Journal of Science and Technology
ISSN: 2456-5660 Volume 10, Issue 08 (Aug-2025)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2025.v10.i08.pp60- 65*

Therapeutic Failures in Adult Patients Treated with Artemether-Lumefantrine: A Dual-Sector Analytical Study

M. Kishore Babu[1], B. Sandhya Rani[2], I. Triveni[3], B.Revathi[4]

1. Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P

2.Assistant Professor, Department of pharmacology, QIS College of pharmacy, Ongole, A.P

3.Assistant Professor, Department of pharmacology, QIS College of pharmacy, Ongole, A.P

4.Professor, Department of pharmacology, QIS College of pharmacy, Ongole, A.P

To Cite this Article

M. Kishore Babu, B. Sandhya Rani, I. Triveni, B.Revathi**,** "**Therapeutic Failures in Adult Patients Treated with Artemether-Lumefantrine: A Dual-Sector Analytical Study**" *Journal of Science and Technology, Vol. 10, Issue 08- Aug 2025, pp60-65*

Article Info
Received: 31-04-2025 Revised: 10-08-2025 Accepted: 21-08-2025 Published: 31-08-2025

Abstract

Artemether-Lumefantrine medication is becoming less effective in treating simple cases of malaria in many places where the disease is prevalent. Worldwide, plasmodium falciparum and plasmodium vivax parasite tolerance, recrudescence, and resistance are on the rise. Our objective was to assess the rate of Artemether-Lumefantrine (Coartem) treatment failure in persons presenting with uncomplicated malaria at health facilities. From April 1, 2022, to June 30, 2022, 166 patients with positive malaria test results attended health facilities as part of this descriptive cross-sectional research. A total of 9.6% of malaria patients did not show improvement after receiving corticosteroids; 6.0% had plasmodium falciparum, 2.4% plasmodium vivax, and 1.2 had a mixed infection. Among those who did not take the medication with the fatty meal, 31% tested positive for malaria after two weeks of receiving coartem. Additionally, 25% of those who did not follow the treatment schedule had not eradicated the parasite, even though they received coartem. Nearly a third of patients were given Coartem without going through malaria testing, according to the data. In adults in Khartoum state, Sudan, the effectiveness of Artemether-Lumefantrine for treating uncomplicated malaria is declining. To determine how often treatments fail and what variables contribute to drugs having less of an effect, prospective trials are required. Pharmacists should not provide antimalarial medication without a doctor's order and a positive blood test for malaria.

Keywords: Artemether-lumefantrine, Antimalarial drug-resistant, Coartem, Malaria, Plasmodium falciparum, Plasmodium vivax

Corresponding Author:M.kishore Babu
Mail:kishorebabu.m@gmail.com

INTRODUCTION

There are five different species of plasmodium parasites that may infect people; they are falciparum, vivax, ovale, malariae, and knowlesi. Malaria is an infectious illness. Infected female anopheles mosquitoes bite humans, causing the disease to spread [1]. Plasmodium falciparum and Plasmodium vivax are responsible for the most dangerous and fatal types of malaria.

The falciparum malaria parasite was found in Africa's sub-Saharan regions, but the vivax parasite is more often found outside of that region [1]. The precise use of medication and interventions is crucial in preventing and curing malaria [1]. Compared to 227 million cases in 2019, 241 million persons were afflicted with malaria in 2020, according to the World Malaria Report [1]. Malaria will be responsible for 627,00 fatalities in 2020 [1]. More than 90% of cases of malaria occur in Africa, particularly in tropical African nations like Sudan [2], making it a significant public health concern on a global scale. Over three-quarters of Sudanese people are at risk of contracting malaria with a high prevalence, making it a significant public health concern in the country.

