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Research Article

Evaluation of the Safety and Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for Treating Childhood Malaria in Ilorin, Nigeria.

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Abstract
Artemether-lumefantrine (AL), the ACT of first choice for the treatment of malaria in Nigeria though efficacious and well tolerated has a 6-dose regimen over three days and requires co-administration with a fatty meal for optimal absorption and efficacy. This may lead to poor compliance and consequent loss of efficacy over time. Dihydroartemisinin-piperaquine (DP) is another ACT with high efficacy and good tolerability available in Nigeria with a more user-friendly dosing regimen. In an open label randomized clinical trial, we compared the safety and efficacy of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) among 110 children aged 6 – 120 months with symptomatic acute uncomplicated malaria in Ilorin north-central Nigeria. Enrolees were followed up for 28days.107 of 110 (97.3%) enrolees completed the study. The mean age of enrolees was 71.95 ±33.25 months (range 7-120) and 47.2% (51/110) were males. Geometric mean parasite density among children who received AL was 19,158/µL (range 1,200 -197,333) and 21,908/µL (range 1024 - 186,182) for those treated with DP (ρ=0.718). Parasite clearance time for AL treated children was significantly shorter than among those treated with DP (2.35 ± 0.71 days versus 2.71±0.61 days) respectively (ρ=0.001). Fever clearance time was also significantly shorter among children who received AL (1.86 ± 0.61 versus 2.17 ± 0.43 respectively (ρ=0.005). Crude D28 cure rate was 100% among both treatment groups. AL and DP were well tolerated. AL and DP were safe and efficacious in the treatment of acute uncomplicated malaria in children from north-central Nigeria.

Key Words: Artemether-lumefantrine, Dihydroartemisinin-piperaquine, malaria, Nigeria

INTRODUCTION

Malaria is a preventable and curable disease but remains a public health issue of great concern in malaria endemic countries of sub-Saharan Africa where it exerts an enormous burden in terms of morbidity and mortality (World Health Organisation, WHO/World Malaria Report, WMR, 2020). Malaria was estimated to have caused 409,000 deaths globally in 2019 with 94% of these deaths in sub-Saharan Africa, 67% of which occur in young African children under 5years of age (WHO/WMR 2020). Notable gains have been made in the fight against malaria in the last two decades. Between 2000 and 2015, malaria incidence rate was reduced by 27% globally, and by 31% in African region and then by less than 2% between 2015-2019. The estimated malaria mortality rates fell by 42% in all age groups and by 48% in children under 5 years of age within the same time interval (WHO/WMR 2020). These successes are largely attributed to malaria control efforts which include adoption of artemisinin-based combination therapy (ACT) in the treatment of malaria, timely and accurate diagnosis of malaria and the use of insecticide bed nets (WHO 2020). These gains made in malaria control have however been stalled since 2015. Contributing to this may be funding gap for optimizing coverage of interventions, vector resistance to insecticides and possibly impact of increasing burden of resistance of parasite to antimalarial drugs which has been reported from South East Asia (Ashley et al., 2014).

Resistance to antimalarial drugs by *Plasmodium falciparum* has been an ongoing global challenge (Kavishe et al., 2014, Ashley et al., 2014). The World Health Organization recommended treatment of malaria with combination therapy with a preference for artemisinin-based combination therapy in 2001 (WHO, 2001).

Artemether-lumefantrine (AL), the first ACT to be pre-qualified by the WHO, is the ACT of choice approved for the

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treatment of acute uncomplicated malaria in Nigeria (WHO, 2015; Federal Ministry of Health, FMoH 2020). There are many reports on its safety and efficacy from Africa, Asia and India subcontinent (Ebenebe et al., 2018; Mekonnen et al., 2015; Falade et al., 2014; Praveen et al., 2016; Cho Naing et al., 2019). A recent publication has however, reported declining efficacy of AL in Nigeria (Sowunmi et al., 2019).

Dihydroartemisinin-piperaquine (DP), a fixed dose combination ACT that became available in Africa recently was approved in 2010 by WHO for the treatment of uncomplicated falciparum malaria. The co-formulation of dihydroartemisinin, the active metabolite of artemisinin derivatives, with piperaquine, a bisquinoline structurally close to chloroquine has proven to be a good alternative to AL (Zwang et al., 2009; Keating, 2012). DP has the advantage of once daily dosing as against the twice daily dosing of AL. DP also has a longer post-treatment chemoprophylaxis compared to AL as a result of the longer half-life of piperaquine. DP has another clear and distinct advantage of not requiring fatty meals to improve absorption as is the case with lumefantrine, the companion drug of AL.

