tablet of 20 mg of artemether and 120 mg of lumefantrine (Novartis, Geneva, Switzerland). All study participants were followed up for 28 days. Patients who failed to respond to AL were treated with Quinine. Patients were observed for at least 30 min to ensure that they do not vomit the drug. When vomiting occurred, the full-treatment dose was repeated. The first dose was given on observation and the rest five doses taken at home under the supervision of trained community health workers. Those who agreed to participate in the study had informed to come back during the scheduled visit for followup on days 1, 2, 3, 7, 14, 21, 28 for both clinical and parasitological assessment. On enrolment day, medical history of each patient was obtained.

2.2. Data Collection and Laboratory Procedures. The health personnel involved in data collection was oriented on the use of the study procedures designed by the WHO. Screening was done by a health officer in an outpatient setting to identify patients meeting the criteria. Data including age, sex, address, and clinical findings (axillary temperature of patients) during screening were retrieved. Blood was collected for malaria smear examination. Patients who did not meet these basic enrollment criteria were treated in accordance with routine practice [10]. Finger prick blood sample collection, preparation, and staining of blood slides were the followed procedures outlined in malaria microscopy [11], using Giemsa staining at pH 7.2. The blood films were prepared for microscopy by a laboratory technician before treatment on day 0 and on days 1, 2, 3, 7, 14, 21, and 28 that the patient was brought to the health center before the next scheduled visit. Duplicate slides were prepared with both thin and thick film preparations using conventional slides. One of the slides was used for rapid staining with 10% Giemsa stain for 10–15 minutes and read while the patient was in attendance. The second slide was used for subsequent standard staining with 3% Giemsa stain for 30–45 min. This slide was used to determine parasite density. The first blood smear for screening was examined for the presence of parasitaemia by counting the number of asexual parasites and the number of white blood cells (WBCs) in limited microscopic fields. Adequate parasitaemia for enrollment requires at least 1 parasite/6–8 WBCs, which corresponds to approximately 1000 asexual parasites/μL. The second blood smear was examined to determine parasite density and the number of asexual parasites per HPF according to the method described in the WHO protocol. Parasitaemia was measured by counting the number of asexual parasites against a number of leucocytes in the thick blood film, based on a putative mean count of 8000 leucocytes per μL. The number of asexual parasites was counted against 200+ leucocytes using Hand Tally Counter. Thus, parasitaemia was calculated using the formula [9]: Parasitaemia/μL = number of Parasites $\times$ 8000/number of leucocytes. When 500+ parasites were identified before counting 200 leucocytes, counting was stopped and parasitaemia was calculated according to the formula above. A blood slide was declared negative when the examination of 100 HPF did not show the presence of asexual forms of *P. falciparum*. Quality control was of microscopy results of parasite counts that were made by cross-checking 10% of the total slides.

2.2.1. Definitions of Terms. Based on the WHO 2003 modified protocol [12], the following definitions of therapeutic responses are used.

Early treatment failure (ETF). It is the development of danger signs for severe malaria on days 1, 2, or 3 in the presence of parasitemia: parasitemia on day 2 higher than day 0 count irrespective of axillary temperature; parasitemia on day 3 with axillary temperature $\geq$37.5 °C; parasitemia on day 3 $\geq$25% of count on day 0.

Late Clinical Failure (LCF). It is the development of danger signs for severe malaria after day 3 in the presence of parasitemia, without previously meeting any of the criteria of ETF; presence of parasitemia and axillary temperature $\geq$37.5°C or history of fever on any day from day 4 to day 28, without previously meeting any of the criteria of ETF.

Late Parasitological Failure (LPF). It is the presence of parasitemia on any day from day 7 to day 28 and axillary temperature <37.5°C, without previously meeting any of the criteria of early treatment failure or late clinical failure.