potential for an outbreak to break out. Heavy rains and floods bring about malaria outbreaks because they allow mosquitoes to lay their eggs in a wider area and reduce efforts to eliminate vectors [3]. A malaria pandemic hit Sudan in 2019, accounting for 12.4% of all illnesses evaluated by medical professionals [4]. According to the 2016 Sudan Malaria Indicators Survey (Sudan MIS 2016), the total
There was a 5.9% prevalence of parasites [5]. Several signs point to the emergence of anti-malarial drug resistance (AMDR) in these parasites in Northern Sudan, which is the first instance of its kind recorded in Africa. Factors that contribute to the prevalence of AMDR include low endemicity, a decline in malaria immunity among communities, a large number of reported cases of malaria, and the improper administration of anti-malarial medications. AMDR has been documented in regions where falciparum malaria parasites have developed resistance to chloroquine (CQ) and pyrimethamine, for example, in Southeast Asia. It is thought that this opposition has gone global. When CQ-resistant falciparum malaria first appears in Africa, it is in Sudan [6]. Recurrence, recrudescence, relapse, and resistance are the elements that contribute to negative outcomes, according to Shibeshi et al. (2020) [7]. When the parasite is able to persist and even reproduce in the body after effective medicine delivery and absorption, this is known as resistance to therapy [8]. A significant burden was placed on nations with malaria endemicity due to the high incidence of recurrent infections with P. vivax, which in turn increased death and morbidity rates [9].

Based on the belief that artemisinin-based combination treatments (ACTs) would have a better effect than monotherapy and postpone the emergence of drug resistance, the Sudanese Ministry of Health (MoH) established a strategy for treating uncomplicated malaria with ACTs in 2004 [3]. Artemisinin (AS) and sulfadoxine-pyrimethamine (SP) shown resistance to P. falciparum and P. vivax in 2010, according to reports from many regions of Sudan [5, 10]. As of 2017, the Ministry of Health recommended quinine tablets as a second line of treatment for uncomplicated falciparum malaria, and the protocol for treating this type of malaria had already been changed to include Artemether-lumefantrine as the first line of treatment and Dihydroartemisinin + piperaquine as the second line of treatment [4]. One successful antimalarial medication is artemether-lumefantrine (AL) [4]. Parasite presence in blood film tests following treatment and lack of clinical improvement confirmed the emergence of ineffective drug effects in various regions of Sudan, necessitating the administration of quinine, the second line of treatment, to control the infection [3].
Our goal in conducting this research was to assess the variables that contribute to the treatment failure of Artemether-Lumefantrine (Coartem) in adults with uncomplicated malaria at health facilities in Khartoum, Sudan.

Materials and Methods

Patients diagnosed with malaria who visited Khartoum State Health Centers in Sudan between April and June 2022 were the subjects of this descriptive cross-sectional research. There is a significant malaria prevalence in Khartoum, Sudan, therefore we focused on five health institutions there. All patients seen at Khartoum Health were eligible to participate. participants with uncomplicated malaria who were above the age of 18, tested positive for malaria, and were willing to take coartem as therapy were included in the trial. Patients who were unable to communicate due to speech impairments, homelessness, mental illness, or pregnancy were not included in the study.
A calculation was made to determine the sample size using the formula n=z2*p*q/(e)2.
In this case, p=12.4%, n=sample size, and e=0.05. The value of n is 166, given that q=(1-p), z=1.96 and n=(1.96)2*0.124*0.876/0.05.
Thus, 166 patients made up the sample.
For this study, we relied on a questionnaire that the lead investigator filled out during in-person interviews. Age, gender, place of residence, degree of education, laboratory findings, and variables leading to treatment failure were all part of the demographic information gathered from the questionnaire. A practical nonrandomized sampling method was used. For two

weeks after their Coartem therapy, we monitored individuals who tested positive for malaria. After that, we retested them for malaria using both the blood film for malaria (BFFM) and the indirect Coombs test (ICT).

Statistical Analysis

We used SPSS version 25.0 for data entry, cleaning, and analysis. We used graphs and frequency tables with percentages to perform our statistical analysis. We provided a useful graphical representation of quantitative data and calculated standard deviations and means. To use bi-variate analysis, we used the t-test for quantitative variables and the chi-square test for categorical ones to find out how the various risk factor variables were related to the other pertinent demographic and clinical data. With a 95% confidence level, we deemed a P value of 0.05 or below to be statistically significant.