Some researchers have reported good tolerability and efficacy of DP in various population groups (Keating, 2012; Plucinski et al., 2015). Robust evidence abounds on the safety and efficacy of DP from east Africa and Asia with some researchers recording similar efficacy profile for DP and AL in the treatment of acute uncomplicated malaria (Kamya et al., 2007; Yeka et al., 2008). DP is available in Nigeria but there is paucity of published works on its safety and efficacy, in the country. There are few reports on the efficacy of DP (Ebenebe et al., 2018) which became available after this study has been conducted. This study was designed to generate additional evidence on current efficacy and safety status of commonly used ACT (AL and DP).

MATERIALS AND METHODS

Study site

The study was conducted at the Paediatrics Out-patient and General Outpatient Departments of the University of Ilorin Teaching Hospital (UITH), and Outpatient Department of Ajikobi Comprehensive Health Centre (CHC), Ilorin, Kwara State. The University of Ilorin Teaching Hospital (UITH) is located in Ilorin East Local Government Area of Kwara state. Inhabitants of Ilorin are predominantly Yoruba while other tribes like Fulani, Hausa, Baruba, Nupe and Igbo also constitute significant proportion of the population. UITH is a 600-bed facility that serves as a referral centre for patients from the entire Kwara State and its environs while Ajikobi Comprehensive Health Centre is a 20-bed State Government Health care facility in Ilorin and provides primary health care to people in its locality.

Study design: In an open-label, randomized controlled study, the safety and efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine was compared among children aged 6 to 120 months with symptomatic acute uncomplicated malaria in Ilorin, North central Nigeria over 28 days using the WHO efficacy protocol. Ethical approval was obtained from the Ethics and Research Committee of the University of Ilorin Teaching Hospital, (UITH) with ethical approval number ERC PAN/2016/08/1592. Written informed consent was obtained from parents/guardians of all study participants. Child's assent was also obtained from children ≥7 years of age. Sample size was calculated using the Sakpal formular. A total of 100 participants was needed for the study, with attrition of 10% this came to 110 making it 55 participants per group.

Inclusion and Exclusion criteria: Male and female children aged between six and 120 month with body weight ≥5 kilograms who presented at the study centres during the study period were enrolled if they had a fever (axillary temperature ≥37.50C) or history of fever in the 24 hours before presentation, patent malaria parasitaemia with asexual parasite density between 1000-200,000/µL. Children above 60 month of age were included in the study, because the prevalence of uncomplicated malaria in the older age group sub-Sahara Africa is on the increase (Nkumama et al., 2017). Provision of a signed informed consent by the parent/guardian of each prospective enrolee was essential for enrolment. Patients with known chronic diseases like sickle cell anaemia, chronic kidney or liver disease, malnutrition and cardiac failure were excluded from the study. Children who had any danger sign or evidence of severe malaria (WHO, 2020), haematocrit <15%, history of allergy to any of the study drugs (artemisinins, piperaquine or lumefantrine), history of any ACT use within two weeks of enrolment, or any clinical condition that could compromise assessment of treatment outcome were also excluded from the study. Participants were withdrawn from the study if there was recurrent vomiting of study drugs, the parents/guardians withdrew consent, received alternative antimalarial drug, occurrence of serious adverse events or lost to follow up.

Enrolment Procedure: Children who satisfied the enrolment criteria were enrolled into the study. All essential information obtained from each study participant such as contact details including parent/guardian's phone number, demographic and socio-economic information were obtained and documented in a case record form (CRF) specifically designed for the study. Detailed clinical history of the illness was taken from parents or guardians of each prospective enrolee followed by a thorough general physical examination. Important details such as weight, axillary temperature (using a digital thermometer), jaundice, pallor, dehydration and others were documented. Study participants had capillary blood sample collected for haematocrit and thick blood smear for detection and quantification of malaria parasites. Enrolled children were randomly allocated to two treatment groups according to a computer-generated randomization table. Those randomized to group one received artemether-lumefantrine (AL) while those randomized to group two received dihydroartemisinin-piperaquine (DP).

