

Efficacy of artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Northeast Ethiopia

Assefa Mulu^{1*}, Berhanu Geresu¹, Yeshiwork Beyene², Muluneh Ademe³

¹Department of Pharmacy, Wollo University, Dessie, Ethiopia, ²Department of Nursing, Wollo University, Dessie, Ethiopia, ³Department of Microbiology, Immunology and Parasitology, Addis Ababa University, Addis Ababa, Ethiopia

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***Correspondence to:**

Mr. Assefa Mulu,

Email: mulubaye@gmail.com

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ABSTRACT

Background: The impact of resistance to antimalarials is insidious and unless efficacy studies are conducted, resistance may go unrecognized. The aim of this study was to assess the efficacy of artemether/lumefantrine, for the treatment of uncomplicated *Plasmodium falciparum* infections in Kemisie Health Center, Northeast Ethiopia.

Methods: Artemether/lumefantrine efficacy study was conducted in Kemisie Health Center, Northeast Ethiopia from September, 2012 to May, 2013. The study participants were febrile people above the age of 6 months with confirmed uncomplicated *P. falciparum* infection. Patients were treated with artemether/lumefantrine. Clinical and parasitological parameters were monitored over a 28 days follow-up period to evaluate drug efficacy. The Kaplan–Meier method was used for statistical analysis of data on drug efficacy.

Results: Among the 66 enrolled participants 72.7% were 15 and above years of age while 15.3% were less than 5 years old. Of these study participants, 53% were male. There was 89.4% fever clearance and 84.8% parasite clearance on day 1, whereas, there was 100% fever clearance and 96.8% parasite clearance on day 3 from the 62 participants who carried on the study. Among 66 participants who had started 28 days of follow-up one patient had an early parasitological failure (parasitemia on day 3) and another patient had a late parasitological failure (parasitemia on day 21).

Conclusions: In general, this study discovered good clinical and parasitological response of *P. falciparum* to artemether/lumefantrine. Further polymeric chain reaction and plasma drug concentration based effectiveness study of artemether/lumefantrine should be conducted throughout the country.

Keywords: Artemether/lumefantrine, *Plasmodium falciparum* malaria, Efficacy, Ethiopia

INTRODUCTION

Malaria is a leading cause of morbidity and mortality in developing areas of the world and remains a major health problem in endemic regions. It is estimated that 300-500 million clinical cases occur every year and that over two million people die every year from the disease.¹

In Ethiopia, the increased resistance of *Plasmodium falciparum* to chloroquine and sulfadoxine-pyrimethamine necessitated a change as a first-line antimalarial drug for the treatment of *P. falciparum*. Consequently, artemether/lumefantrine (Coartem[®]) was adopted in 2004. Currently, the drug is being used as the first-line drug for the treatment of uncomplicated malaria.²

As the trend of malaria changes over time, the efficacy of the recommended treatments shall be monitored. Emphasis should particularly be given to monitoring the emergence of resistance to the anti-malarial drugs in use.^{2,3}

Resistance to antimalarial medicines has been documented in all classes of antimalarials, including the artemisinin derivatives, and it is a major threat to malaria control.⁴

Reports of artemisinin resistance from the Thai–Cambodian border, the epicenter of drug resistance, raise global concern for the long-term efficacy of artemisinin-based combination therapy (ACT).^{5,6}

A 28 days therapeutic efficacy study of artemether/lumefantrine against *P. falciparum* conducted between 2007

and 2008 in Kersa, Southwest Ethiopia proved that cure rate was very high, 96.3%, adequate clinical and parasitological response (ACPR) to be 100% for children under 5 and 97.4% and 87.3% for children aged 5-14, and adults, respectively. There was no early treatment failure in all age groups.⁷

Eight years have passed since artemether/lumefantrine was adopted as first-line therapy in Ethiopia, which coincided with the Federal Ministry of Health's (FMOH's) ambitious plan to provide universal access to prompt malaria diagnosis and treatment – as recently recommended by World Health Organization (WHO).⁸ WHO generally recommends that the efficacy of first- and second-line medicines be tested at least once every 24 months at all sites.⁹ Since data on the efficacy of ACT in Ethiopia is limited, we found that the finding of this study is essential to generate a baseline data so that the FMOH of Ethiopia will take informed decision regarding antimalarial treatment guidelines.

