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Therapeutic Efficacy and Safety of Artemether-Lumefantrine (Coartem®) in Uncomplicated P. Falciparum Malaria in Wolaita Zone, Southern Ethiopia.

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Abstract
Malaria is an important cause of death and illness in children and adults, especially in tropical countries. The emerging resistance to ACTs by *p. falciparum* malaria threatens the health of the hundreds of millions of people routinely exposed to the risk of infection with this organism. One-arm prospective evaluation of clinical and parasitological responses of directly observed Artemether-Lumefantrine (Coartem®) treatment of uncomplicated *Plasmodium falciparum* malaria as per WHO protocol 2009 was conducted at Baddessa Health Center in Wolaita Zone, Southern Ethiopia from Feb to March, 2015. A total of 88 study participants were enrolled and followed for 42 days and 86 participants were completed follow up. There was 100%% an adequate clinical and parasitological response among participants who completed 42 days of follow-up. Two participants were excluded from study: one participant at day 7 due to self withdrawal and one participant at day 28 due to loss to follow up. However, relatively high proportion of patients (5.7%) still positive on day 3 in this study would indicate possible threat of artemisinin resistance development in the area and regular surveillance should to be continued as WHO recommendation.
Keywords: plasmodium palfarum, artemether-lumefantrine, therapeutic efficacy, safety, Ethiopia.

Background

Malaria is an important cause of death and illness in children and adults, especially in tropical countries (WHO 2010). The burden of malaria is not limited only in life losses, but it also runs in money costs and resource expenditures. It is estimated that African countries spend more than 12 billion USD every year in direct losses for malaria control and averagely it retards the economic growth of the continent by 1.3% per year (WHO 2005). Up to 40% of African health budgets are spent on malaria aspects each year and averagely malaria suffering family loses a quarter of its income through treating and preventing the disease. Likewise, East African households spend significant sums (US$ 0.39 to 3.84/capita) per year in Sub-Saharan Africa to prevent and treat malaria (Joel G 2004).

In Ethiopia malaria is still wide spread. Approximately 75% of Ethiopia‘s landmass is malaria-endemic; areas of disease are primarily associated with altitude and rainfall (Jima D 2010). In 2009/2010, malaria was the leading cause of outpatient visits and health facility admissions, accounting for 14% of outpatient visits and 9% of admissions (FMOH 2011). In 2010 about 4,068,764 clinical and confirmed malaria cases were reported as recorded in the 2011 World Malaria Report (WHO 2011). The estimated annual number of malaria-related illnesses, however, may range even higher (7 to 8 million per year), considering there is only 40% reporting completeness by Public Health Emergency Management (PHEM). *P. falciparum* and *P. vivax* are the dominant species of the malaria parasite in Ethiopia, in respective order (MIS 2011).

Currently, Coartem® a fixed dose combination (FDC) drug of Artemether and Lumefantrine is used for the treatment of uncomplicated malaria and found to be safe and effective against *P.falciparum* and mixed infections including *P. falciparum*. In addition, it is effective against drug sensitive and resistant *P. falciparum,* and is recommended in areas where *Plasmodium* parasites are resistant to other antimalarial drugs (Payen *et al*. 2005, Katzung *et al*. 2009). Ethiopia adopted Coartem® as the first line of drug for the treatment of uncomplicated *P.falciparum* malaria since 2004, after treatment failure reported to the previous anti malarial drugs (EFMOH 2004).

Expanding access to artemisinin-based combination therapies (ACTs) in malaria-endemic countries has been integral to the remarkable recent success in reducing the global malaria burden. However, emerging resistance to ACTs by *p. falciparum* malaria threatens the health of the hundreds of millions of people routinely exposed to the risk of infection with this organism. More recently, there are reports in which *p. falciparum* is endemic. This is among major public health problem, which hinders the control of malaria (WHO 2010).

In Ethiopia Artemether-Lumefantrine (Coartem®) efficacy was conducted at the national level in 2004 during the replacement of previous *P.falciparum* anti-malaria drugs and recorded as 100% including Bahir Dar town (Kefyalew T *et al.* 2009). But, recent reports show the emergence of Coartem® resistance *P.falciparum* parasite (Eshetu *et al* 2012, Kinfu *et al* 2012). However, few studies were conducted relating to Artemether-

Lumefantrine (Coartem®) efficacy and safety since national efficacy survey. Despite of wolaita being among malarious area there is no a single therapeutic efficacy study. So this study basically designed to assesses the current clinical and parasitological efficacy of six-dose regimen of Coartem® to fill this critical gap in the study area.