Treatment phase: The treatment phase consisted of a three-day dosing period between days 0 and 2. Enrolees in group 1 received AL as dispersible Coartem™ (Novartis Pharma, Basil, Switzerland) using the standard six-dose regimen. Each tablet of Coartem™ dispersible consists of artemether 20 mg and lumefantrine 120 mg. Children weighing 5 - <15 kg received one tablet, 15 - <25kg received two tablets, and 25 - <35kg received three tablets at 0 hour, 8, 24, 36, 48 and 60

hours. Participants randomized to group 2 received dihydroartemisinin-piperaquine (DP) Paediatric as Duocotexin™ (Holley-Cotec pharmaceuticals, China). Each paediatric tablet of Duocotexin™) contained (20 mg dihydroartemisinin and 160 mg piperaquine. Patients with body weight between 5 - <6 kg received half of one tablet daily for three days; 6 - <9 kg: one whole tablet daily for three days; 9 - <14 kg: two tablets on day 0, then one tablet on days 1 and 2; 14-19 kg: two tablets daily for three days.

All doses of DP and the 1st, 3rd and 5th doses of AL were administered supervised by the research nurse or physician. Study participants who vomited within 30 minutes of drug administration were re-dosed with full dose while those who vomited after 30 minutes of drug administration received half the initial dose. For study participants between age 6 month and 2 years, DP was crushed, mixed with water and administered as slurry. AL was dissolved in a small volume of water and administered supervised to the enrolees. Mothers were encouraged to breast feed soon after drug administration for babies still on breast milk. Study participants who had been weaned off the breast or above 2 years received a drink of full cream milk after drug administration. Mothers/guardians received a sachet of full-cream milk with the 2nd, 4th and 6th doses of AL to dissolve in water for administration of AL. They were also encouraged to give a fatty meal e.g., bean porridge or fried plantain to the children after AL administration. Extra doses were given to caregivers and parents of such participants should there be a need to re-dose at home.

Parents and caregivers were instructed on how and when to administer the 2nd, 4th and 6th doses of AL at home and phone calls were put through to the parents/guardians to remind them about 30 minutes before each dosage was due. Enrolees whose axillary temperature ≥ 38ºC received paracetamol at a dose of 15 mg/kg/dose during the treatment phase until fever subsided.

Follow-up phase: After the treatment phase, study participants were followed-up on days 3, 7, 14, 21, and 28, as well as any other day the child was unwell or the parent/guardian had any concern about the enrolee's health during the study period. At each contact time, all study participants had full clinical assessment to evaluate the progress and resolution of clinical signs and symptoms. Thick blood smears were prepared during all follow-up visits for malaria parasite detection and quantification. Haematocrit was measured on all follow up days and all contact times.

All study participants were given a token of ₦200 per visit as transport fare and mobile phone recharge card of ₦100/visit each a total of ₦300 (~84 USA Cents). This was to encourage compliance by providing incentives for study participants and their parents/caregivers to come for follow-up and call researcher in case of any observed adverse event or concern.

Malaria microscopy: Capillary blood obtained by aseptic technique from a finger prick was used to prepare thick blood smears and fill microhematocrit tube for measuring packed cell volume. Dried thick blood smears were stained with 10% fresh Giemsa at pH 7.2 and were read by two independent microscopists for presence and quantification of malaria parasites. Parasite density was calculated by counting asexual parasites against 200 white blood cells (WBC) using an assumed total white cell count of 8000/mm^3. A blood smear was considered negative if no asexual stage of malaria parasite was seen after 100 high power fields have been screened. The slides were read primarily by a level II WHO certified Microscopist. Following the initial reading, samples were taking to the Institute for Advanced Medical Research and Training (IMRAT) laboratory in Ibadan and read again. Significantly discordant results were further reviewed by a very senior microscopist.

Efficacy assessment: The primary outcome was adequate clinical and parasitological response (ACPR) without correction for reinfection and was based on WHO criteria (2015) of treatment outcome as follows; (1) Early treatment failure (ETF; danger signs or severe and complicated malaria or failure to adequately respond to therapy on days 0–3); (2) Late clinical failure (LCF; danger signs or severe and complicated malaria or fever and parasitaemia on days 4–28 without previously meeting criteria for ETF or LPF); (3) Late parasitological failure (LPF; asymptomatic parasitaemia on days 7–28 without previously meeting criteria for ETF or LCF); (4) Adequate clinical and parasitological response (ACPR; absence of parasitaemia on day 28 without previously meeting criteria for ETF, LCF, or LPF).

Parasite clearance time (PCT), Fever clearance time (FCT) and symptom clearance time (SCT) were also assessed among the study participants. Parasite Clearance Time was defined as time from administration of first dose of AL or DP until first total and continued disappearance of asexual parasite forms for at least 48 hours while fever clearance time was defined as time from first dose of AL or DP for a body temperature ≥37.5°C to drop below and remained less than 37.5ºC for at least a further 48 hours. Gametocyte carriage was defined as proportion of patients with gametocytes at a given time point.

