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Comparative assessment of two Artemisinin based combination Therapies in the treatment of Uncomplicated Malaria among University students in Nigeria

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Abstract

Background: In line with the recommendation of artemisinin-based combination therapy (ACT) by WHO in the effective treatment of uncomplicated malaria, African nations including Nigeria changed their malaria treatment policy to combination therapies. To date, about 15 African nations adopted artesunate /amodiaquine (AA) as their first line agent while Nigeria adopted artemether /lumefantrine (AL).

Objective: The objective of this study is to compare the treatment outcome among patients treated with AA to those treated with AL for acute uncomplicated malaria.

Method: The study was conducted at Nnamdi Azikiwe University campuses using quantitative methods. Two hundered and ninety six patients were randomly allocated to one of two treatment group- AA and AL with 148 patients per group. All the patients were educated about the drugs and adherence. Adherence and treatment outcomes including parasite clearance and the drugs' effects on biochemical parameters among others were assessed by follow up visits on third, seventh, fourteenth and twenty eighth-day post treatment. Data were analysed using Cox Regression model on SPSS 17.0.

Result: Both drugs were well adhered to and tolerated. One case of Steven Johnson-like reaction was observed with AL. Fever resolution and parasite clearance was similar in both groups with adequate clinical and parasitological response (ACPR) by day 28 for AL and AA being 70.3% and 85.1% respectively.

Conclusion: Our findings is in favour of higher efficacy of AA with respect to their ACPR. More controlled studies will be needed to ascertain the adoption of AL as first line drug in malaria treatment in Nigeria.

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Key words:
Artemesinin combination therapy (ACT), artemether /lumefantrine, artesunate /amodiaquine, efficacy, malaria.

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INTRODUCTION

Malaria remains a major cause of death and illness in children and adults in tropical settings. Malaria is a

life-threatening vector-borne disease transmitted through the bite of an infected anopheles mosquito. Malaria poses a tremendous public health challenge both in Nigeria and other African countries. According to the world Health Organisation, there were 219 million cases of malaria leading to 660,000 deaths among African childern in 2010 [1].In Nigeria, malaria accounts for about 60% of outpatient visits and 30 percent of hospitalizations among children under five years of age [2]. According to this report [2], with a population of 170 million people, one-quarter of all cases of malaria in Africa occur in Nigeria and more malaria related deaths occur in Nigeria than other countries.

An integrated strategy is recommended which ensures access to treatment with effective anti-malarials, while also undertaking preventive measures that target vector control [3]. The affordable and widely available antimalarial chloroquine that was in the past the mainstay of malaria control is now ineffective in most countries and there is high incidence of resistance to most monotherapies especially the sulfadoxine-pyrimethamine[4]. The discovery of artemesinin derivatives has provided a new class of highly effective antimalarials. Hence,Artemisinin-based combination therapy (ACT) became the recommended treatment for uncomplicated malaria, as resistance emerged to conventional monotherapies, including sulfadoxine-pyrimethamine (SP), chloroquine and amodiaquine among others. Over the last decade, countries have revised their national malaria treatment policies to adopt ACT as the first-line recommended treatment for uncomplicated malaria. Although these policies are now well established, there are persistent problems with their implementation and treatment outcomes. Evidence from several settings on malaria case management reports problems with the choice of treatment, showing that ACT is often underused and many patients continue to receive less effective anti-malarial, such as SP[3, 5]. There are also concerns about the availability and use of artemisinin monotherapy, as drug resistance is more likely to develop if artemisinin derivatives are taken without a combination drug [6, 7]. Problems with malaria treatment have also been observed with patients receiving inadequate doses and without advice on how the medicines should be taken [3, 8].