Methods and materials

Study setting and period

One-arm prospective evaluation of clinical and parasitological responses of directly observed Artemether-Lumefantrine (Coartem®) treatment of uncomplicated *Plasmodium falciparum* malaria as per WHO protocol 2009 was conducted at Baddessa Health Center in Wolaita Zone, Southern Ethiopia from Feb to March, 2015. Wolaita is a Zone found in 329km south of Addis Ababa in Southern Nations, Nationalities and Peoples Region (SNNPR). Wolaita Zone is bordered on the south by Gamo Gofa, on the west by the Omo River which separates it from Dawro, on the northwest by Kembata Tembaro, on the north by Hadiya, on the northeast by the Oromia Region, on the east by the Bilate River which separates it from Sidama, and on the south east by the Lake Abaya which separates it from Oromia Region. The administrative center of Wolayita is Sodo. Based on 2007 Population and housing census 2007 conducted by Central Statistical Authority of Ethiopia the zone has total population of above 1.5 million (Census 2007).

Population

Patients with the diagnosis of confirmed *p.falciparum* malaria at the study health facility in Wolaita Zone during the study period who has *P. falcifarum* mono-infection, asexual parasite count > 1000/µl; axillary temperature ≥ 37.5 °C or presence of history of fever during the 48 h before recruitment; ability to swallow oral medication; ability and willingness to comply with the protocol for the duration of the study and to comply with the study visit schedule; absence of a clinical condition due to *P. falcifarum* malaria requiring hospitalization; absence of severe malnutrition according to WHO child growth standards (WHO, 2006); absence of a febrile condition due to diseases other than malaria; absence of regular medication, which might interfere with antimalarial pharmacokinetics; and perceived negative pregnancy or not breastfeeding were included in the study.

Sample size determination

The sample size was calculated using formula for single proportion in the population assuming a maximum of 5% treatment failure in the population, at a confidence level of 95% and a precision of 5%. With a 20% increase to allow loss to follow-up and withdrawals during the 42 day follow-up period, a total of 88 study participants were enrolled.

Patient recruitment and follow-up evaluation

Treatment

People with uncomplicated *p.falciparum* malaria who met the study inclusion criteria was enrolled, treated with six doses ***Coartem®*** (Artemether 20mg + Lumefantrine 120mg in a fixed dose combination tablet) as per WHO 2010 malaria treatment guideline based on age and body weight. Each dose of drug was administered under direct supervision at site and the study patients were observed for 30 minutes after medicine administration for vomiting. Any patient who vomits during this observation period was re-treated with the same dose of medicine and observed for an additional 30 minutes.

Follow-up

The follow-up will consist of a fixed schedule of check-up visits on days 0, 2, 3, 7, 14; 28 and 42 and corresponding clinical and parasitological examinations. Physical examination was being performed at the baseline (day 0 before dosing) and on days 2, 3, 7, 14, 28 and 42. A demographic information and contact details, complete medical history including malaria signs and symptoms and medication history were being screened at baseline in outpatient department and medical and medication history had been continuously assessed on each patient visit.

Parasitological Investigation

Finger-prick blood samples were collected from consenting patients for microscopic glass slides for thick and thin blood film preparation. Thick and thin blood films were prepared and stained with 10% Giemsa stain for parasite counts and was examined for screening on day 0 to confirm adherence to the inclusion criteria. Thick blood films were also examined on days 2, 3, 7, 14, 28, 42 or on any other day if the patient returns spontaneously. Parasite count was based on the number of asexual parasites observed against 200 leukocytes. This number was then multiplied by 40, to find an approximate count per microlitre of blood.

$$\text{Parasite density (per µl)} = \frac{\text{Average number of parasite counted x (600-800) WBCs}}{\text{Average number of leukocytes counted}}$$

Haematological assessment (haemoglobin/haematocrit)

Finger-pick blood sample was used to measure heamoglobin level using hematocrit technique on the scheduled days 0, 14 and 28 as per WHO 2009 protocol.

