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Clinical Evaluation of the Curative Effects and Hematological Consequences of Ivermectin, Artemether-Lumefantrine, and their Combination in Malaria Treatment

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Abstract

Aim: Malaria remains a global health challenge, necessitating ongoing research into effective treatments. Ivermectin and Artemether-Lumefantrine (AL) have shown promise individually, with their potential synergistic effects warranting investigation. This study aimed to clinically evaluate the curative effects and hematological consequences of Ivermectin, Artemether-Lumefantrine, and their combination in malaria treatment in adult subjects.

Methods: Ethical approval was obtained for this study. Seventy-five volunteers with confirmed malaria parasite infestation were randomly assigned into three groups: AL treatment for 3 days (Group 1), Ivermectin treatment for 1 day (Group 2), and a combination of AL (for 3 days) followed by Ivermectin for 1 day (Group 3). Blood samples were collected on day 0 and day 14 for hematological and parasitological evaluations. The percentage recovery was calculated. Statistical analysis was performed using one-way ANOVA and Tukey's post hoc test.

Results: Demographic characteristics indicated a near-even gender split but a significant age gap between males (41.6 years) and females (28.0 years). Group 3 exhibited the highest percentage recovery (80%), significantly outperforming Group 1 (40%), while Group 2 showed a non-significant recovery (20%). Mean parasitemia was significantly elevated on day 0 in all groups but significantly reduced on day 14 in the order Ivermectin < Artemether-Lumefantrine < Ivermectin + Artemether-Lumefantrine). Haematological parameters were significantly altered on day 0 but restored to relatively normal on day 14 in all groups.

Conclusion: The combination therapy of AL and Ivermectin demonstrated the highest curative efficacy in treating malaria, significantly outperforming monotherapy with either drug. This study provides valuable insights into potential treatment strategies for malaria, highlighting the synergistic effects of combination therapy and its reversal of malaria-induced haematological effects. These findings underscore the importance of further research into optimizing combination therapies for malaria control.

Keywords: Artemether-lumefantrine; Ivermectin; Malaria; Parasitemia; Haematological Parameters

Abbreviations: AL: Artemether-Lumefantrine; ACT: Artemisinin-Based Combination Therapy; WBC: White Blood Cells; RBC: Red Blood Cell, HB: Hemoglobin; PCV: Packed Cell Volume; IM: Ivermectin

Introduction

Malaria continues to be a major public health concern, particularly in sub-Saharan Africa, where it remains a leading cause of morbidity and mortality [1]. The WHO estimates that in 2020, there were approximately 241 million cases of malaria worldwide, resulting in 627,000 deaths, most of which occurred in children under the age of five [1]. Despite ongoing efforts to control or eliminate the disease, the emergence and spread of drug-resistant parasites pose significant challenges to malaria treatment and control [1]. Artemisinin-based combination therapy (ACT), particularly artemether-lumefantrine (AL), has been the

standard first-line treatment for uncomplicated malaria cases since 2001 [1]. AL offers high efficacy, a rapid parasitic clearance rate, and a good safety profile [1]. However, concerns regarding the development of drug resistance and potential haematological consequences have prompted the need for alternative or adjunctive therapies [1]. Ivermectin, a macrocyclic lactone with established anti-parasitic activity against a broad range of parasites, including malaria, has shown promise as a potential adjunctive therapy in the treatment of malaria [2]. In addition to its anti-parasitic effects, ivermectin has also been found to have immunomodulatory and anti-inflammatory properties [3]. These mechanisms of action make it an attractive candidate for investigation in combination with existing anti-malarial treatments [2].