Safety assessment: Safety assessment was based on WHO criteria of safety outcome as risk of serious adverse events and common adverse events of any severity (WHO/Uppsala monitoring centre, 2000). An adverse event was defined as any untoward medical occurrence i.e., signs, symptoms or abnormal laboratory findings not present at enrolment, but occurred during follow-up, or being present at day 0 and became worse during follow-up despite clearance of parasitaemia irrespective of its suspected relationship to the study drugs. At each follow-up visit, study participants were assessed for any new or worsening adverse event. All adverse events were graded using the WHO ADR (WHO/Uppsala monitoring centre, 2000) severity index (none, mild, moderate, severe, life-threatening) and the relationship of the ADR to study drugs was assessed using Naranjo's ADRs probability score (doubtful, possible, probable, or definite). A serious adverse drug reaction was defined as any adverse experience that resulted in death, life-threatening experience, inpatient hospitalization, persistent or significant disability or incapacity, or specific medical or surgical intervention to prevent serious outcome. This study monitored and recorded all adverse drug reactions whether volunteered, discovered on questioning or detected by clinical examination during treatment and follow-up phase of the study.

Statistical analysis: Data generated during the study was entered into a computer spreadsheet for cleaning and storage. Quantitative and qualitative data obtained were analysed using

the Statistical Package for Social Sciences Service Solution version 21.0 (IBM Corp. Armont, NY, USA). Chi-square test was used to test the difference between categorical variables. The student's t-test was used to test for statistical differences between means and standard deviation for normally distributed continuous variables. Continuous variables were expressed as means ± standard deviation. Median and interquartile range was used for data not normally distributed. Categorical variables were expressed as frequencies in percentages. Comparison of variables that were not normally distributed (like the parasite density) was done using non-parametric statistical test (Mann-Whitney U test). A p-value <0.05 was considered statistically significant

RESULTS

Patient disposition: The study was conducted between May 2017 and February 2018. A total of 260 children who presented at the study centres with fever and clinical features suggestive of acute uncomplicated malaria were screened for inclusion into the study. About two-thirds [170/260 (65.4%)] of the prospective enrolees had patent parasitaemia. Sixty of these 170 were excluded from the study for various reasons which included concomitant febrile illnesses like otitis media, measles and pneumonia, refusal to provide informed consent and malaria parasite density below the lower limit of recruitment (1000/µl). Full study profile is shown in Figure 1. The 110 prospective enrolees who satisfied the inclusion criteria were enrolled and randomized into two groups according to a pre-generated randomization code. Those randomized to group one received artemether-lumefantrine (AL) while those in group 2 received dihydroartemisinin-piperaquine (DP). One hundred and seven (97.3%) study participants completed the scheduled 28 days follow up and are considered as the per-protocol population while the 110 enrolled were considered the intent-to-treat population. Three participants; one in the AL arm and two in the DP arm failed to show up for follow up on day 28 and all efforts to trace them failed.

Baseline demographic characteristics:

The mean age of the total study population was 72.0 months ± 33.5 (range 7 - 120). The mean age of participants who received AL was 76.1 months ± 34.03 (range - 12.0 - 120.0) while that of those treated with DP was 67.8 ± 32.8 months (range - 7.0 - 120.0) (ρ= 0.198). Over half (55.1%) of the study participants were ≤ 60 months of age. The median age for both groups was 72 months. Further demographic details are shown on Table 1. The prevalence of anaemia (defined in this study as haematocrit < 30%) among enrolees in both arms of the study was 32.7%. Majority of the participant (67.3%) had packed cell volume above 30%.

Presenting Complaints: Presenting complaints among study participants were similar among both study groups. The three most prevalent presenting complaints among study participants apart from fever which is an inclusion criterion were headache (65.4%), rigor (32.7%) and chills (20.6%). The mean duration of symptom before presentation was similar for both treatment groups at 2.24 ± 0.77 versus 2.27 ± 0.73 (ρ= 0.800) for the AL and DP groups respectively. The symptom duration before presentation for both groups ranged between 1-4 days.