Adequate Clinical and Parasitological Response (ACPR). It is the absence of parasitemia on day 28 irrespective of axillary temperature without previously meeting any of the criteria of ETF, LTF, or LPF. The secondary outcomes were fever clearance rate; proportion of patients who have fever cleared at day 1, 2, and 3. Parasite clearance rate: proportion of patients with negative thick blood film smears on days 1, 2, and 3. Gametocyte carriage: proportion of patients with gametocytes during the course of the study.

Fever Clearance Time (FCT). It was defined as the time from drug administration until the body temperature decreased to <37.5°C and remained so for 48 hours.

Parasite Clearance Time (PCT). It was defined as the time from drug administration until the first in series of negative blood smears.

Parasite Resistance. It was defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject.

2.3. Ethical Considerations. The therapeutic efficacy test was conducted under supervision of qualified medical officer. Ethical clearances were obtained from Tigrai Regional Health Bureau and Institutional Review Board (IRB) of the Medical School of Addis Ababa University. Informed written consent was obtained from all eligible participants/parents or guardians of under 18 years of age children.

2.4. Data Analysis. Data were analysed using SPSS for Windows, version 15. Descriptive statistics as percentages, mean, median, standard deviation, and range were applied as appropriate. The efficacy assessment was done by modified intention to treat (ITT) and per protocol (PP) analysis. The ITT population was used for analysis of variables, primary and secondary efficacy end points. The PP employed Kaplan Meir used for analysis of primary outcomes (ETF, LCF, LPF, and ACPR). Bivariate analysis was used to compare means. For all statistical tests the significance level (P) was set at 0.05.

3. Results

3.1. Characteristics of the Study Population. A total of 303 patients with fever were screened for malaria. Of these, 107 (35.3%) were positive for plasmodium species of which 77 (72%) were with *P. falciparum* and 30 (28%) *P. vivax.* Of the 77 patients with *P. falciparum* infection, 73 (94.8%) fulfilled the inclusion criteria set by WHO. Of the 73 cases, two patients were lost to in the followup on days 1 and 7. Thus, 71 patients were successfully followed up in the course of the study. The age group 5–15 years represented most patients, 30 (41.1%) followed by the group >15 years of age 29 (39.7%) (Table 1). The smallest age group was the under 5 years 14 (19.2%). The median age of the study population was 14 years (2–70 years), and the majority 45 (61.6%) of the study cases were males. The mean body weight was 36.2 ± 17.3 kg (range: 9–74 kg). On recruitment, 64/71 (90.1%) of the patients receiving AL had body temperature >37.6°C. The mean temperature and parasite count were 38.2°C and 20,672 rings/μL, respectively.

Table 1: Baseline characteristics of the study population at Tumuga Health Center, Alamata, November 2009.

Variables	Value
Sex	
Female, no. (%)	26 (36.6)
Age (years)	
Mean	15.2
Median	14
Range	2–70
No. (%)	
<5	13 (18.3)
5–15	30 (42.3)
>15	28 (39.4)
Body weight (kg)	
Mean	36.2 ± 17.3
Range	9–74
Temp (°C), mean	38.2
Parasite count	
Mean density (ring/μL)	20,672
Rate (%)	35.3

3.2. Parasitaemia, Fever/Parasite Clearance Time, and Treatment Responses. The association between initial parasite density at recruitment and length of parasite clearance time was significant ($P = 0.030$) (Tables 2 and 3). Concerning the fever clearance time and parasite density at day 0, no significant association was found ($P = 0.067$) (Table 3). Clinical failure (LCF) was 2.8% observed on day 21 and day 28, 1.4% LCF on each days. The cure rate (ACPR) was 97.2% on the study site and the parasite clearance is rapid and complete clearance of parasitaemia within 32 hours was observed in all (100%) patients. The mean parasite clearance time (PCT) was 26.5 ± 2.3 hrs. Proportion of patients with gametocytes at enrolment was 1.4% by day 7. From day 14 onwards, no patient had gametocytes. Fever and parasite cleared rapidly over 32 hours after starting treatment (Table 4). Therefore all, (100%) patients had cleared fever after 32 hours. The rate of parasite clearance was 100% after 32 hours of starting treatment and patients were no longer parasitaemic by day 2. No major adverse events were observed throughout the 28 days followup. The Kaplan Meier survival analysis of the data showed estimates of success of 1.00 from day 0 to 20, 0.986 from day 21 to 27 and 0.972 on day 28. The estimate of failure cumulative incidence was 0.00 from day 0–20, 0.014 from day 21–27, and 0.028 on day 28. The proportion of success and failure of patients at each point in time is not significant as the (95%CI, 0.933–1.010) and (0.067–0.010), respectively. Thus, the estimate of success (cure) rate was 97.2% and estimate of failure was 2.8%

