Case Study

Treatment Failure of Artemether-Lumefantrine (Coartem) in Treating Malaria Among Adults. A Cross-Sectional Study

Amel Saif Mohamed[1], Musa Mohamed Kheir[1], Sufian Khalid Noor[2], Mohamed Osman Elamin[3], Wahaj Khan[4*], Hatim A. Natto[5], Ahmed Osman[6], Fowzi Elamin[3], Mashael Alfifi[5], Hatim Matooq Badri[7]

[1]Department of Medicine, Faculty of Medicine, University of Khartoum, Khartoum, Sudan. [2]Department of Medicine, Faculty of Medicine, University of Nile Valley, Khartoum, Sudan. [3]Department of Health Education and Promotion, Faculty of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia. [4]Department of Occupational Health, Faculty of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia. [5]Department of Epidemiology, Faculty of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia. [6]Department of Medicine, Faculty of Medicine, Kassala University, Khartoum, Sudan. [7]Department of Environmental Health, Faculty of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia.

Abstract

Treatment failure of Artemether-Lumefantrine drug in treating uncomplicated malaria is increasing in many endemic malaria countries. Tolerance, recrudescence, and resistance of plasmodium falciparum and plasmodium vivax parasites to the drug are increasing all over the world. We aimed to measure the treatment failure of antimalarial Artemether-Lumefantrine (Coartem) and it is contributing factors in uncomplicated malaria among adults in health centers. This study was a descriptive cross-sectional health-facility-based study conducted from the first of April to the end of June 2022 and included 166 malaria patients with positive test results for malaria visited health centers. 9.6% of malaria patients were not responding to coartem, 6.0% of them were plasmodium falciparum, 2.4% were plasmodium vivax, and 1.2 were mixed infections. Thirty-one percent of those not taking the drug with the fatty meal tested positive for malaria after two weeks of receiving coartem, and 25% of those not adherent to the treatment timetable have not cleared the parasite despite receiving coartem. The results showed that nearly one-third of the patients received Coartem without laboratory tests for malaria. Artemether-Lumefantrine is becoming less effective in the treatment of uncomplicated malaria among adults in Khartoum state, Sudan. Prospective studies are needed to assess the frequency of treatment failure and the contributing factors that assist in decreasing drug efficacy. We also encourage pharmacists not to give antimalarial treatment without a medical prescription and a positive test.

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

Introduction

Malaria is an infectious disease caused by plasmodium parasites in humans with 5 species namely falciparum, vivax, ovale, malariae, and knowlesi. The transmission happens when the infected female anopheles mosquito bites individuals [1]. The most severe and lethal forms of malaria are caused by P. falciparum and P. vivax. P. falciparum occurred in sub-Saharan areas in Africa while P. vivax is mainly outside sub-Saharan Africa [1]. Malaria can be prevented and cured if the required treatment and interventions are applied correctly [1]. The World Malaria Report in 2020 revealed that there were 241 million people affected by malaria that year versus 227 million patients affected in 2019 [1]. The number of deaths caused by malaria is reaching 627000 in 2020 [1]. Globally, malaria poses a major public health challenge, and more than 90% of infections occur in Africa, especially in tropical African countries such as Sudan [2]. In Sudan, malaria appears as a major public health challenge, with more than three-quarters of Sudanese people at risk of acquiring malaria with a high risk of epidemic occurrence. Malaria epidemics are associated with heavy rains and floods that cause wide egg-hatching by mosquitoes and diminished vector control activities [3]. In Sudan, in 2019 malaria epidemic occurred and caused 12.4% of all diseases investigated by health workers [4]. Sudan Malaria Indicators Survey was conducted in 2016 (Sudan MIS 2016), and it revealed that the overall

Address for correspondence: Wahaj Khan, Department of Occupational Health, Faculty of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia. wakhan@uqu.edu.sa