METHODS

Study design

This surveillance study is a one-arm prospective evaluation of clinical and parasitological responses to directly observed treatment for uncomplicated malaria. The WHO protocol “methods for surveillance of antimalarial drug efficacy” was used.⁹

Study settings

The study was conducted in Kemisie Health Center, which serves the town and the neighboring *Kebeles*. The health center is found in Kemisie Town of Oromiya zone, Amhara Region, Northeast Ethiopia. Both *P. falciparum* and *Plasmodium vivax* are endemic to this area. The health center is located at an altitude of 1424 m above sea level which is favorable for malaria transmission. The study was conducted during September, 2012 to May, 2013.

Study participants

As this is a single-arm efficacy study, sample size determination was based on an expected proportion of treatment failures in the study population and the desired levels of confidence (95%) and precision (5%). Taking a failure rate of 3.7% that leads to the maximum sample size by a previous study at Asendabo, Southwest Ethiopia (7), a confidence level of 95% and a precision level of 5%; the sample size was calculated to be 66 patients including additional 20% patients to account for those who are likely to be either lost during follow-up or withdraw as recommended by WHO.⁹

The study participants consisted of patients with uncomplicated *P. falciparum* malaria attending the study health clinic that were above 6 months of age. Other

inclusion criteria were mono-infection with *P. falciparum* detected by microscopy; parasitemia of 1000-1,00,000/ μ l asexual forms; axillary temperature $\geq 37.5^{\circ}\text{C}$ or history of fever during the past 24 hrs; and able to swallow oral medications. Whereas, patients with severe malnutrition, febrile conditions due to diseases other than malaria and other known underlying chronic or severe diseases, regular medication, which may interfere with antimalarial pharmacokinetics, history of hypersensitivity reactions or contraindications to any of the medicines being tested; a positive pregnancy test or breastfeeding, unable to comply with the study protocol were excluded.

Clinical and laboratory procedures

Artemether-lumefantrine was administered as of a tablet containing 20 mg of artemether and 120 mg of lumefantrine. The dosing was based on the number of tablets per dose according to predefined weight bands (5-14 kg: 1 tablet; 15-24 kg: 2 tablets; 25-34 kg: 3 tablets; and >34 kg: 4 tablets), given twice a day for 3 days. Tablets of artemether/lumefantrine (20/120 mg) were obtained from Novartis Pharma, Basel, Switzerland through WHO to Ministry of Health, Ethiopia.

Female patients of child-bearing age, defined as those who menstruate or were aged over 12 years, were asked to take a urine pregnancy test before enrolment in the study, because artemether/lumefantrine is contraindicated during the first trimester. They were asked to take a urine pregnancy test on day 28 or on early withdrawal from the study.

A standard physical examination were performed at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, and 28. Axillary temperature was measured at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, and 28.

Thick and thin blood films for parasite counts were obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films were also examined on days 2, 3, 7, 14, 21, and 28.

The blood smear was used to calculate the parasite density, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter. When more than 500 parasites had been counted before 200 white blood cells had been reached, the count was stopped after the reading of the last field has been completed. Parasite density was calculated as:

$$\text{Parasite density (per } \mu\text{l)} = (\text{number of parasites counted}) \times \frac{8000}{\text{Number of leukocytes counted}}$$

Two qualified medical laboratory technicians read all the slides independently, and parasite densities were calculated by averaging the two counts.

Treatment outcomes

Treatment outcomes were classified on the basis of an assessment of the parasitological and clinical outcome of antimalarial treatment according to the latest WHO guidelines.⁹ Thus, all patients were classified as having an early treatment failure, late clinical failure, late parasitological failure or an ACPR.

Data processing and analysis

Data analysis was conducted using SPSS version 20.0. The Kaplan–Meier method was used for statistical analysis of data on drug efficacy. All the baseline and follow-up data collected on a patient until the day of censoring – the last day the patient was observed and was not classified as a failure – were included in the analysis, even for patients who did not complete the study.

RESULTS

Screening, admission and follow-up of patients

Patients who were febrile or had a history of fever with in past 24 hrs of diagnosis were sent from outpatient department to laboratory and diagnosed for malaria. During the study period, 2542 febrile cases and other clinically suspected to be infected with malaria were tested for the presence of the parasite. Of these febrile cases, 253 (10.2%) had malaria positive slides and 109 (43.1%) of them had *P. falciparum* mono-infections. Of those *P. falciparum* mono-infected patients, 6 could not be enrolled in the study for having a parasite load below 1000 parasites per microliter of blood. Of the rest 103 patients, 37 were excluded for the following reasons: 29 were out of the reachable area, 5 were pregnant, and another 3 took anti-malaria drugs before initiation of the study.

Totally, 66 patients fulfilled all the criteria and enrolled in the study but 6 were excluded due to their failure to attend the scheduled visits (3 at day 2, 1 at day 3, and 2 at day 21). Two patients were excluded at the 3rd and 21st day as they were found to have treatment failure.