This study aims to evaluate the curative effects and haematological consequences of ivermectin, artemether-lumefantrine, and their combination in the treatment of malaria. Understanding the efficacy and potential adverse effects of these treatments is crucial for optimizing malaria treatment strategies and reducing the burden of the disease. Prior preclinical studies have demonstrated the potential synergistic effects of combining ivermectin with other anti-malarial drugs. In a study conducted by Georgewill et al. [4], a 99% reduction in parasitemia was reported when combining ivermectin with artemether-lumefantrine in a rodent model. These findings suggest that the combination may have a greater curative effect than either drug alone. The haematological consequences of anti-malarial treatment are of particular concern, as they can significantly impact patient outcomes. Both ivermectin and artemether-lumefantrine have been associated with haematological alterations. Ivermectin has been reported to cause mild transient decreases in white blood cells (WBCs) and platelets [5], while artemether-lumefantrine has been associated with a decrease in reticulocyte count and a delay in erythrocyte recovery [6]. However, the specific effects of combining these drugs on haematological parameters in humans remains unclear and require further investigation. To address these research gaps, a randomized controlled trial was designed and implemented in a malaria-endemic region in Nigeria.

Materials and Methods

Experimental Design

The experimental design allows for the evaluation of the curative effects of ivermectin, artemether-lumefantrine, and their combination in the treatment of malaria, and the assessment of their impact on haematological parameters and malaria parasite density in the subjects.

Drugs and Dose Selection

Ivermectin (IM) (manufactured/distributed by Merck and Co Inc., United States of America) and Artemether-Lumefantrine (AL) (manufactured by Olive Healthcare, India) were purchased from Denson Pharmaceutical Store, located in Oploo, Bayelsa State, Nigeria. Ivermectin was given at 0.17 mg per kilogram [4], while Artemether–Lumefantrine was given at 80/480 mg (usual dose for adults) in its combination form [7].

Preparation of drugs

The Ivermectin tablets were orally given according to the weight of the patients at a one-off dose of 0.17 mg/Kg while an 8-hour starting dose of Artemether – Lumefantrine (80/480 mg), and a subsequent 12 hourly AL (80/480 mg) dose for three days.

Experimental subjects

Seventy-five (75) volunteers who were confirmed to have been infested by the malaria parasite by microscopic examination of blood sample were used. The inclusion criteria were adults (18 years and above), non-immunocompromised persons, women who were not pregnant, and mentally stable persons. Pregnant women, children, mental patients, and immune-compromised persons were excluded from this study. These subjects were seen at Metrix Med Clinic, Yenagoa, Bayelsa State, Nigeria at the outpatient clinic. Consent was obtained from them after been counseled on the clinical trial. The subjects' phone numbers and home addresses were taken for a follow–up to ensure their availability on day 14 for blood sample collection to compare the results of samples collected on day 0.

Collection of blood sample

Four (4) milliliters of venous blood were drawn and transferred separately into normal tubes and tubes containing heparin. Heparinized blood was centrifuged at 900g for 10 minutes and plasma was separated from the packed erythrocytes. Packed erythrocytes were washed with normal saline two times to remove leftover plasma and leukocytes.

Determination of Haematological parameters

Haematological parameters were determined by using an automated, CELL-DYN 1800 Hematology Analyzer. Malaria parasite density was determined by counting the asexual parasites against 200 WBCs and then calculated by using the standard formula [8].

Determination of curative activity

The curative activity was determined using the method of Ryley & Peters [9] as reported by Ameja [10]. Seventy-five (75) persons (adult) were randomly assigned into 3 groups (n=25). Twenty-five malaria parasite-infested persons were treated with only artemether-lumefantrine (80/480 mg/kg) for 3 days as group 1. Whereas in group 2, another twenty-five-malaria parasite infested person was treated with only ivermectin (0.17 mg/kg) for a day, and in group 3 another twenty-five-malaria parasite-infested person was treated in combination therapy of artemether-lumefantrine and ivermectin (80/480 mg + 0.17 mg/kg) for 3 days and a day therapy. To ascertain the presence

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or absence of malaria infection, the subjects were diagnosed on the basis of clinical symptoms and a parasite-positive blood film. Percentage recovery was calculated with the formula below;

$$\% \text{ Recovery} = \frac{\text{Number of recovered Patients in a group}}{\text{Number of Patients in a group}} \times 100$$

Method of Data Analysis

The results were computed statistically using Statistical Package for Social Science (IBM SPSS, Version 25.0) software. Values were expressed as mean ± SEM (standard error of the mean). Values were analyzed using one-way ANOVA, followed by Tukey's post hoc test. P values less than 0.05 were considered significant.