With the consideration of ACT as the best current treatment for uncomplicated falciparum malaria [4], Nigeria recommended and adoptedartemether-lumefantrine (AL) as the first line treatment agent though, treatment with artesunate-amodiaquine (AA), artesunate-mefloquine (AM) and dihydroartemisinin-piperaquine (DHAPQ) are also considered acceptable [9]. The policy also states that SP is reserved for intermittent preventive treatment in pregnancy, and cases of severe malaria should be treated using quinine injection, artemether injection, or artesunate (either as an injection or suppository). However, several undocumented clinical and laboratory failures have been observed in the hospitals and there have been lots of oral reports from some health care providers on malarial treatment failure with AL.Hence, studies on the assessment of the effectiveness of the different artemesinin combinations are very necessary to establish their efficacies. Therefore, this study focuses on the assessment of the effectiveness of AL and AA to determine their efficacies and to re-examine if AL should still be adopted as first line drug in the treatment of uncomplicated malaria in Nigeria. The significance of this study is to know if the results will be in accordance with the national treatment guideline or if a change in policy should be advocated.

METHODS

STUDY AREA AND POPULATION

This study was carried out in three different campuses of Nnamdi Azikiwe University, South east of Nigeria. The three campuses include the pre-science study centre at Mbaukwu, Awka campus and Nnewi campus. The university covers in total an area

of 7162km ^{2} and is located in the rain forest region of Nigeria. Total population of the students based on data from Students Affairs Department at the time of the study was 36,668. Mean monthly temperature of the area ranges from 24°C to 34°C, and the average rainfall is about 1250 mm per annum, creating optimal conditions for malaria transmission throughout the year.

About 60% of daily hospital visits to the university medical centre are patients treated for malaria and more than 60% of drugs procured annually at the clinic are antimalarials according to records from pharmacy department. This study was conducted in the months of March and September 2012.

PATIENTS' SELECTION AND ENROLLMENT

A total of two hundred and ninety six patients were selected from the four hundred and fifty students recruited for the study.The patients were recruited from those who were clinically diagnosed of uncomplicated malaria from students that visited the university medical centers and responding to well-defined inclusion and exclusion criteria.

Patients greater than 15 years of age or with body weight greater than or equal to 40kg,those with a laboratory confirmed malaria parasite infection, and those with measured axillary temperatures greater than or equal to 37.5^{o}c or history of fever in the last 48 hours and also those within the second and third trimesters of pregnancy (if pregnant) were all included in the study.A patient is excluded if he presented with the general danger signs according to WHO definition or signs of severe/complicated malaria according to WHO definition. Other exclusion criteria include history of hypersensitivity to any of the drugs under study or any of its components, those with severe malnutrition, those that received full course of the treatment or one of the treatments under study in the past 10 days and those in the first trimester of pregnancy or breastfeeding.

This study was approved by Ethics Committee of Nnamdi Azikiwe University Medical Centre, Awka. The study participants were enrolled after obtaining informed written consent.

RANDOMIZATION AND TREATMENT

Selected patients were randomized by simple random sampling technique into two groups of 148patients per group to receive either AL or AA. At inclusion, the patients' names, age, sex, weight, educational qualification, mobile phone numbers, and addresses were collected.

Group 1 received oralArtesunate plus Amodiaquine (Winthrop by Mapha Laboratories, Morocco), prescribed according to body weight (i.e., bodyweight ≥ 50Kg received 100 mg of artesunate and 270 mg of amodiaquine and bodyweight <50 Kg received 50 mg of artesunate and 150 mg of amodiaquine). These drugs were administered once daily for 3 days after food.

Group 2 received oralArthemether/Lumefantrine (IPCA Laboratories, India), also administered based on body weight. Greater than 35kg received4 tablets twice daily for 3days; the second dose was taken 8 hours after the first dose to achieve adequate plasma concentration and the other doses continued at 12 hr interval for the next two days.

All participants in each group received the first dose of antimalarial under observation and were educated about AL and AA dose regimen and the need to adhere to therapy. They were also advised on the need to take the drugs immediately after meals especially fatty food. Patients were advised to repeat the dose should vomiting occur immediately after swallowing.

Participants in both groups were sent short message services (SMS) using a mobile telephone at appropriate times they were supposed to take the drugs on the second and third days of treatment and same was used to summon them on post-treatment days (3rd, 7th, 14th, and 28th day) to evaluate their clinical and laboratory outcomes. Participants were

also assessed on the third day of treatment for adherence to the treatment regimen. At each visit a symptom assessment questionnaire was used to determine a patient's clinical outcome. Participants found not to be improving were referred to the clinician for review and further treatment.