How to cite this article: Mohamed AS, Kheir MM, Noor SK, Elamin MO, Khan W, Natto HA, et al. Treatment Failure of Artemether-Lumefantrine (Coartem) In Treating Malaria Among Adults. A Cross-Sectional Study. Arch Pharm Pract. 2023;14(4):44-8. https://doi.org/10.51847/ZGQOpHeUaP

parasite prevalence was 5.9% [5]. In Northern Sudan, there are several indicators for the appearance of anti-malarial drug resistance (AMDR) in such parasites which occurred for the first time and was reported in Africa. AMDR occurrence is facilitated by some factors such as low endemicity, decreasing the number of populations having malaria immunity, wide spread of malaria cases, and incorrect use of anti-malarial drugs. AMDR occurrence is reported in certain areas of the world such as South East Asia which had falciparum malaria parasites resistant to chloroquine (CQ) and pyrimethamine. This resistance is believed to be spread to other areas of the world. Sudan is the first country in Africa that report the appearance of CQ-resistant falciparum malaria [6]. Shibeshi *et al*. (2020) argue that the contributing factors that prevent positive outcomes are recurrence, recrudescence, relapse, and resistance [7]. Resistance to treatment exists when the parasite can survive and/or multiply in the body after good administration and absorption of the drug [8]. Recurrent infections are observed frequently with P. vivax which added a huge burden on the countries with malaria endemicity as well as an increase in the morbidity and mortality rates [9].

In 2004, the Sudanese Ministry of Health (MoH) introduced a protocol for treating uncomplicated malaria with artemisinin-based combination therapies (ACTs) which were believed to have a more positive outcome than using monotherapy as well as delaying the appearance of drug resistance [3]. In 2010, resistance to the ACTs was reported in several areas of Sudan as artemisinin (AS) and sulfadoxine-pyrimethamine (SP) showed resistance to P. falciparum and P. vivax [5, 10]. In 2017, MoH changed the protocol for treating uncomplicated falciparum malaria by introducing Artemether-lumefantrine as the first line of treatment and Dihydroartemisinin + piperaquine as the second line of treatment, while recommending the administration of Quinine tablets as a second line of treatment [4]. Artemether-Lumefantrine (AL) is one effective antimalarial treatment [4]. However, the emergence of ineffective drug effects is reported in several areas of Sudan, and evidence was confirmed by the presence of the parasite in blood film test after treatment, as well as no clinical improvement, which required administration of the second line of treatment (quinine) to control the infection [3].

In this study, we aimed to measure the treatment failure of Artemether-Lumefantrine (Coartem) in treating Adults with uncomplicated malaria and its contributing factors in Khartoum health centers, in Sudan.

Materials and Methods

This was a descriptive cross-sectional health facility-based study of malaria-positive patients attending Khartoum State Health Centers, Sudan during the period between April and June 2022. We targeted 5 health centers in Khartoum, Sudan where there is a high frequency of malaria. The inclusion criteria comprised any patient who attended Khartoum health centers during the study period, of age more than 18 years, tested positive for malaria, accepted to take coartem as the treatment, and had uncomplicated malaria. We excluded any pregnant or lactating mothers, mentally ill or homeless patients, and patients who could not speak or had a communication problem.

The sample size was calculated by using the equation n=z2*p*q/(e)2.

Where n=sample size e= 0.05, p=prevalence of malaria 12.4%. q=(1-p), z=1.96 n= (1.96)2*0.124*0.876/ (0.05)2=166

Therefore, the sample size was 166 patients.

We used a questionnaire as a data collection tool filled by the principal investigator with direct face-to-face interviews. The questionnaire contained demographic characteristics age, gender, residence, educational level, laboratory results, and questions related to contributing factors to treatment failure. We used a convenient nonrandomized sampling technique. We followed participants who tested positive for malaria for two weeks after receiving the Coartem treatment, then we repeated the malaria test by using both blood film for malaria (BFFM) and indirect Coombs test (ICT)test.