Table 2: Temperature at recruitment versus mean parasite and fever clearance time at Tumuga Health Center, Alamata, November 2009.

Temperature (°C) day 0	Mean PCT	*P* value	Mean FCT	*P* value
≤37.0	25.43		25.57	
37.1–37.5	29.00		29.50	
37.6–38	26.52		26.00	
38.1–39	26.61		26.32	
≥39.1	26.00		25.00	
Total	26.47	0.392	26.08	0.178

PCT: parasite clearance time; FCT: fever clearance time.

Table 3: Parasite densities at day 0 versus mean parasite and fever clearance time at Tumuga Health Center, Alamata, November 2009.

Parasite density day 0	Mean PCT	*P* value	Mean FCT	*P* value
1000–11000	25.53		25.20	
11001–21000	26.93		26.47	
21001–31000	26.90		26.80	
31001–41000	27.38		26.50	
41001–51000	29.00		28.40	
51001–61000	26.00		27.00	
>61000	25.67		25.00	
Total	26.47	0.030	26.08	0.067

Table 4: Parasite counts at recruitment, parasite clearance time and fever clearance time at Tumuga Health Center, Alamata, November, 2009.

	Parasite count per micro liter blood	Parasite clearance time (hrs)	Fever clearance time (hrs)
Mean	20672	26.5	26.0
Median	14800	26.0	25.0
SD	47295	2.3	2.4
Range	1440–73920	9.0	8.0
Minimum	1440	23.0	24.0
Maximum	73920	32.0	32.0

during the 28 days followup. In the intent to treat analysis, the lost to followup were included in the denominator of the study analysis, but were excluded in the per-protocol analysis approach. The study outcomes by follow-up days showed 0% on day 7 and day 14, but 1.4% LCF on day 21 and 2.8% LCF by day 28. The ACPR was 100% on day 7 and day 14 but 98.6% on day 21 and 97.2% on day 28 (Table 5).

4. Discussion

AL treatment failure was 0% after 14 days and 0.09% after 28 days followup in the first line treatment of uncomplicated *P. falciparum* malaria at national level [12]. The present study showed that the standard six-dose of AL first line treatment was effective against uncomplicated *P. falciparum* malaria with rapid clearance of fever and parasitaemia and cure rate of 97.2% in 28 days. According to the Kaplan Meier survival analysis, the data obtained was 0.972 (95%CI, 0.933–1.010) showing the effectiveness of the drug. The failure cumulative incidence was 0.028 (95%CI, 0.067–0.010). The finding 97.2% of adequate clinical and parasitological response (ACPR) is consistent with the therapeutic efficacy study done in the country during deployment of the drug in 2004. The aggregated mean of clinical and parasitological treatment response to AL was 100% and 99.01% (PCR unadjusted) for 14 and 28 days followup, respectively. In addition the study showed consistency with other therapeutic efficacy studies with 100% adequate clinical and parasitological response [13]. Another study on therapeutic efficacy of AL for the treatment of uncomplicated *P. falciparum* malaria in rural endemic area of Ethiopia showed PCR unadjusted ACPR of 95.8% and 96.2%, respectively, and the PCR corrected ACPR in the two sites was 96.8% and 97.4%, respectively [14]. Our study results had shown 97.2% ACPR without PCR correction. This is much higher than the study done in African children where they found 86.5% ACPR without PCR correction [15]. The higher efficacy of AL in this study may be due the relatively shorter period of deployment. Another study conducted in Zambia, which assessed therapeutic efficacy of a pediatric formulation of AL for the treatment of uncomplicated malaria in children less than 10 kg in 2005 was same ACPR after 28 days followup (100% PCR corrected but 96.0% PCR uncorrected)

Table 5: Classification outcomes by follow-up days in percent at Tumuga Health Center, Alamata, November 2009.