LABORATORY INVESTIGATIONS

TEST FOR PRESCENCE OF PARASITAEMIA

After validating the rapid diagnostic test kit for plasmodium falciparum, thick films were prepared, stained with 10% Giemsa solution for 30 minutes and dried. The smears were read with x100 oil immersion objective to confirm the prescence of parasitaemia.

HAEMATOLOGICAL AND BIOCHEMICAL ASSAYS

Venous blood samples (6 ml) were obtained from the patients using sterile needles and syringes (10ml), prior to and after treatment and usedforhematological and biochemical assays.

HAEMOGLOBIN MEASUREMENT

One (1 ml) of blood was put in a 1M Na_2EDTA container (1.5mg per ml of blood) to be used to measure haemoglobin content and to prepare thick films for malaria parasite count [10].

5mls of freshly prepared Drabkin's Solution 1:250 dilutions was put in a set of test tubes. 0.02mls of whole blood put in EDTA container was collected using a pipette after mixing the blood through gentle turning. This was then put in the Drabkin's solution. A portion of this mix was poured into a cuvette and haemoglobin reading taken, using a ciba corning colorimeter 252 at 540nm wavelength.

MEASUREMENT OF ALT, AST AND CREATININE ACTIVITIES

Five(5 ml) of blood was put in a test tube, allowed to clot over 1 hour and serum separated from the whole blood. The serum samples were used to assay the ALT, AST and Creatinine. The sera for ALT, AST and Creatinine were collected and stored in the freezer at -20^{o}cthroughout the study period and analysed same period using the Mindray automated BS 120 Chemistry Analyzer.The serum samples to be analyzed were placed in the sample disks, eight samples in a cycle.

The respective Mindray reagents for the different parameters were placed in the reagent disks and then, caps removed. The parameters to be analyzed were keyed into the system. The sample disks and reagents disk numbers were also keyed into the system and the tests started.

The auto analyzer mixed the respective reagents with each sample and incubated at a given period in the reaction disc. The final solution in cuvette was read off using respective wavelengths. The final optical density was read off from the graph and result displayed on the monitor and copied.

OUTCOME MEASURES

The main outcome measures were adequate clinical resolution and parasite clearance rate of AL and AA as well as adherence to therapy among patients in the two drug combinations under study. Drug adherence was assessed by direct observation of the blister package of AL and AA tablets. This was defined as the number of tablets of AL or AA left on the third day (day of treatment when the treatment regimen was expected to be completed). Parasite clearance rates on days 7, 14 and 28 were determined by the proportion of study participants in each group without parasitaemia by microscopy and resolution of presented clinical symptoms and side/adverse effects of the drugs as reported on symptom assessment questionnaire filled by each patient on the follow up days.

DATA ANALYSIS

Data was analysed under six variables: an event identifier (status), the time to event occurrence (time), covariates: sex, Age, weight, and drug type using cox regression model, on SPSS 17.0 was used

for the analysis due to interest on determining risk/status of interest indexed by a time parameter.

RESULTS

A total of 450 patients were screened for the study of which 296 patients were eligible and 154 were ineligible.Ofthe 154 ineligible participants, 120 showed absence of parasitaemia, 25 who were mainly post graduate students were not resident in the study area, 7 of the patients refused to sign consent while 2 of the patients were in first trimester of pregnancy. The two hundred and ninety six eligible patients were randomized into AL and AA groups. Each treatment group had a total of 148 patients. The demographic data of the patients with respect to weight, age and educational characteristics are as shown in Table 1. Table 2 shows the number of participants at the different university clinics and their distribution by sex and drug type.From table 1, greater percentage of the patients' weight falls within 54-63 kg that has 36.5% of the patients followed by 64-73 kg with 27.7 % with the least being those within 94-103 kg with 1.3% patients. In the age distribution, 15-19 years of age has the highest number of patients with percentage of 40.5 followed by 20-24 (35.1) and 35-39 being the least with 2 %.