Ethical Approval

This study was approved by the Research Ethics Committee of the University of Port Harcourt with the approval reference number UPH/CEREMAD/REC/MM80/017.

Results

Table 1 summarizes key demographic characteristics of a sample of 75 individuals, categorized by gender. It indicates a near-even split between males and females (36 vs. 39) for a balanced representation. However, a significant age gap exists, with males averaging 41.6 years and females 28.0 years, suggesting potential life experience variations. Marital status reveals more married males (26) and single females (18). Employment status shows more employed males (25) and more unemployed females (19), relevant to economic and lifestyle analyses. Most participants are Christians (with 34 males and 35 females), while a small number identified as Muslim (2 males, 4 females). Table 2 shows a significant difference ($p<0.05$) in the mean percentage recovery between the Artemether/Lumefantrine (40%) and Ivermectin + Artemether/Lumefantrine (80%) groups, while the mean percentage recovery in the Ivermectin treated group (20%) was not significant. Table 3 shows the effects on mean percentage parasitemia. The result obtained on day 0 showed significant ($p<0.05$) elevation in mean parasitemia in all the groups compared to the normal parasitemia range for healthy humans. However, day 14 results showed a significant reduction in mean parasitemia ($p<0.05$) in all the treated groups (IM<AL<IM/ACT) compared to results obtained on day 0. Table 4 shows the effects of Ivermectin, Artemether-Lumefantrine, and Ivermectin + AL on hematological parameters of plasmodium-infested patients. Results obtained on day 0 showed a significant ($p<0.05$) decrease in red blood cell (RBC) count, Hemoglobin (Hb) concentration, and Packed cell volume (PCV) in all the groups compared to normal values. It also showed a significant increase in the white blood cell (WBC) count in the groups compared to normal values. However, after treatment (day 14), RBC count, PCV and Hb concentration, and WBC were restored to relatively normal range.

Table 1: Socio-demographic data of Patients.

N = 75		
Parameters	**Male**	**Female**
Sex	36	39
Age	41.6±2.56	28.0±1.60
Marital Status		
Single	10	18
Married	26	21
Employment Status		
Employed	25	20
Unemployed	11	19
Religion		
Christian	34	35
Muslim	2	4

Table 2: Curative activity of Ivermectin, Artemether-Lumefantrine, and Ivermectin + Artemether-Lumefantrine in malaria-infested Patients.

Parameters	NIP (Day 0)	NRP (Day 3)	% Recovery
AL	25	10^a	40^a
IM	25	5	20
IM/AL	25	20^b	80^b

AL: Artemether-Lumefantrine; IM: Ivermectin; IM/AL: Ivermectin + AL; NIP: Number of Infested Persons; NRP: Number of Recovered Persons (n = 25). Means within the same column (in each parameter) carrying different superscripts (a, b) are significantly different ($p<0.05$). The doses of the drugs given in the various groups are AL (80/480mg), IM (0.17mg) and IM/AL (0.17mg + 80/480mg).

Discussion

Malaria could be life-threatening and is caused by Plasmodium parasites transmitted through the bite of infected Anopheles mosquitoes that is prevalent in mostly the tropical and subtropical countries [11]. It continues to pose a significant global health burden, particularly in sub-Saharan Africa. According to the World Health Organization World Malaria Report 2020, there were about 241 million cases of malaria in the world, with estimated deaths of 627,000 deaths worldwide [12]. Although substantial progress has been made in the treatment and control of malaria, the malaria parasites have continued to develop resistance to antimalarial drugs and thus, it is imperative to continue to search for new treatments and the use of combined therapies such as the Artemisinin- based Combination Therapy (ACT) hold promise. The current study evaluated the clinical efficacy of Ivermectin, Artemether-Lumefantrine, and their combination in malaria treatment. The study enrolled patients diagnosed with uncomplicated malaria, who were randomly assigned to receive either Ivermectin alone, artemether-lumefantrine alone, and the combination of both drugs. Artemether-lumefantrine (AL) is a highly effective combination therapy for uncomplicated malaria,

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particularly when caused by Plasmodium falciparum [13]. AL offers rapid symptom relief, high efficacy, and a reduced risk of resistance development [13]. However, correct dosage, adherence to the full treatment course, and careful monitoring are essential for its successful use [13]. Ivermectin is primarily known for its use in treating parasitic infections, such as river blindness and strongyloidiasis [14], and as a preventive measure against diseases like lymphatic filariasis [15]. While it is not a standard treatment for malaria, there has been some interest in exploring its potential role in malaria control due to its broad-spectrum antiparasitic properties [5].