Statistical Analysis

We entered, cleaned, and analyzed data by using SPSS version 25.0. We conducted analytical statistics in terms of frequency tables with percentages and graphs. We measured Means and standard deviations and presented a relevant graphical representation of quantitative data. We applied bi-variable analysis to determine the associations between the different risk factors variables and the other relevant demographical/clinical characteristics by using the Chi-square test for categorical variables and the t-test for quantitative variables. We considered a P value of 0.05 or less to be statistically significant and the confidence level was 95%.

Ethical Consideration

The ethical clearance was obtained from the ethics review committee of the Sudan Medical Specialization Board and Council of Internal Medicine, Ministry of Health, Sudan for approval of the study and ethical clearance was obtained from hospital administrative authorities. We obtained written consent from all participants after explaining the nature and purpose of the study.

Results and Discussion

In this study, 166 study participants were enrolled fulfilling all inclusion criteria. We found that the majority of the patients were female 104 (62.7%) and 62 (37.3%) of them were males with female to male ratio of 1.67:1. More than half of the patients were younger (less than 30 years old) followed by 49 (29.5%) aged 30-50 years old and 29 (17.5)

aged more than 50 years old. About half of the study population is in the younger age group **(Table 1)**. The educational level of most of the participants is secondary school graduates 100 (60.2%); 45 (27.1%) were university graduates, 18(10.8%) just had primary school education, and 3(1.8%) were not educated **(Table 1)**. Regarding the plasmodium species; most Malaria infections are caused by plasmodium falciparum 84.9%. where mixed infection (positive for both falciparum and vivax) is about 9.6% and plasmodium vivax is about 5.4% **(Table 2)**. Adherence to the drug timetable is practiced by 90% of the participants and nearly four-fifths of the participants take the drugs with a fatty meal while recurrence of symptoms is observed in 10% of the patients and only one patient did not complete the six tablets **(Table 3)**. Slightly less than one-tenth of the patients did not report improvement of symptoms after compulsion of the treatment **(Table 3)**. Persistence of symptoms is reported by 10% of the patients **(Table 3)**. In our current study after repetition of the malaria test, the treatment failure by lab evidence was found to be 6.6% were still positive for plasmodium falciparum, 2.4% vivax positive and 1.2% were still positive for both falciparum and vivax **(Table 4)**. One-quarter of those non-adherent to treatment tested positive for malaria compared to eight percent among adherent ones (P value = 0.005) **(Table 5)**. There is high statistical significance between taking drugs with fatty meals and recurrence (P value = 0.001) **(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%)

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%)
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 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.

This study aimed to assess the response to anti-malarial Artemether-Lumefantrine As treatment for uncomplicated malaria in Khartoum health centers, Sudan during the period (April-June 2022) and included 166 study participants who enrolled in this study.

In this study, we found that the female-male ratio was 1.67:1. This gender variation could be explained by the time when data was been collected, in the morning shift, when females were available and males were at work, and in health centers, males usually come to the night shift. Age distribution revealed that most of the patients were younger than 30 years old and this reflects the affection of the productive age group. The educational level of most of the participants is secondary school graduates. This could be explained by the study being conducted in less developed areas where high educational levels are still not common.

Regarding the plasmodium species, we found that most of the malaria infections are caused by P. falciparum and this is not far from the results found in the Sudan Protocol for Malaria, Federal Ministry of Health National Protocol for the Treatment of Malaria 2015 where the main species identified was P. falciparum representing 87.6% of cases. Regarding compliance with the treatment, most of the study participants were adherent to the drug timetable and took the drug in intervals as prescribed and this is agreed with a previous study conducted in Kenya in 2009 about levels of adherence to Coartem, as they concluded that more than three-quarters of patients were probably adherent to the treatment [11]. Vomiting could be one of the factors that may reduce drug efficacy, however during taking the drug we observed that most of the participants (nearly all of them) did not experience vomiting during the treatment period and they completed the 6 tabs of Coartem. This gives a clue that vomiting of the drug or discontinuation is not one of the factors that lead to Coartum failure among our study population. We noticed that most of the participants were improved, but some of them did not show any symptomatic improvement after completing the treatment.