Table 1: Demographic data distribution of the patients at inclusion

Demographic characteristics	Interval	N(%)
Weight (kg)	44-53	76(25.7)
	54-63	108(36.5)
	64-73	82(27.7)
	74-83	19(6.4)
	84-93	7(2.4)
	94-103	4(1.3)
Age (Years)	15-19	120(40.5)
	20-24	104(35.1)
	25-29	41(13.9)
	30-34	25(8.5)
	35-39	6(2)
Sex	Male	145(49.0)
	Female	151(51.0)
Campus	Mbaukwu (Pre-science)	92(31.1)
	Awka	141(47.6)
	Nnewi	63(21.3)

N = frequency or no of participants, (%) = valid percentage

Table 2: Frequency distribution of the study participants into the study drugs

Drug	AA		AL	
Sex	M	F	M	F
Pre-science students at Mbaukwu	24	26	18	24
Students at Awka Campus	36	34	35	36
Students at Nnewi Campus	15	13	17	18
Total	75	73	70	78

M = Male F = Female
AL-Artemether-lumefantrine
AA-Artesunate-amodiaquine

Patients from Awka campus which is the main campus of the university contributed 47.6 % of the study population followed by those from Mbaukwu campus (31.1 %) and then those from Nnewi campus contributed 21.3 %.

Table 3 shows the patients adherence behaviour to the drugs while figure 1 shows the effects of the drugs on fever resolution in the patients.

The result shows that a total of 134 out of the 148 patients treated with AL completed their drugs, giving 90.5% adherence, while 137 patients on AA completed their therapy at the appropriate time, giving 92.6% adherence.Figure1, shows that both drugs had similar effect on fever resolution. By day 14, 83.3% of patients on AA had normal body temperature, while 86.5% on AL had normal body temperature while on day28th; the effect was 89.3% and 91.9% respectively.

Table 4 shows the results of the 28-day therapeutic efficacies of the drugs with respect to adequate parasite clearance and clinical response. The result shows that 81.8% of patients treated with AA achieved adequate parasite clearance and clinical response (ACPR) by day 14 while 85.1% achieved ACPR by day 28. On the other hand 68.9% of patients on AL achieved ACPR by day 14 while 70.3% of the patients achieved ACPR on day 28.

Both drugs had same number of patients (4.7 %) who presented with vomiting on the first day of treatment as shown in Figure 2.By the 3rd day of treatment, vomiting had reduced in most of the patients, but the effect was higher on AL patients (2.7 %), and by day

seven, no patient in both treatment groups presented with vomiting. Skin rash was more prominent in AL group (3.4%) by the 7th day, as shown in Figure 3. This however disappeared completely by day 28. Figures 4 and 5 show the effects of the drugs on body weakness and bitter taste respectively.

Table 3: Patients' adherence behavior to the drugs

Drug type	AA	AL
Adherence Pattern	N(%)	N(%)
.00	11(7.4)	14(9.5)
1.00	137(92.6)	134(90.5)
Total	148(100)	148(100)

Zero (0): Patients that did not adhere to therapy.

One (1): Patients that adhered to therapy

N = Number of patients (Frequency)

% = Percentage of the frequency

AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

Table 4: Patients who achieved adequate clinical and parasitological response (ACPR) on different days of the study

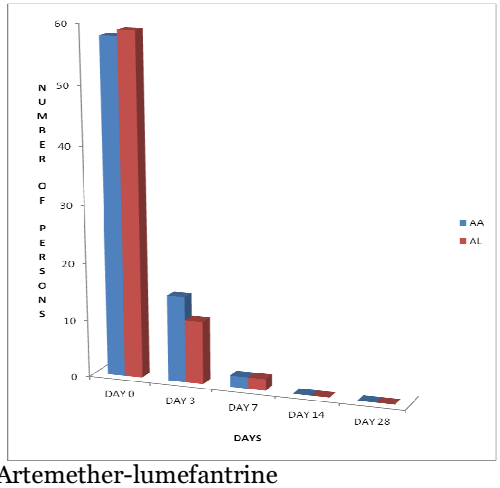
Day	7		14		28	
Drug	AA	AL	AA	AL	AA	AL
MP Clearance(%)	62.2	54.1	81.8	68.9	85.1	70.3