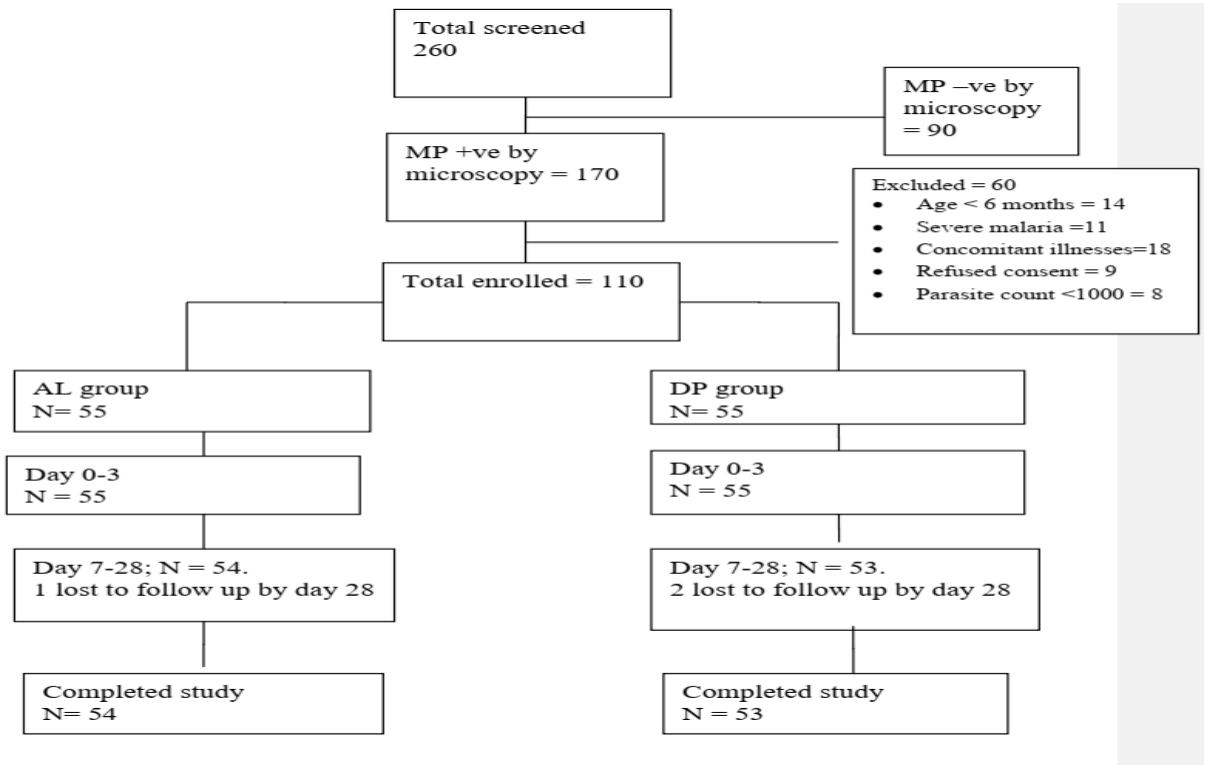

Figure 1:
Flow chart of the study profile which evaluated the comparative efficacy of AL versus DP among Nigerian children suffering from acute uncomplicated malaria

Table 1:
Baseline Demographic and Clinical Characteristics of Children from Ilorin, Kwara state, Nigeria with Acute Uncomplicated Malaria Treated with artemether-lumefantrine or dihydroartemisinin-piperaquine.

Variable	Group AL N = 54	DP N = 53	Total	*p* - value
Age (months)				
≤ 36	9 (16.7)	12 (22.6)	21 (19.6)	
37 – 60	16 (29.6)	11 (20.8)	27 (25.2)	0.506
> 60	29 (53.7)	30 (56.6)	59 (55.1)	
Mean ± SD	76.73 ± 34.03	67.82 ± 32.75	71.95 ± 33.5	0.98
Range	12.0 – 120.0	7.0 – 120.0	7.0 - 120	-
Gender				
Male	25 (46.3)	26 (49.1)	51 (47.7)	0.446
Female	29 (53.7)	27 (50.9)	56 (52.3)	
Weight (kg)				
5 - < 10	3 (5.6)	6 (11.3)	9 (8.4)	0.855
10 - < 15	8 (14.8)	9 (17.0)	17 (15.9)	
15 - ≤ 25	36 (66.7)	30 (56.6)	66 (61.7)	
> 25	7 (13.0)	8 (15.1)	15 (14.0)	
Mean ± SD	19.18 ± 5.48	18.44 ± 6.04	18.81 ± 5.75	0.502
Range	8.0 – 28.7	8.0 – 28.8		
Haematocrit (%)				
Mean ± SD	33.19 ± 3.77	31.22 ± 4.25	2.568	
Range	27-39	24-48		0.012
No with PCV <30%	35	3		
Tribe				
Yoruba	44 (81.5)	32 (60.4)	76 (71.0)	0.021*
Hausa	4 (7.4)	17 (32.1)	21 (19.6)	
Igbo	6 (11.1)	4 (7.5)	10 (9.3)	
Temperature (>37.5°C)				
Mean ± SD	38.23 ± 0.50	38.86 ± 0.81	38.54± 9.74	<0.0001
Range	37.5-40.0	37.5-40.4	37.5 – 40.4	