And some of them have partial improvement and their symptoms recurred. This may be attributed to plasmodium-resistant strains that recently appeared and this is in agreement with the findings of Mahittikorn *et al*. (2021) [12], who found that most malaria recurrence occurs in less than 28 days.

In our current study after repetition of the malaria test, the treatment failure by lab evidence was found to be 6.6% were still positive for plasmodium falciparum, 2.4% vivax positive and 1.2% were still positive for both falciparum and vivax. These findings are in agreement with the study conducted by Kiaco *et al*. (2015) where the cure rate was 91.3% and still some patients 12.6 % had parasitemia [13]. On the other hand, this finding disagrees with the Ethiopian study among 91 patients, the cure rate was about 97% for falciparum and no parasite was detected on day 3 and onward [14]. Treatment failure in this study is linked to inappropriate use of Coartem, as about a third of the population does not do a malaria test when they feel symptoms of malaria and they straightforwardly go to the pharmacy and bring antimalarial drugs. Malaria symptoms are similar to other common diseases which can present in the same way. Furthermore, some patients took the drug despite negative results of malaria tests this was supported by the study of Rakotonandrasana, Tsukahara, and Yamamoto-Mitani (2018) as they identified that even healthcare workers continued to prescribe antimalarials despite negative test results [15]. It is valuable to note that about one-third of patients who did not take AL with a fatty meal tested positive for the second time compared to 3.8% who took the drug with a fatty meal. This indicates that this is an important contributing factor to drug failure. Fatty food enhances the absorption of AL [16].

Conclusion

The most common cause of malaria infection is due to plasmodium falciparum followed by mixed P. falciparum + P. vivax infection and plasmodium vivax infection is less common. There is a statistical association between treatment failure of AL and adherence to the drug timetable and taking the drug with a fatty meal. In our study, about 8.4 % of patients did not get clinical improvement after completion of treatment, 10 % got temporal improvement and recurrence of symptoms and 9.6 % did not get parasitological clearance of the plasmodium two weeks after completion of treatment. The treatment failure of coartum among adult uncomplicated malaria is reaching 6.4% for falciparum, 2.4% for vivax, and 1.2% for mixed infection. It has been found that about 31.3% of patients feeling symptoms of malaria were receiving AL without having any malaria test, this may contribute to decreasing drug efficacy.

Recommendations

Leaders in healthcare systems need to regularly assess the efficacy of treatment of uncomplicated malaria in endemic malaria areas such as Sudan. Follow up of patients by laboratory test is highly recommended if they are still symptomatic. Further studies are needed to determine the drug efficacy of Al on different malaria species. Pharmacist should follow the malaria protocol and are encouraged not to give AL to patients unless it has been written in a medical prescription and they have a positive test.

Limitations of the Study

This study was a convenient nonrandomized study, this may make the result less representative for the whole community, a randomized large study is needed to better assess the true treatment failure and the contributing factors. Also, the limited laboratory investigation did not allow us to show exactly the plasmodium gene mutation for AL resistance. The specific brand name of Artemether-Lumefantrine plays of important role in the efficacy of the drug. This could not be assessed in our study because most of the patients did get rid of the tablet box or don't remember the brand name of the drug. Lastly, the duration of the study was short, and the time when data was collected, to clarify the percentage of people that did not respond to AL.

ACKNOWLEDGMENTS: We would like to acknowledge University of Khartoum and Umm Al-Qura University for their support to conduct this study.
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: This project was supported by University of Khartoum and Umm Al-Qura University.
ETHICS STATEMENT: This study was approved by the ethical committee in University of Khartoum.