MP-Malaria parasite

AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

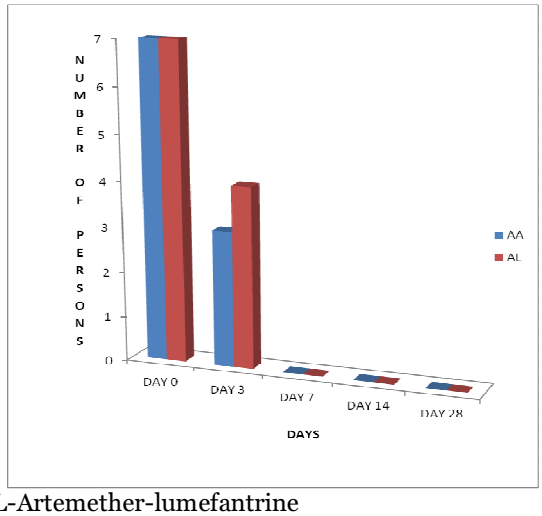
Figure 1: Effects of drugs on fever resolution



AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

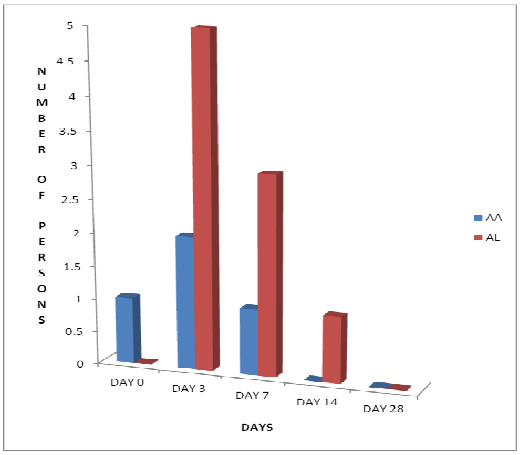
Figure 2: Effects of drugs on vomiting



AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

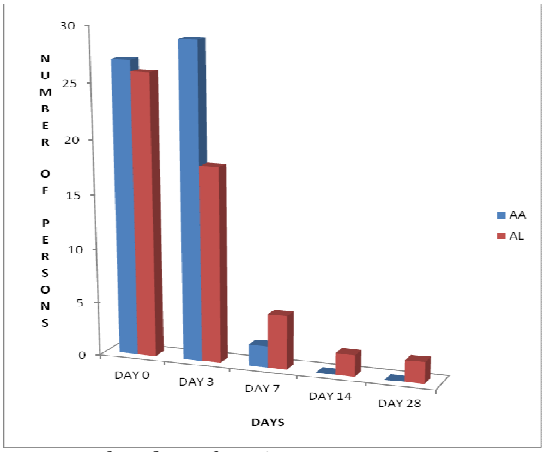
Figure 3: Effects of drugs al and aa on skin rash



AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

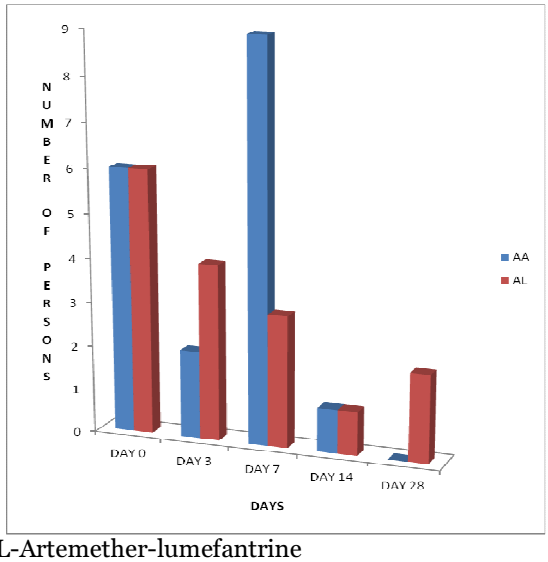
Figure 4: Effects of the drugs on weakness



AL-Artemether-lumefantrine

AA-Artesunate-amodiaquine

Figure 5: Effects of drugs bitter taste



AL-Artemether-lumefantrine
AA-Artesunate-amodiaquine

At inclusion, both groups had relatively equal number of patients who presented with weakness (16.9 and 16.5%), for AA and AL respectively. This was however significantly higher in the AA group on day 3 (18.9 %), with AL being 12.1 % on the same day. By the 7th day of treatment, there were almost complete resolutions of weakness in both groups of patients. By day 28, bitter taste was completely resolved in AA group while about 1.4% of the initial presentation was still observed in AL group.