Efficacy and Safety Evaluation

Treatment outcomes were classified on the basis of an assessment of the parasitological and clinical outcome of antimalarial treatment according to the WHO 2009 protocol as early treatment failure, late clinical failure, late parasitological failure or an adequate clinical and parasitological response.

The incidences of any adverse events were documented. All patients were asked routinely about previous symptoms and about symptoms that had emerged since the previous follow-up visit and recorded on the case report form.

Quality Assurance

The investigators had strictly followed that the study protocol was being adhered to and that all data were collected and recorded correctly on the case report form. Parasite count was done by two laboratory technician so that any discordance on parasitic load calculation was done by averaging the two closest counts. Ten percent of randomly sampled slides were cross checked by a skilled parasitologist from Wolaita Sodo University Medical School.

Data Analysis

Data collected from *in vivo* therapeutic efficacy test was double entered and analyzed using SPSS software (version 20.0).

Ethical Considerations

Approval by the institutional ethical review committee was obtained before the study. Patients were included in the study only when they or guardians in the case of children gave informed consent. All information on patients remained confidential and shared only by the study team.

Results

Patients who were febrile and/or had history of fever with in past 24 hours of diagnosis were sent from outpatient department (OPD) to laboratory and diagnosed for malaria. Within study period total of 215 malaria cases were identified. Among which 27 were *p.vivax*, 32 were mixed infection, and remaining 156 cases were *p.falciparum*. Among positive cases, total of 127 malarial cases were excluded from study due to 27 *p.vivax*, 32 were mixed infection and 68 *p.falciparum* mono infections were excluded because of administration of other medication, severe malaria, pregnancy and low parasite load. Finally 88 *p. falciparum* malarial cases fulfilled inclusion criteria and were enrolled. Among 88 enrolled 1 was with drown from study at day 7 and 1 was lost to follow up at day 28 and 86 were completed 42 days of follow up. Among 88 participants 88.6% were adults and 60.2% were male (table 1).

At day of enrollment the average axillary temperature was 39.5^{o}C and mean hemoglobin level was 10.79mg/dl (table 2). When baseline clinical parameters of study participants distributed to age and sex relatively higher parasite density was recorded by adults than pediatrics and higher parasite density in male than female (table3). However, we did not find statistically significant difference between age groups in t-test for equality of means ($p = 0.81$) and between sex in t-test for equality of means ($p = 0.36$). We found higher day 0 parasite load in patients with anemia (4484.65/ µl) than non-anemic (3211.76/ µl) group which was statistically significant by t-test for equality of means ($p = 0.025$). There was no significant difference in hemoglobin concentration among age groups by t-test for equality of means ($p = 0.508$).

Generally fever and parasite clearance rate look like collinear as shown on figure1. There was 59.1% fever clearance and 72.2% parasite clearance on day 2. On day 3 there was 93.2 % fever clearance and 94.3% parasite clearance. However, we did not detected any significant correlation between fever clearance time and parasite clearance time (Pearson correlation, $r = 0.061$, $P = 0.57$).

There was no treatment failure among participants who completed 42 days of follow-up. Two participants were excluded from study: one participant at day 7 due to self withdrawal and one participant at day 28 due to loss to follow up (Table 4).

At day of enrollment 80.69% participants were anemic and it was decreased to 65.9% at the 28th day of follow up (Table 5). There is linear increment of hemoglobin level in both age groups. Safety profile of Artemether-Lumefantrine recorded during follow up period was presented on table 6 below.

Discussion

In this study, we carried out therapeutic efficacy study of artemether-lumefantrine (Coartem®) on uncomplicated *P. falciparum* for the first time in this study area since adopted as a first fine drug in Ethiopia in 2004. In general, this study revealed that the efficacy of the drug was 100% without any severe adverse effects. The high cure rates noted in this study are consistent with the baseline assessment conducted in 2003 prior to the implementation of artemether-lumefantrine as first line drug in Ethiopia (Jima D 2005), more recent studies in Ethiopia (Kefyalew T *et al*. 2009, Hwang *et al*. 2011) and studies in other African countries (Ogouyèmi‐Hounto *et al.* 2016, Abuaku *et al*. 2016). However, in other studies in Ethiopia there were failure reports (Kinfu *et al*. 2012, Eshetu *et al*. 2012). This is true in other African studies that some area had failure reports and other area had 100% adequate clinical and parasitological response (Ogouyèmi‐Hounto *et al*. 2016).