Socio-demographic characteristics

Among the 66 enrolled participants, 72.7% were 15 and above years of age while 15.3% were less than 5 years of old. Of these study participants, 53% were male. The socio-demographic characteristics of the study participants are displayed in Table 1.

Clinical characteristics

Among the study participants, body temperature had a range from 37 to 39°C and parasite load varies from 1080 to 29640 count/μl on the day of enrollment. Explanatory results are presented in Table 2.

In age and sex distribution of clinical characteristics, relatively higher geometric mean parasite load and mean axillary temperature was documented in under five age group while relatively lower in the age of 15 and above as indicated by Table 3.

Table 1: Socio-demographic characteristics of the study participants on the day of enrollment, Kemissie Health Center, Northeast Ethiopia, 2013.

Characteristics	Value at day of admission (day 0) (%)
Age groups (years)	
<5	10 (15.26)
5-14	8 (12.1)
15 above	48 (72.7)
Sex	
Female	31 (47.0)
Male	35 (53.0)
Mean height (cm)	1.45
Mean weight (kg)	46.02

Table 2: Clinical characteristics of the study participants on the day of enrollment, Kemissie Health Center, Northeast Ethiopia; 2013.

Characteristics	Value at day of admission (day 0)
Mean body temperature in degree celsius±SD	38.17 (±0.3748)
History of fever (N/%)	59 (89.4)
Geometric mean initial parasite/μl±SD	10454 (±5670)

SD: Standard deviation

Table 3: Baseline clinical characteristics of participants stratified by age and sex, in Kemissie Health Center, Northeast Ethiopia, 2013.

Age in year	Sex	Mean body Temperature (°C)	History of fever Within past 24 hrs/%	Geometric mean Parasite/μL
<5	Male	38.48	100	17505
	Female	38.30	100	13823
5-14	Male	38.14	100	11697
	Female	38.35	100	9943
>14	Male	38.12	92.6	9446
	Female	38.09	76.2	9307
All age group	Male	38.17	94.3	10625
	Female	37.17	83.9	10263
Total		38.17	89.4	10454

Fever and parasite clearance rate

As indicated in Table 4, there was 89.4% fever clearance and 84.8% parasite clearance on day 1. Whereas, on day 2 there was 98.5% fever clearance 93.9% parasite clearance among 63 participants who continued in the study. There was 100% fever clearance 96.8% and parasite clearance on day 3 from the 62 participants who carried on the study.

Treatment outcome

Among 66 participants who had started 28 days of follow-up one patient had an early parasitological failure (parasitemia on day 3) and another patient had a late parasitological failure (parasitemia on day 21) (Table 5). A 25-year-old female participant had recurrent parasitemia on day 3 with parasite load of 5100/ μ l and a 6-year-old male patient had recurrence parasitemia on day 21 with asexual parasite load of 2300/ μ l. Both of them had the clinical symptom of malaria at the day of recurrence.

According to Kaplan–Meier analysis the total cumulative incidence of treatment failure was 3.28% (95% confidence interval: 1.32, 5.24). As the exclusion of the four participants from the study (on day 2 and day 3) was before treatment failure (on day 3) censoring of these participants did not alter the cumulative incidence of treatment failure. However, the exclusion of two participants from the study (on day 21) was after treatment failure (on day 3) where censoring of these participants altered the cumulative incidence of treatment failure. Exclusion from the study was due to loss to follow-up in all six participants.

DISCUSSION

Artemether/lumefantrine clears fever and parasitemia caused by *P. falciparum* within, at most, 72 hrs of the first dose. Previously, it was 100% effective in the treatment of *P. falciparum*.⁴ This study revealed 96.72% effectiveness of the drug at the end of 28 days follow-up.

In this study, at the day of enrollment 89.4% of patients were febrile and 98.5% cleared within 48 hrs and 100% within 72 hrs of the follow-up. Parasite clearance rate was 93.9% on day 2 and 96.8% on the day 3. This is similar with studies which were conducted in Kersa district⁷ and central Ethiopia¹⁰ in which almost all patients were cleared of parasites on the day 3.

In this study, there were one early parasitological failure and one late parasitological failure in a 25-year-old female participant and a 6-year-old male participant. The female patient on the day of enrollment had an axillary temperature of 38.2°C and 2500/ μ l of parasite load. Fever cleared within 48 hrs where parasite load decreased to 7200 count/ μ l on day 2 and persist to day 3 with a parasite load of 5100 count/ μ l.