The results of the effects of the drugs on the patients' Haemoglobin (Hb) contents as shown in table 5, shows marked reduction of Hb in 82.4% of patients treated with AA and 79.7% of patients treated with AL on day 3. This effect was however reduced by day 7, with 63.5% of patients on AA and 43.2% on AL achieving normal Hb range. By the 28th day, 81.1% of patients on AA had achieved normal Hb level while 90.5% of patients on AL achieved normal Hb level.

Summary of the results on biochemical parameters as shown on Table 6 shows that, there was a significant rise in the level of AST for both patients on AA and AL prior to treatment and this rise experienced a fall by day 7, with majority of the patients' AST activity within normal range by day 14 (AA 89.2% and AL 77.7%). Similar trends were also observed with ALT and creatinine as also shown on the table.

Table 6: Percentage (%) number of patients on drugs with AST, ALT and CREATININE within normal range on different days of the study.

Table 5: Effects of drugs on haemoglobin (Hb) content

Day	3		7		14		28	
Drug	AA	AL	AA	AL	AA	AL	AA	AL
0.00 (%)	82.4	79.7	36.6	56.8	16.2	2.7	18.9	9.5
1.00 (%)	17.6	20.3	63.5	43.2	83.8	97.3	81.1	90.5
Total (%)	100	100	100	100	100	100	100	100

Zero (0): % number of patients with lowered Hb level
One (1): % number of patients with normal Hb level.
AL-Artemether-lumefantrine
AA-Artesunate-amodiaquine

Table 6: Percentage (%) number of patients on drugs with AST, ALT and CREATININE within normal range on different days of the study

Day	DAY 0		DAY 7		DAY 14	
Drug	AA	AL	AA	AL	AA	AL
AST	25.7	8.1	85.1	60.8	89.2	77.7
ALT	34.5	37.8	66.2	62.2	87.8	77.0
CREAT	16.9	9.5	36.5	50.7	74.3	73.0

AST – AspartateTransaminase
ALT – AlanineTransaminase
CREAT – Creatinine

DISCUSSIONS

Malaria is an important cause of death in children and adults in tropical countries [4]. On the students' population, this has been a serious burden because of its gross effects on their lectures, social activities, work output and has consequently affected their academic performances hence, the choice of the study population.

Malaria treatment requires the use of effective antimalarias and the discovery and development of ACT came with a big relief to malaria treatment. In choosing an ACT for treatment of malaria, one has to consider several factors such as therapeutic efficacy, side effects, cost, availability and accessibility of the drug in question and patients' perception about the

treatment regimen. While side effects and treatment regimen are key determinants to patient's adherence, perception of illness, treatment-seeking behaviour, and acceptability and affordability of the drug will also influence adherence [11].Both drugs under investigation have been duly subsidized by the Federal Government through the donor agencies hence, the problems of cost and affordability has been eliminated.

In "survival data", the endpoint of interest is the efficacy of the drugs in clearing the malaria parasite, resolving presented symptoms and effects on biochemical parameters. Survival data require special methods of analysis because they often contain right censored observations. That is, observations for which the endpoint of interest has not occurred during the period of observation.