Day three fever and parasite clearance rate in this study were 93.2 % and 94.3 respectively. This finding is relatively consistency with some studies conducted in Ethiopia and other parts of the Africa (Ebstie *et al*. 2015, Getnet *et al*. 2015). However, the rate of parasite clearance time is somewhat longer than older reports in Ethiopia (Kefyalew T *et al* 2009, Kinfu *et al*. 2012). The emerging resistance to artemisinins can be characterized by slow parasite clearance in vivo and increased day 3 positive cases (Dondorp AM *et al*. 2009, Noedl H *et al.* 2008, Stepniewska K *et al*. 2010). In this regard the observed higher parasite clearance time may necessitate regular monitoring therapeutic efficacy according to WHO recommendation (WHO 2009).

Parasite clearance time is not associated with both age and sex of participant (OR= 1.140, CI (0.434, 2.994), p-value=0.79) and (OR= 1.160 CI (.297, 25.930), p-value=0.84) respectively. Binary logistic analysis showed that the only base line characteristic that affected parasite clearance time was parasite density at day 0. The parasite clearance time was significantly associated with baseline parasite load (p= 0.013). This was because of the higher density of the parasite at day 0 which prolongs the parasite clearance time. Geometric mean parasite at day 0 for all participant was 4238/ µl where as geometric mean parasite density among participants for those parasitemia cleared after day 2 was 5189 which was significantly higher (p=0.009). This result is similar with studies in Ethiopia (Kinfu *et al*. 2012) Sudan (Salah 2006). Even though, parasite clearance is look like collinear with fever clearance statistically there was insignificant correlation (Pearson correlation, $r = 0.061$, $P = 0.57$). This is consistent with a study was conducted in Northern Ethiopia (Ebstie *et al*. 2015).

Baseline parasite density was significantly higher in anemic individuals than non-anemic individuals (p = 0.025). Anemic cases decreased from 80.7 % at baseline to 65.9% at day 28. Even though at day 7 parasite clearance was 100%, the anemic cases decreased by only 14.8% at day 28. This may be due to anemia may have risk factors like nutrition or intestinal helminthes which is common in the area (Bereket and Zewdneh 2015, Assefa 2010).

The observed adverse effects of AL in the study were similar between adults and children and commonly reported by also other studies and are mild to moderate (Ebstie et al. 2015, Kefyalew T et al 2009). The most common adverse events were headache, abdominal pain, and loss of appetite.

Conclusion

Artemether-lumefantrine remains a effective and well tolerated drug for the treatment of uncomplicated *falciparum* malaria in the study area. However, relatively high proportion of patients still positive on day 3 in this study would indicate possible threat of artemisinin resistance development in the area and regular surveillance should to be continued as WHO recommendation.

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Tables and Figures

Table 1. Age and sex of the study participants on the day of enrollement, in Wolaita Zone, Feb to March, 2015.

Demographic Characteristics		Value at day of admission (Day 0)
Age groups (years)	5–14	10(11.4%)
	>14	78(88.6%)
Sex	Male	53(60.2%)
	Female	35(39.8%)

Table 2. Baseline clinical parameters of study participants in Wolaita Zone, Feb to March, 2015.

Clinical parameters	Mean ± SD	Range (Min. Max)	
Axillary temperature in degree celicious	39.549 ±1.3265	37.0	42.0
Asexual parasite count	4238.75 ± 2109.498	1297	11000
Hemoglobin level	10.79 ± 1.6157	7.0	14.0

Table 3. Base line clinical characteristics of participants stratified by age and sex in Wolaita Zone, Feb to March, 2015.