χ^2: Chi square test, ^{Y}: Yates corrected, t: Independent samples T test, *: *p* value < 0.05 (statistically significant)

Results of Efficacy Evaluation

Fever clearance

All participants recorded temperature ≥ 37.5ºC at enrolment. There was a steady reduction in body temperature among participants in both arms of the study during treatment and follow up. Within 24 hours of commencing treatment 29.6% of study participants in AL and 5.7% in DP group became afebrile. This was statistically significant (p=0.001) in favour of AL. Majority of the participants became afebrile within 72 hours of treatment with the study drugs. The pattern of fever clearance is as shown in the figure 2. The fever clearance time was significantly shorter among study participants who received AL compared to those who received DP – (1.86 ± 0.61 versus 2.17 ± 0.43 days: ρ = 0.005)

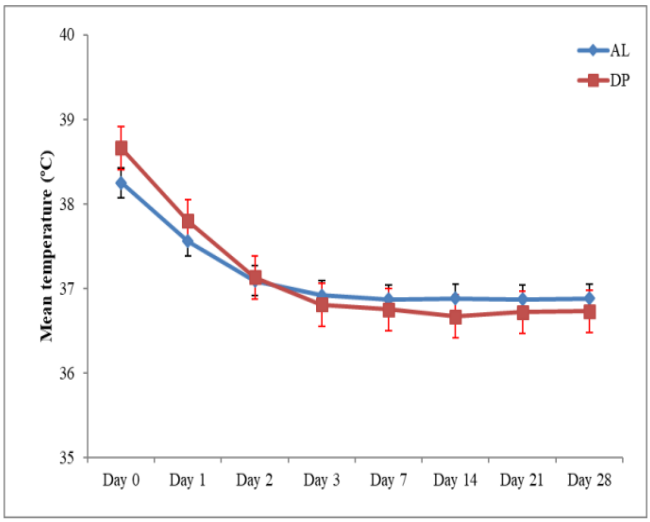

Figure 2:
The pattern of fever clearance among Nigerian children aged 6 months - 10 years with acute uncomplicated malaria treated with artemether-lumefantrine or dihydroartemisinin-piperaquine.

Parasite Clearance

About half [53.7% (29/55)] of the enrolees treated with AL were cleared of malaria parasite within 24 hours while 34.0% (18/55) of participants treated with DP cleared parasitaemia within the same time frame (ρ = 0.038). The parasite clearance time among children treated with AL was significantly shorter than that of children who received DP (2.36 ± 0.71 versus 2.71 ± 0.61 days: ρ=0.009 respectively). Four (7.6%) of the 53 participants who received DP still had patent parasitaemia on day 3 while only one (1.9%) of 54 participants treated with AL had patent parasitaemia on day 3 (ρ=0.162). Over 95% of study participants (98.1%) among those treated with AL and (96.2%) of those who received DP were free of patent parasitaemia within 72 hours of starting the study drugs. All participants (100%) remained free of malaria parasitaemia throughout the follow up phase up to D28. All participants in the two arms of this study were thus classified as having adequate clinical and parasitological response (ACPR). This is illustrated in figure 3

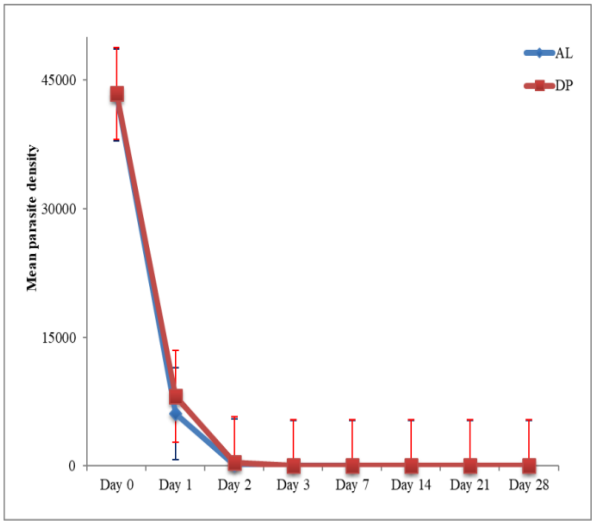

Figure 3:
The pattern of parasite clearance among Nigerian children aged 6 months to 10 years with acute uncomplicated malaria treated with artemether-lumefantrine or dihydroartemisinin-piperaquine.