From the result on patients' demographic characteristics, there was no statistical significant difference in the baseline characteristics between the two treatment groups and there were no association between age, sex, education and adherence to treatment regimen with AL and AA**.** In this study, there was a high adherence rate with the patients which may be due to education and counseling given to the patients prior to treatment as well as continuous phone calls and SMS sent to them at periods they were supposed to take the drugs. Education and counseling interventions have been shown to improve completion of treatment [12] and hence, improved adherence. Despite all these, we still experienced some level of non adherence to therapy. Adherence to treatment is likely to be affected by factors such as age, number of tablets and duration of treatment. The three days administration of AA and AL to the study patients resulted in high levels of adherence to treatment. However, the use of students who are educated and have adequate knowledge of diseases and drugs for the study must have contributed to this since it will ensure good self administration, unlike in children where a care giver must do the administration and in geriatrics that are prone to forgetfulness [13, 14]. The higher level of adherence observed in AA (92.6%) could be attributed mainly to its once daily administration of only two tablets at a time, unlike AL (90.5%adherence) which was taken four tablets at 0, 8,24,36,48 and 60 hours interval. According to Haynes et al, increasing the effectiveness of adherence interventions may have greater impact on the health of the population than any improvement in specific medical treatments [14]. This is because taking the correct dose of the drugs prescribed at the right time gives adequate and sustained plasma level of the drug, leading to increase in cure rate and reduction in development of resistance.

The key criterion used to assess the efficacy of an anti-malarial agent is the elimination of malaria parasites, which in turn leads to resolution of symptoms such as fever. Unless otherwise stated, the primary efficacy endpoint in the studies outlined below was the 28-day parasitological cure rate. This describes the proportion of patients with clearance of asexual parasitaemia within seven days of initiating study treatment without recrudescence at day 28, based on blood smears result. In this study however, the 28-day cure rate was not corrected by polymerase chain reaction (PCR) to differentiate between recurrence of the initial infection and a new infection. The evaluable population included all patients with confirmed *P. falciparum* malaria who received at least one dose of any of the study drugs and had parasite counts performed at the pre-specified time points, including day 28, or who discontinued due to unsatisfactory therapeutic effect (censored). From our result, greater percentage of people in the AA group achieved malaria parasite clearance on days 7, 14 and 28 when compared to the percentage in the AL group. AA achieved 81.1 % and 85.1 % ACPR in days 14 and 28 respectively which is similar to the study by Meremikwu et al in Calabar Municipal Counsel in Nigeria [15] but fall short of the studies performed in Kenya, Senegal and Gabon that had cure rates of 90 % and above on the 14th day [16].

However, the 28th cure rate is comparable to those of Senegal and Gabon (16).With artesunate and amodiaquine as an ACT, the artemisinin component has rapid parasite clearance while the longer acting component, amodiaquine, kills the residual parasite. The results of a study on adult Malaysian healthy volunteers by Orrel et al [17] using a cross-over design shows that AA is readily absorbed and well tolerated when co-administered either as loose products (in a non-fixedv combination) or as a fixed-dose combination.

On the other hand, the result of the AL cure rate is lower than that of other studies which were much higher than 70 % from day 14 [15, 18, 19] where as our result shows 68.9 % and 70.3 % at days 14 and 28 respectively.This differences is however not unexpected as there has been massive utilization of the drug with many using sub-therapeutic doses, leading to development of resistance and clinical failures [3].

However, this work may not be a true representative as it was not controlled which is a limitation to this study. A more reliable result would have been achieved if the patients were kept in the same environment were drug administration and food intake adequately controlled.

Owing to the complex dosage form and the need to take fatty meals before taking AL, a more reliable result should be one in which the patients are kept in one environment, administration of drugs supervised and adequate feeding maintained.

There was statistical increase in ACPR from day 14 to day 28 in both groups, but the difference in ACPR between the two drugs was not statistically significant (P=0.601 at 95% confidence interval). On further analysis, it was observed from the result of Cox regression analysis for malaria parasite that the odds of a male still having malaria was 1.145 times greater than that of a female (Exp (B) =1.145). It was equally observed that the hazard of drug AL on MP was 1.176 times greater than that of drug AA, given that its hazard function Exp(B) = 1.176.There were no statistical significant relationship between parasite clearance and sex, age, weight and drug type considering their P-values of 0.321, 0.741, 0.569 and 0.227 respectively at 95% CI. Fever resolution which directly occurs with immediate reduction in parasite biomass is attributable to the artemisinin group which is a blood schizontocide, with rapid parasite and fever clearance [20] and the temperature reduction is similar to that seen in a work conducted by Broek et al in Congo republic [21].The result of the drugs on fever shows that both drugs had similar effect on fever resolution with little or no difference throughout the study period with good outcome. The percentage that still had temperatures not within normal range may be those with late treatment failures due to recrudescence or reinfection as this was not differentiated by parasites genotyping, or may be due to the presence of infection, hormonal changes or those with sub normal temperatures.