Demographic		Mean body Temp.(°C)	Geometric mean parasite/µl	Mean Hemoglobin level
Age group	5–14	39.27	4088.3	10.47
	>14	39.58	4258.04	10.83
Sex	Male	39.43	4406.42	10.56
	Female	39.73	3984.86	11.14

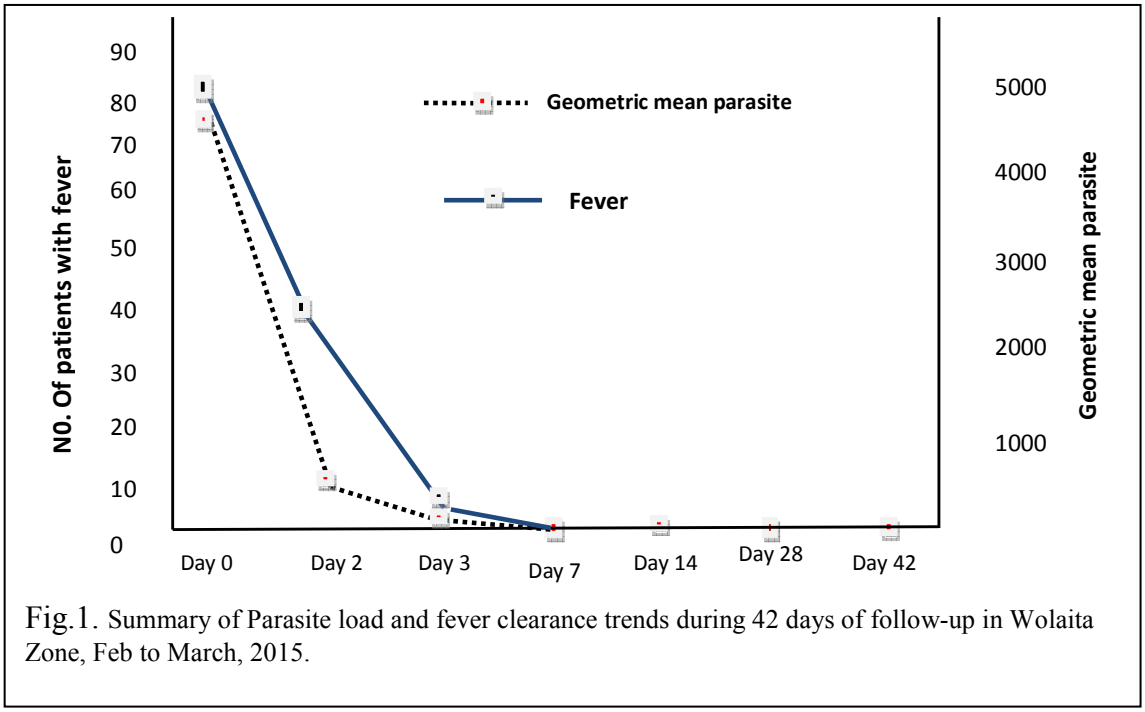

Fig.1. Summary of Parasite load and fever clearance trends during 42 days of follow-up in Wolaita Zone, Feb to March, 2015.

Table 4. Treatment outcome of study participants versus days of follow up, in Wolaita Zone, Feb to March, 2015.

Follow-up days	PR	W	ACPR %	Treatment Failures			TTF
				ETF	LCF	LPF	
0	88	0	-	-	-	-	-
2	88	0	100	0	0	0	0
3	88	0	100	0	0	0	0
7	87	1	100	0	0	0	0
14	87	0	100	0	0	0	0
28	86	1	100	0	0	0	0
42	86	0	100	0	0	0	0

PR=Population at risk, W=Excluded from the study (1 withdrawal and 1 loss to follow up), ACPR = Adequate clinical and parasitological response, ETF = Early treatment failure, LCF = late clinical failure, LPF = late parasitological failure, TTF= Total Treatment failure.

Table 5. Summary of average hemoglobin level stratified by age in Wolaita Zone, Feb to March, 2015.

Age group by years	Mean Hemoglobin level by g/dl		
	Day 0	Day 14	Day 28
5–14	10.47	11.65	12.18
>14	10.83	11.96	12.45
Total mean	10.8	11.9	12.4

Table 6. Adverse effects of drug reported during study period stratified by age group in Wolaita Zone, Feb to March, 2015.

Adverse effect	**Age group in years**		**Total (89)**
	5–14 (10)	>14 (78%)	
Headache	2 (20%)	15(19.2%)	17(19.3%)
Abdominal pain	2 (20%)	12(15.4%)	16(18.18%)
Loss of appetite	3 (30)	10(12.8%)	13(14.77%)
Weakness	2 (20%)	5(6.4%)	7(7.9%)
Dizziness	0	6(7.7%)	6(6.8%)
Sore throat	1(10%)	2 (2.5%)	3(3.4%)
Joint pain	0	3(3.8%)	3(3.4%)