Gametocyte carriage

A total of ten study participants (9.1%) in both groups had gametocytaemia at enrolment. This represents 6 participants (11.1%) in the AL arm of the study and 4 participants (7.6%) in the DP arm. Gametocytaemia cleared rapidly with only two enrolees in each study group still positive for gametocytaemia by Day-2 and none with gametocytaemia by day 7. There was no recurrence of gametocytaemia up to Day 28.

Haematological recovery

The mean packed cell volume at baseline was 33.19% ±3.77 for participants in the AL group and 31.22% ±4.25 for the DP group (ρ=0.017). This difference in the baseline haematocrit was an unexpected finding. It was not likely to be due to bias because the pre-enrolment randomization procedure was diligently followed and there was no significant difference in other baseline clinical details including parasite density and age. There were three study participants in the DP group who were anaemic (packed cell volume 24%) which could have skewed the mean packed cell volume that randomization could not correct. Thirty-five (32.7%) study participants were anaemic (PCV <30%) at enrolment. Though there was good haematological recovery in the two study groups that of AL group remained better than those in the DP group.

Safety Assessment

Adverse Events

The safety of the study drugs was assessed by evaluating adverse events that occurred among the participants during the period of the study. Most adverse events were mild to moderate in severity and were similar to symptoms of malaria. Overall, there was no significant difference in the proportion of study participants in the two treatment arms who experienced adverse events. 90.7% of patients in AL group had at least one adverse event while 98.1% of patients in the DP arm had at least one adverse event. The five most frequent adverse effects observed during the study were vomiting (73.6%), nausea (53.7%), anorexia (45.3%), diarrhoea (43.4%) and generalised body weakness (22.6%). Nausea had the highest frequency (53.7%) in the AL group while vomiting had the highest frequency (73.6%) in the DP group which was statistically significant. Participants who vomited within 30 minutes of the dose were re-dosed with full dose of the drug but those who vomited after 30 minutes of administration received half the initial dose.

Most adverse events were mild to moderate in severity and overlap with symptoms observed during malaria infection. There were no incidences of serious adverse events and no enrolee was withdrawn as a result of recurrent vomiting or other adverse event.

DISCUSSION

During this study, we evaluated the safety and efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine at standard dosage in the treatment of acute uncomplicated malaria among children aged six months to 10 years in Ilorin, north-central geopolitical zone of Nigeria.

Both artemisinin-based combination therapies were found to be well tolerated and efficacious among the study population. Parasite clearance was good in both study arms of the study. DP treated children were free of patent parasitaemia by D2 and there was also a marked reduction in parasite density among those who still had parasitaemia by day 3. The detection of patent parasitaemia among our study participants at Day 3 is however of concern as this points to some degree of delayed parasite clearance. Falade et al., (2008) working on AL in south-west Nigeria reported no study participant had patent parasitaemia by Day 3 in their study. Our finding is however similar to a report by the same authors in 2014 when an enrolee treated with AL had patent parasitaemia (Falade et al., 2014).

The age distribution in this study reflects what has become the new pattern of increased prevalence of malaria among children >60 months of age (Nkumama et al., 2017) and also among adults as reported from Ghana by Abaku et al. (2021). This may be a direct result of many years of concentrating malaria control efforts on the under-5-year age group with the result that children actually start developing malaria immunity later than in the past.

Response to treatment was monitored during follow up using different parameters which include fever clearance time. The

mean fever clearance time was significantly shorter among AL-treated children compared to those who received DP. This is similar to report by Assefa et al., (2021), Plucinski et al. (2015) and Agarwal et al. (2013) in Kenya. It is however noteworthy that almost all study participants in both treatment arms became afebrile by Day 3, an indication that both study drugs (AL and DP) were efficacious in treatment of acute uncomplicated malaria despite the initial delay in the fever clearance with DP. Plucinski et al. (2015) in Angola reported a different finding where the initial fever clearance time for DP was found to be the same as that of AL though, eventually all participants in AL and DP arms of their study became afebrile by Day 3.