The difference in fever resolution between the two drugs under study shows no statistical significant difference between the two drugs (P-value of 0.793 at 95% CI). There was also no association between fever resolution and the independent variables.

Both drugs were well tolerated and only one serious adverse effect was reported with AL, during the study. This was Steven Johnson-Like type of reaction which started on the third day, after completion of therapy. This was adequately treated at the centre and no other complaint was received from the patient. Other actual adverse effects reported by these patients include; vomiting, abdominal pain, pruritis, blurred vision, nausea, dizziness, body pains, diarrhea, skin rash, fatigue, fever, headache, sleep disturbances, anorexia, palpitation and fever. Majority of the side effects, which are also common presenting symptoms of malaria, could be related to the plasma drug concentrations. Most of the side effects resolved before the completion of the study. The most common side effects seen with the patients in the different groups were shown on tables 2, 3 and 4 in the result section.

Weakness could be attributed to the massive breakdown of the parasitized RBCs causing anaemia and subsequent effect of the antimalarial on blood sugar and Hb which further reduces the Hb and its oxygen carrying capacity, leading to dyspnea and weakness.

There was a significant increase in the proportion of anaemia among the study participants. A decrease in haemoglobin levels was observed on day 2 following treatment. In this study, there was an initial drop in haemoglobin followed by an increase by day 14. This is similar to a report in artesunate-mefloquine study by Agomo et al who observed a slight decrease in hemoglobin values on day 7 before returning to normal on day 28 however, not significant [22]. The fall in Hb from day 0 to day 3 was however, statistically significant between the treatment groups considering its P-value of 0.001 at 95% CI. Sex and drug type contributed mainly to the statistical difference in Hb, with P-values of 0.004 and <0.000 respectively. Female gender and drug AA were therefore involved in causing significant fall in Hb level.

Fall in Hb as a result of feminine gender could have correlation with their monthly cycle and the effect was made more significant by those on AA probably due to higher level of DAFH. The effect however normalized by completion of study.

Summary of the results as shown on Table 6 shows that, there was a significant rise in the level of AST for both patients on AA and AL prior to treatment and this rise experienced a fall by day 7, with majority of the patients' AST activity within normal range by day 14. The result of the AST level by day 3 was not computed but reports has shown an increase in liver enzymes by artemesinin and its derivatives [23] indicated a rise from day zero to day 3 before declining by day 7.The period of rise is in line with the period of massive destruction of parasitized red blood cells by the liver and further increase by day 3 was associated with the effect of the drugs on liver enzymes. On completion of the drugs, the transaminase enzyme activity gradually returned to normal. The difference in the activity of the enzyme AST in AA and AL group of patients was however, not statistically significant (P – value =0.603). Furthermore, there was no association between AST and the independent variables, such as age, sex, weight, and drug type.

Transaminase (ALT) and creatinine also show similar trend in its activity as that in AST between the two drugs under study. Artemesinin and its derivatives has been reported to cause a rise in liver enzymes [23].The difference in the result of the activity of the ALT enzyme in patients treated with AA and AL was also, not statistically significant (P – value = 0.966 at 95% CI) as shown on Table 7. There was no association between the ALT enzyme and the independent variables such as drug type, age, sex, and weight. The difference in creatinine level between the two drugs under study was also not statistically significant with P-Value of 0.449 and there was also no association between creatinine and the independent variable.

CONCLUSION

There were good adherence rate to the two drugs under study and their tolerability were high. Parasite clearance rates and fever resolution were similar in both drugs with AA achieving greater clearance on day 28. However, WHO recomendended the withdrawal of any antimalaria with ACPR below 75 %. Therefore, AL with its ACPR of 70.3 % on day 28 should be revisited and further studies carried out to ascertain this so that its adoption as the drug of choice in Nigeria will be revisited.

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