This study evaluated the comparative response of patients to different antimalarial drugs namely Artemether/Lumefantrine, Ivermectin, and a combination of Ivermectin and the ACT. The first notable finding was the significant difference in the percentage recovery among the treatment groups. The group treated with Artemether/Lumefantrine alone had a recovery rate of 40%, which increased to 80% when Ivermectin was added to the treatment regimen. However, Ivermectin as a monotherapy showed only a 20% recovery rate, which was not statistically significant. This suggests that the combination of Artemether/Lumefantrine and Ivermectin is more effective in improving patient recovery compared to the use of either drug alone. This shows the synergistic efficacy of ivermectin in treating humans infested with Plasmodium falciparum and the importance of expanding the clinical use of the drug or repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching [16]. This result is in line with a study conducted by Georgewill [4] that showed that Ivermectin + Artemether/Lumefantrine had a significant curative effect in malaria-infested mice. In the present study, the Ivermectin + ACT treated group displayed the highest percentage inhibition (96.64±2.42 %) which is also consistent with the findings of Georgewill [4]. The enhanced recovery rate observed with the combination therapy can be attributed to several factors. Ivermectin's broad-spectrum antiparasitic properties is likely responsible for this synergy [7]. Moreover, the combination may provide dual mechanisms of action, directly targeting the malaria parasite. This empirical result underscores the significance of on-target drug repurposing procedure, where a known pharmacological mechanism of a drug molecule is applied to a new therapeutic indication and the experimental based approach of drug repositioning which is also known as activity-based repositioning which refers to the screening of original drugs for new pharmacological indications based on experimental assays [17]. It involves protein target-based and cell/organism-based screens in in vitro and/or in vivo disease models without requiring any structural information of target proteins. Several approaches of experimental repositioning are target screening approach, cell assay approach, animal model approach and clinical approach.

Malaria parasitemia and some haematological parameters were also evaluated in this study. Results obtained also showed that on day 0, there was a significant increase ($p<0.05$) in mean parasitemia in the Plasmodium infested groups compared to the normal standard value of parasitemia. However, after treatment, on day 3, there was significant reduction in the mean parasitemia. As shown in Table 3, the Ivermectin treated group showed the least percentage inhibition (63.13±1.34%) while the Artemether/Lumefantrine treated group demonstrated a high percentage inhibition (84.8±2.4%). The Ivermectin + ACT treated group displayed the highest percentage inhibition (96.64±2.42 %). This demonstrates that the combination of Ivermectin and ACTs can be a very effective therapy in malaria treatment, and as such drug repositioning is effective in this model of experiment. This underscores the potential of this combination to expedite the recovery from anaemia, a common complication of malaria infection. Anaemia has been identified as one of the most important complications of malaria infection, especially in children and pregnant women [18]. The pathogenesis of anemia in malaria infection is said to result from the parasite's primary target of the red blood cell resulting in the damage of the red blood cells. During malaria infection, there is also accelerated removal of both parasitized and non-parasitized RBCs [19] and bone marrow dysfunction [20].

Table 3: Effects on Mean Percentage Parasitemia.

	Day 0	Day 3	% Inhibition
AL	57.67±1.63^{a}	8.75±1.47^{a}	84.8±2.4^{a}
IM	54.68±2.82^{a}	21.34±2.21^{b}	60.97±2.01^{b}
IM/AL	58.56±1.82^{a}	2.13±1.08^{c}	96.64±2.42^{c}

AL: Artemether-Lumefantrine; IM: Ivermectin; IM/AL: Ivermectin + Artemether-Lumefantrine. Data are expressed as the mean ± SEM (n = 25). Means within the same column (in each parameter) carrying different superscripts (a, b, c,) are significantly different ($p<0.05$). The doses of the drugs given in the various groups are AL (80/480mg), IM (0.17mg) and IM/AL (0.17 mg + 80/480mg).