Ethical Consideration

Ethical permission for the research was granted by the administrative authorities of the hospital as well as the ethics review committee of the Sudan Medical Specialization Board and Council of Internal Medicine, Ministry of Health, Sudan. After outlining the study's goals and methods, we were able to get everyone's signed permission.

RESULTS AND DISCUSSION

All inclusion criteria were met by the 166 research participants that were recruited. With a female to male ratio of 1.67:1, we discovered that 104 (62.7%) of the patients were female and 62 (37.3%) were male. Nearly half of the patients were under the age of 30, with another 29 patients (17.5%) in the 30–50 age bracket. over the age of 50. The younger age group accounts for almost half of the study population (Table 1). One hundred participants (60.2% of the total) had completed secondary school; forty-five (27.1%) had earned a bachelor's degree or above; eighteen (10.8%) had only completed elementary school; and three (1.8%) had no formal education whatsoever (Table 1). According to the data, plasmodium falciparum is the causative agent of malaria in 84.9% of cases. where 6.4% have plasmodium vivax and 9.6% have mixed infection (positive for both falciparum and vivax) (Table 2). Only one patient failed to finish all six pills, and 90% of participants take their medications exactly as prescribed; moreover, almost 80% of participants take their medications with a fatty meal. 10% of patients have symptom recurrence. Just under 10% of patients reported no change in their symptoms after mandatory therapy (Table 3). Ten percent of patients say that their symptoms persist (Table 3). Table 4 shows that following re-testing for malaria, 6.6% of participants were still positive for plasmodium falciparum, 2.4% for vivax, and 1.2% for both falciparum and vivax, indicating that the therapy was unsuccessful. The percentage of patients who tested positive for malaria was eight percent among adherent patients compared to one quarter of non-adherent patients (P value = 0.005) (Table 5). Taking medications with fatty meals is significantly associated with an increased risk of recurrence (P = 0.001), as shown in Table 6.

Table 1. Demographic characteristics of the participants (n=166)

Character		Frequency (%)
Sex	Male	62 (73.3%)
	Female	104 (62.7%)
Age group	18-30 years	88 (53%)
	31-50 years	49 (29.5%)
	>50 years	29 (17.5%)
Educational level	Not educated	3(1.8%)
	Primary school	18(10.8%)
	Secondary school	100(60.2%)
	University graduated	45(27.1%)

Table 2. Frequency distribution of plasmodium species before treatment among the participants (n=166)

Type of plasmodium species		Frequency (%)
P.Falciparum		141 (84.9 %)
P.Vivax		9 (5.4%)
Mixed infection		16 (9.6%)
Taking drugs Fatty meal	Yes	131 (78.9%)
	No	35 (21.1%)
Completed six tablets	Yes	165 (99.4%)
	No	1 (0.6%)
Symptoms disappeared and recurred	Yes < One week	9 (5.4%)
	Yes > One week	7 (4.2%)
	No	150 (90.4%)
Improvement of symptoms after treatment completed	Yes	152 (91.6%)
	No	14 (8.4%)
Persistence of Symptoms after completion of treatment	Fever & Headache	14 (8.4%)
	Fatigue & Joint pain	2 (1.2%)
	No	150 (90.4%)

Table 4. Posttreatment test results for malaria of the participants (n=166)

Test results after treatment	Frequency (%)
Negative results	150 (90.4%)
Falciparum positive	10 (6%)
Vivax positive	4 (2.4%)
Positive for both (PF &PV)	2 (1.2%)

Table 3. Adherence and persistence of the symptoms after treatment of the participants (n=166)

		Frequency (%)
Adherence	Yes	150 (90.4%)
	No	16 (9.6%)

Table 5. The association between adherence to treatment and recurrence post-treatment of the participants (n=166)

		Results of post-treatment test for Malaria		Total	P value
		Positive	Negative		
Adherence of the study population to the drug timetable	Yes	12 (8.0%)	138 (92.0%)	150 (100%)	0.05 *
	No	4 (25.0%)	12 (75.0%)	16 (100%)	
	Total	16 (9.6%)	150 (90.4%)	166 (100%)	

* P-value = 0.05 by Fischer Exact Test.