In the 6-year-old male patient, on the day of enrollment, he had an axillary temperature of 38.9°C and fever were cleared within 24 hrs. Parasite load on enrollment was 24460 count/ μ l and he was cleared of parasitemia on day 3. Despite fast clearance of fever and parasitemia, there was reappearance of parasitemia on day 21 without a clinical symptom of malaria.

According to Kaplan–Meier analysis, in the case of loss to follow-up and withdrawn from study, participants should be excluded from study but for analysis, censored last day of follow-up according to timetable for lost to follow-up and censored last day of follow-up according to timetable before withdrawal or protocol violation for withdrawals.

In this study, six participants were lost to follow-up despite of every effort (three on day 2 and one on day 3 and two on day 21 of follow-up). The two treatment failures occurred on day 3 and on day 21. Therefore, three participants on day 2, two participants on day 3 and three participants on day 21 were excluded from the study. For the treatment failure that occurred on day 3 censoring for withdrawal do not affect the cumulative incidence of treatment failure. However, for the treatment failure that occurred on day 21 censoring for withdrawal affect the cumulative incidence of treatment failure. Therefore, our cumulative incidence of treatment failure was 3.27%.

Table 4: Fever and parasite clearance rate (%) of the study participants stratified by age and sex, Kemisie Health Center Northeast Ethiopia, 2013.

Age group	Sex	Day 1		Day 2		Day 3	
		Fever	Parasite	Fever	Parasite	Fever	Parasite
<5	Male	100	50.0	100	75	100	100
	Female	66.7	66.7	83.3	100	100	100
5-14	Male	100	75.0	100	75	100	66.7
	Female	100	100	100	100	100	100
>14	Male	92.6	88.9	100	96.3	100	100
	Female	90.5	90.5	100	95.2	100	95
All groups	Male	94.3	82.9	100	94.1	100	97.1
	Female	87.1	87.1	96.8	96.8	100	96.6
Total		89.4	84.8	98.5	93.9	100	96.8

Table 5: Treatment outcome of study participants versus days of follow-up, in Kemisie Health Center, Northeast Ethiopia, 2013.

Follow-up days	TF	W	PR	II (%)	CITF (%)	95% CI
Day 0	-	-	66	-	-	-
Day 1	0	0	66	0	0	-
Day 2	0	3	63	0	0	-3.40, 3.40
Day 3	1	1	62	1.61	1.61	-0.35, 3.57
Day 7	0	0	61	0	1.61	-0.35, 3.57
Day 14	0	0	61	0	1.61	-0.35, 3.57
Day 21	1	2	59	1.695	3.28	1.32, 5.24
Day 28	0	0	58	0	3.28	1.32, 5.24

PR: Population at risk, W: Excluded from the study, TF: Treatment failure, II: Interval incidence, CI: Confidence interval, LL: Lower limit, UL: Upper limit, CI describes range of probability under which cumulative incidence of treatment failure may fall

Recurrence parasitemia may be due to various reasons; recrudescence, reinfection or resistance. The day 3 recurrence is most probably resistance strain and less probably reinfection, because plasma therapeutic concentration sustains more than 21 days after three-day standard dosage of artemether/lumefantrine. Even if it is reinfection, it is most probably resistance strain. However, our study lacks test of the therapeutic level of artemether/lumefantrine in the blood to conclude accordingly. Recurrence on day 21 may be due to any of above mentioned reasons which can only be determined genotyping in addition to blood drug concentration. Unfortunately, our study puts up with limitation of the absence of genotyping of *P. falciparum* species.

The findings of this study showed that artemether/lumefantrine maintained as an efficacious regimen in Kemisie Health Center. The high cure rate illustrated in this study is consistent with recent studies in Ethiopia^{7,10} with cure rates of 93.3% and 96.3%, respectively, and studies from somewhere else in Africa.¹¹ The cure rate for this study at day 28 was 96.72%. It is also in parallel with the global study of antimalarial drug efficacy and drug resistance between 2000 and 2010.¹²

CONCLUSIONS

In general, this study discovered good clinical and parasitological response of *P. falciparum* to artemether/lumefantrine. Our study also showed fast clearance of fever and parasitemia within maximum of 72 hrs of the start of medication. With reported response rate, the artemether/lumefantrine can be continued as first line medication for uncomplicated *P. falciparum* malaria in the study area. Further polymeric chain reaction and plasma drug concentration based effectiveness study of artemether/lumefantrine should be conducted throughout the country.

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Conflict of interest: None declared

Ethical approval: The study has got ethical clearance from Wollo University Ethical Review Committee

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