Results obtained on day 0 (before treatment) show that red blood cell (RBC) count, hemoglobin (Hb) concentration, and packed cell volume (PCV) were reduced in malaria patients compared with the standard values (Table 4). Contrarily, results also show that the White blood cell (WBC) count was significantly reduced among malaria patients compared to the normal reference values; indicative of anemia. However, on day 14 (after treatment), There was significant restoration of levels of RBC, Hb, and PCV ($p<0.05$) in the groups treated with Ivermectin + AL. The study demonstrated that the combination of Ivermectin and AL relative to Artemether/lumefantrine and Ivermectin alone results in a faster and better recovery from anemia. The possible mechanism of action of Artemether/Lumefantrine involves inhibiting the growth and replication of the malaria parasite, while Ivermectin acts by targeting other parasites such as filarial worms [14]. The combination therapy is thought to provide a dual action against the different types of parasites, resulting in higher efficacy. The mechanism of action of Ivermectin resulting in curative action is through the inhibition of the growth of the malaria parasite.

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Ivermectin works by binding to specific receptors in the parasite's nervous system, causing paralysis and death of the parasite [21]. According to a study on the activity of Ivermectin and its metabolites against asexual blood stage Plasmodium falciparum and its interactions with antimalarial drugs, Ivermectin and its metabolites showed potent activity against asexual blood stages of Plasmodium falciparum [22].

Table 4: Effects of Ivermectin, Artemether-Lumefantrine and Ivermectin + AL on hematological parameters of plasmodium infested Patients.

	RBC (x 10^6/µl)		WBC (x 10^3/µl)		PCV (%)		Hb (g/dl)	
	Day 0	Day 14	Day 0	Day 14	Day 0	Day 14	Day 0	Day 14
AL	4.12±3.13a	6.31±3.11a	7.35±0.17a	4.35±0.17a	20.4±2.30a	28.65±1.62a	11.48±4.91a	15.82±2.11a
IM	4.04±1.62a	5.29±2.21b	7.65±3.53a	5.67±3.01b	20.98±2.8a	25.94±2.86b	11.49±4.02a	14.86±2.45a
IM/AL	4.06±3.23a	6.38±3.23a	7.14±2.14a	4.14±2.11a	20.2±4.13a	31.82±4.14c	11.68±2.33a	15.68±3.23a

AL: Artemether-Lumefantrine; IM: Ivermectin; IM/AL: Ivermectin + Artemether-Lumefantrine; RBC: Red blood cells; WBC: white blood cell; PCV: Packed cell volume; Hb: Hemoglobin. Data are expressed as the mean ± SEM (n = 25). Means within the same column (in each parameter) carrying different superscripts (a, b, c,) are significantly different ($p<0.05$). The doses of the drugs given in the various groups are AL (80/480mg), IM (3mg) and IM/AL (0.17mg + 80/480mg).

The findings of this study are novel in that they demonstrate the efficacy of the combination therapy of Artemether/Lumefantrine and Ivermectin in treating uncomplicated malaria in humans. The results of this study are consistent with other studies that have highlighted the efficacy of Artemether/Lumefantrine and Ivermectin in treating malaria. However, the novelty of this study lies in its demonstration of the efficacy of the combination therapy of the two drugs. The limitations of this study include its small sample size and the short-term evaluation of the treatment's effects. Further research and larger-scale clinical trials are necessary to validate these findings and provide more robust evidence for the use of combination therapy in the treatment of this condition.

Conclusion

This study provides valuable empirical evidence supporting the use of combination therapies, specifically the combination of Ivermectin and Artemether-Lumefantrine, as an effective approach in malaria treatment. The demonstrated synergistic effects on recovery rates, reduction in parasitemia, and restoration of haematological parameters offer promising insights for the future of malaria control. The significance of this study lies in its contribution to knowledge by highlighting the potential of combination therapies and the experimental-based approach of drug repositioning, ultimately advancing our efforts to combat malaria and improve patient outcomes. The novelty of this study lies in its empirical validation of these therapeutic strategies, paving the way for further research and clinical exploration in the field of malaria treatment and control.

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