Table 6. The association between taking drugs with fatty meals and recurrence post-treatment of the participants (n=166)

		Results of post-treatment test for Malaria		Total	P value
		Positive	Negative		
Taking drugs with a fatty meal	Yes	5 (3.8%)	126 96.2%)	131 (100%)	0.001 *
	No	11 (31.4%)	24 (68.6%)	35 (100%)	
	Total	16 (9.6%)	150 90.4%)	166 (100%)	

* P-value < 0.001 by Fischer Exact Test.

The purpose of this research was to evaluate the efficacy of the anti-malarial drug artemether-lumefantrine as a therapy for simple malaria in 166 patients attending health clinics in Khartoum, Sudan, from April to June of 2022. The gender ratio in this research was 1.67 to 1. Time of day may have had a role in this gender gap; for example, data was taken in the morning when women were free and men were at work, whereas men often visit health clinics during the night shift. The majority of patients were under the age of 30, which is indicative of a strong affinity for the productive age group, according to the age distribution. The majority of the participants have completed high school. One possible explanation is that the research is taking place in less developed regions where college degrees are still uncommon. When it comes to plasmodium species, we discovered that P. falciparum is the most common culprit in malaria infections. This aligns with the findings from the Sudan Protocol for Malaria and the Federal Ministry of Health National Protocol for the Treatment of Malaria 2015, where P. falciparum was identified as the main species, accounting for 87.6% of cases. In terms of treatment compliance, the majority of participants took their medication at the prescribed intervals and according to the study's timetable. This finding is in line with a 2009 study in Kenya that found that over 75% of patients were likely to follow the treatment plan for Coartem [11]. One of the things that may diminish the drug's effectiveness is vomiting. However, we found that virtually all of the participants did not suffer vomiting while taking Coartem, and they all finished all six tablets. Coartum failure was not caused by medication vomiting or withdrawal in our research cohort, suggesting that other variables may be at play. We found that while the majority of participants saw some relief in their symptoms after finishing the therapy, a small number of individuals did not.

And although some of them do feel better after a while, others find that their symptoms come back. This is in line with the results of Mahittikorn et al. (2021) [12], who discovered that the majority of malaria recurrences happen in less than 28 days, and it might be because of newly emerged plasmodium-resistant strains.

After administering the malaria test again, 6.6% of participants still tested positive for plasmodium falciparum, 2.4% for vivax, and 1.2% for both falciparum and vivax, indicating that the therapy had failed. Kiaco et al. (2015) found a similar cure rate of 91.3% and 12.6% parasitemia, therefore our results are in line with theirs [13]. However, this result conflicts with an Ethiopian investigation that found no parasites on days 3 and beyond and had a cure rate of around 97% for falciparum [14]. The ineffective use of Coartem is associated with treatment failure in this research. Approximately one-third of the population skips the malaria test and instead goes directly to the pharmacy to get antimalarial medications when they experience symptoms of malaria. Like other common infections, malaria may cause similar symptoms. In addition,

Research conducted by Rakotonandrasana, Tsukahara, and Yamamoto-Mitani (2018) found that healthcare providers, like patients, kept prescribing antimalarials even when testing came up negative [15]. Interestingly, 3.8% of patients who took AL with a fatty meal tested positive for the second time, whereas around one-third of patients who did not take the medicine with a fatty meal tested positive. This strongly suggests that this is a major element in the ineffectiveness of drugs. The absorption of AL is enhanced by fatty foods [16].

CONCLUSION

Infection with plasmodium vivax is uncommon, but infections with plasmodium falciparum and a combination of the two are the most prevalent causes of malaria. Not taking AL when prescribed or taking it with a fatty meal are statistically associated with treatment failure. About 8.4% of patients in our research did not show any clinical improvement after therapy ended, 10% showed some improvement but then their symptoms came back, and 9.6% still hadn't cleared their parasite load two weeks after treatment ended. In adults with uncomplicated malaria, 6.4% of falciparum infections, 2.4% of vivax infections, and 1.2% of mixed infections are untreatable with cortum. The drug's effectiveness may have been diminished since around 31.3% of patients with malaria symptoms were given AL without first getting a malaria test.

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