Outcome	Day 7 %	Day 14 %	Day 21 %	Day 28 %
ETF	0	0	0	0
LCF	0	0	1.4	2.8
LPF	0	0	0	0
ACPR	100	100	98.6	97.2

ETF; Early treatment failure, LCF; Late clinical failure, LPF; late Parasitological failure; TTF; total treatment failure; ACPR; Adequate clinical and parasitological response.

[16]. A study conducted in India in 2006 also showed a cure rate of 100% (PCR corrected) in the treatment of uncomplicated *P. falciparum* malaria with six-dose AL regimen [17]. Our study showed fast parasite clearance time with mean time of 26.5 hrs and good compliance due to fixed dose combination and short treatment duration. The failure to adherence in this study was 2 (2.7%).The fast parasite and fever clearance is due to the rapidly absorbed and its main active metabolite dihydroartemisinin (DHA) achieve a fast reduction in parasite biomass and prompt symptomatic improvement, while the lumefantrine concentrations that persist in the blood after the three days treatment course eliminate any remaining parasites to prevent recrudescence [18].

The proportion of female patients was found low (38.4%) in the study group compared with male patients (61.6%). The proportion of female patients was found 30% in a study done in two study sites in Zambia with 49% and 54.6% [16]. In a study conducted among children <5 years in Eastern Sudan, the proportion of female patients was 31.8% [19]. The low proportion of female patients in our study may be related to difference in health seeking behavior rather than difference in disease prevalence.

The mean temperature of the patients on day 0 was $38.2^{\circ}\text{C} \pm 0.86$. Similar mean temperature $38.5^{\circ}\text{C} \pm 0.6$ was reported from Sudan [19] and 38.7°C from Zambia [16].

In our study, the mean fever clearance and parasite clearance times were 26 and 26.5 hours, respectively. In a study conducted in 2003 for the efficacy of AL for uncomplicated malaria, fever clearance and parasite clearance time were 47 and 36 hours, respectively [20]. In another study, the median fever clearance time was 24 hours and the median parasite clearance time 48 hours [21]. In our study the median fever clearance and parasite clearance time were 25 and 26 hrs, respectively. The variation of fever and clearance time in different areas may be due to differences in parasite density at day 0. It may also be due to differences in times of the drug deployments in the different regions. Generally, the fever clearance time was fast because the drug has antipyretic property and the drug is fast acting on different stages of the parasite which makes the parasite clearance time shorter [18].

Bivariate analysis showed that the only base line characteristic that affected parasite clearance time was parasite density at day 0. There was an association between the mean parasite clearance time and parasite density ($P = 0.030$). This was because of the higher density of the parasite at day 0 which prolongs the parasite clearance time [19]. Regarding with temperature at recruitment and clearance time association, it was not found to be significant ($P = 0.392$ and 0.178) and this may be due to uses of antipyretic drug like paracetamol. Similarly, there was no association between parasite density at day 0 and fever clearance time ($P = 0.067$) for the same reasons mentioned above.

Limitations. The study was conducted without fat intake. This may have impact in reduced absorption of the drug.

In conclusion, AL was safe and effective drug for the treatment of uncomplicated *falciparum* malaria in the study area 5 years after the deployment of the drug. This highly efficacious drug showed rapid fever and parasite clearance and the efficacy (97.2%) met the WHO criteria for efficacy (>95%) in malaria endemic regions. The efficacy of this ACT needs to be carefully monitored periodically since the treatment failures can occur due to resistance as well as subtherapeutic levels due to inadequate absorption or low adherence to the drug. For better absorption, the drug may be administered after diet with fat.

Disclosure

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