REFERENCES

1. World Health Organization (WHO). Malaria. 2020. Available from: www.who.int/health-topics/malaria#tab=tab_1.
2. Federal Ministry of Health. Sudan Malaria Indicator Survey 2018. CNCDCD, Federal Ministry of Health, Khartoum, Sudan. 2018. Available from: https://web-archive.lshtm.ac.uk/www.linkmalaria.org/sites/link/files/content/country/profiles/Sudan%20PR%20risk%20map%20Final%20Report-2018.pdf
3. White NJ. Antimalarial drug resistance. J Clin Invest. 2004;113(8):1084-92. doi:10.1172/JCI21682
4. Federal Ministry of Health. National protocol for treatment of malaria 2017. Available from: https://reliefweb.int/report/sudan/sudan-malaria-diagnosis-and-treatment-protocol-2017
5. Federal Ministry of Health, National malaria strategic plan 2014-2016. Available from: https://www.emro.who.int/sdn/programmes/malaria-sudan.html
6. Adeel AA. Drug-resistant malaria in Sudan: A review of evidence and scenarios for the future. Sudan J Paediatr. 2012;12(1):8-20.
7. Shibeshi MA, Kifle ZD, Atnafie SA. Antimalarial drug resistance and novel targets for antimalarial drug discovery. Infect Drug Resist. 2020;13:4047-60. doi:10.2147/IDR.S279433
8. Popovici J, Pierce-Friedrich L, Kim S, Bin S, Run V, Lek D, et al. Recrudescence, reinfection, or relapse? A more rigorous framework to assess chloroquine efficacy for Plasmodium vivax malaria. J Infect Dis. 2019;219(2):315-22. doi:10.1093/infdis/jiy484
9. John GK, Douglas NM, von Seidlein L, Nosten F, Baird JK, White NJ, et al. Primaquine radical cure of Plasmodium vivax: a critical review of the literature. Malar J. 2012;11:280. doi:10.1186/1475-2875-11-280
10. World Health organization (WHO). Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019). 2020. Available from: https://www.who.int/publications/i/item/9789240012813
11. Kokwaro G, Mwai L, Nzila A. Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. Expert Opin Pharmacother. 2007;8(1):75-94. doi:10.1517/14656566.8.1.75
12. Mahittikorn A, Masangkay FR, Kotepui KU, Milanez GD, Kotepui M. The high risk of malarial recurrence in patients with Plasmodium-mixed infection after treatment with antimalarial drugs: A systematic review and meta-analysis. Parasit Vectors. 2021;14(1):280. doi:10.1186/s13071-021-04792-5
13. Kiaco K, Teixeira J, Machado M, Do Rosário V, Lopes D. Evaluation of artemether-lumefantrine efficacy in the treatment of uncomplicated malaria and its association with pfmdr1, pfatpase6 and K13-propeller polymorphisms in Luanda, Angola. Malar J. 2015;14:1-0. doi:10.1186/s12936-015-1018-3
14. Nega D, Assefa A, Mohamed H, Solomon H, Woyessa A, Assefa Y, et al. Therapeutic efficacy of artemether-lumefantrine (Coartem®) in treating uncomplicated P. falciparum malaria in Metehara, Eastern Ethiopia: regulatory clinical study. Plos one. 2016;11(4):e0154618. doi:10.1371/journal.pone.0154618
15. Rakotonandrasana DH, Tsukahara T, Yamamoto-Mitani N. Antimalarial drug prescribing by healthcare workers when malaria testing is negative: A qualitative study in Madagascar. Trop Med Health. 2018;46:1-9. doi:10.1186/s41182-018-0096-7
16. Djimdé A, Lefèvre G. Understanding the pharmacokinetics of Coartem®. Malar J. 2009;8(1):1-8. doi:10.1186/1475-2875-8-S1-S4