Reduction in parasite density and time to parasite clearance during treatment and follow up were also used as a measure of the efficacy of the study drugs. Parasite clearance was similar in both treatment arms even though there was a significant difference in the rate of reduction in the parasite density in both arms of the study. The initial reduction in parasite density within the first 24 hours was more rapid in the AL group compared to the DP group and this is consistent with previous studies in Nigeria and Kenya (Egunsola and Oshikoya, 2013; Ogutu et al., 2014). The finding that AL has a higher initial and more rapid reduction in parasite density when compared to DP is consistent with the findings by Assefa et al. (2021), Ogutu et al. (2014) and Plucinski et al. (2015) in their studies by Day 3 of follow up only three study participants still had patent parasitaemia and the parasite densities were quite low.

The clinical and parasitological parameters are direct tools put forward by WHO to assess the response of study participants and patients to antimalarial chemotherapy and they measure the efficacy of the drug (WHO, 2020). During this study, all participants (100%) had adequate clinical and parasitological response (ACPR). The clinical response was also mirrored by symptom resolution including fever clearance and parasitological response as depicted with the time to parasite clearance and continued absence of patent parasitaemia throughout the duration of follow up.

The ACPR of 100% recorded for both study drugs indicate their sustained efficacy in the treatment of acute uncomplicated malaria. This finding is similar to reports in literature by previous researchers (Agarwal et al., 2013; Sondo et al., 2015; Assefa et al., 2021). Most studies across Africa still show that these drugs are efficacious in the treatment of acute uncomplicated malaria (Agarwal et al., 2013; Egunsola and Oshikoya 2013; Ogutu et al., 2014; Dama et al., 2018). However, there are also a few studies that reported reduced efficacy of these study drugs in Africa (Sowunmi et al., 2019). Resistance to artemisinin combination therapy has been documented in south east Asia particularly in Thailand and Cambodia (Sahr et al., 2001; Denis et al., 2006; Amaratunga et al., 2016) unlike the findings in this study which show that AL and DP remain efficacious in Ilorin north-central Nigeria.

The haematocrit of the participants at recruitment and follow up values could be used as a surrogate in monitoring response to treatment. It was noticed that after initiating therapy there was an initial drop in the haematocrit particularly during the treatment phase (day 1 - 2) which is believed to have resulted from haemolysis of parasitized red blood cells. After this phase the haematocrit rose progressively during the follow up right to the end of the study for both drug groups. This is consistent with the improvement in participants' clinical state having been cured of the malaria infection. The improvement in health and resolution of symptoms is believed to be due to the efficacy of the study drugs on parasite clearance. Resolution of anorexia leading to improved food intake by the participants after resolution of symptoms would have also contributed to improve the haemogram (Adam et al., 2010; Sondo et al., 2015).

Gametocytes are integral to the transmission and propagation of malaria resistance. The changes found in the gametocyte carriage in this study were significant. Few participants who had gametocytaemia at enrolment with none of the enrolees recording appearance of new gametocytes during follow up. Gametocyte clearance was also rapid and persisted to the end of the study. The artemisinins are known to have gametocidal effect (Noedl et al., 2009; Petersen et al., 2011; Dama et al., 2018). This is also corroborated by this study as there was no recurrence of gametocytes after 48 hours of treatment. This effect means that both study drugs have the added advantage of reducing transmission of malaria from an infected individual to healthy individuals.

The safety of AL and DP was assessed by recording the adverse effect profiles of the two study drugs which were monitored using the treatment emergent signs and symptoms questionnaire (Koh et al., 2010). This included adverse effects volunteered by the participant or the caregiver and the ones detected during clinical examination of the participant on treatment and follow up days. The profile of adverse effects detected were similar to the clinical features of malaria as previously reported in literature by other workers (Arinaitwe et al., 2009; Agarwal et al., 2013; Ogutu et al., 2014). The most predominant adverse events recorded during this study were gastrointestinal disturbances. This is consistent with the reports of previous workers (Arinaitwe et al., 2009; Agarwal et al., 2013; Ogutu et al., 2014). Overall, the study drugs were well tolerated, there was no serious adverse event and no study participant was withdrawn from the study as a result of adverse drug reaction. This finding is comparable to previous findings (Ogutu et al., 2014; Falade et al., 2014; Plucinski et al., 2015; Assefa et al., 2021) who also reported that none of their study participant was withdrawn on account of adverse event and no death was recorded from the adverse event during their studies.

CONCLUSION

This study confirmed the safety and efficacy of AL and DP in the treatment of acute uncomplicated malaria among children in Ilorin, north-central Nigeria.

Limitations of the study

1. Small sample size
2. Termination of both arms of the study at D28 instead of 42 for the DP arm as recommended by WHO. This is because Piperaquine has a long half-life.
3. We did not plan to conduct a PCR evaluation because of cost but this did not impact on the study was as we did not record any treatment failure.

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