Original Research Article

Dihydroartemisinin-piperaquine for the routine treatment of uncomplicated malaria in Northern Ghana

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ABSTRACT

Background: Dihydroartemisinin-piperaquine is a first line treatment for uncomplicated malaria in Ghana. A facility-based study was undertaken to examine the effectiveness of the treatment in the routine health care system.

Methods: The study was undertaken at the Navrongo demographic surveillance area. Patients presenting with acute febrile illness were enrolled after informed consented and confirmation by microscopy. Patients were randomized into supervised group who received treatment under direct observation and unsupervised group which had only the first treatment given under supervision. Treatment was according to bodyweight and 42 days follow-up was undertaken.

Results: A total of 194 patients were enrolled; 54.1% were females and 51% had supervised treatment. The median age and weight were 6.7 years and 20.0 kg respectively. Mean baseline temperature, haemoglobin concentration and parasite density were, 37.6 °C, 11.1 g/dl and 11,098 parasites per microliter of blood respectively. Study completion rate was 93.3%, day 42 polymerase chain reaction-unadjusted adequate clinical and parasitological responses rate (ACPR) was 93.4% by evaluable and 87.1 % by intention-to-treat (ITT). The day 42 ACPR by evaluable was 92.3% in the supervised arm compared to 94.4% in the unsupervised arm. The day 42 ACPR by ITT was 85.7% in the supervised and 88.5% in the unsupervised arms. The fever resolution and haemoglobin concentration changes for the two arms were similar.

Conclusions: The results show that dihydroartemisinin-piperaquine is effective and good first-line antimalarial in the routine health delivery system.

Keywords: Effectiveness, Dihydroartemisinin-piperaquine, Uncomplicated malaria, Ghana

INTRODUCTION

The African Region of the World Health Organization (WHO) disproportionately takes the largest share of the global malaria burden. Approximately nine out of every ten cases and deaths of malaria reported worldwide occur in this region particularly in high to moderate transmission areas.1,2 In these settings, malaria accounts for more than two thirds of the total deaths in young children and takes the life of a child every few minutes during the high transmission season.1,3 The epidemiology of the disease in endemic areas continues to be influenced by the environmental changes that affect the Plasmodium parasite, the anopheles vector and the human host.1,3

Presently, the major preventive tools for malaria control involve the long-lasting insecticide-treated nets, the indoor residual spraying (IRS) with insecticides, the intermittent...
preventive treatment in children and pregnant women, and the seasonal malaria chemoprevention. Besides, these preventive measures, is the need for prompt diagnoses and treatment of the acute disease to prevent severe outcomes and to reduce transmission. The current recommendation is that all suspected malaria cases should have confirmed diagnoses before treatment using artemisinin-based combination therapies (ACTs) and be tracked for outcomes.\textsuperscript{1-3}

The increased investments directed at the development of new anti-malarials means that high malaria burdened countries need robust information to inform policy decisions about the choice and implementation of new products.\textsuperscript{4,5} Effectiveness of data on how new antimalarials work when delivered outside clinical trial conditions will help prioritize and integrate new drugs into the routine health systems. Weaknesses in health systems are the primary cause of the erosion of treatment efficacy resulting from system problems affecting delivery and utilization.\textsuperscript{6,7}

The World Health Organization recommends to all malaria endemic countries to use ACTs in the treatment of \textit{Plasmodium falciparum} malaria.\textsuperscript{8} However different ACTs are selected as the first line treatments for uncomplicated malaria based on efficacy, compliance, cost effectiveness and the appropriateness for treating malaria in children under five years and in pregnancy.\textsuperscript{8} In 2004, Ghana changed her anti-malarial drug policy from chloroquine to artesunate-amodiaquine combination as first line treatment.\textsuperscript{9,10} The implementation process was initially faced with some challenges related to adverse drug reactions and limited treatment options. This led to a review of the policy to address those recognized concerns. Additional treatment options including artemether-lumefantrine were added to cater for those who for one reason or another could not tolerate the artesunate-amodiaquine combination brand.\textsuperscript{9,10}

Recently dihydroartemisinin-piperaquine has been added to the two first line treatments bringing the number to three. Dihydroartemisinin-piperaquine is a fixed dose combination medication for malaria treatment. The piperaquine component is a bisquínoline and highly lipophilic, characterized by slow absorption and a long biological half-life and a Tmax of about 4-5 hours after single and repeated dose.\textsuperscript{11} Piperaquine can accumulate in patients’ plasma after multiple doses with an accumulation factor of around three due to its slow elimination. The increase in piperaquine concentration is more pronounced when administered with a high fat or high calorie meal and the effect is of clinical relevance due to prolonged QTc interval.\textsuperscript{11} The dihydroartemisinin is an active metabolite of artemisinin compounds, which is fast acting but has a short biological half-life. Dihydroartemisinin is very rapidly absorbed with Tmax being about 1–2 hours after single and multiple dosing.\textsuperscript{11}

To date, the reaction of the health systems to multiple first line antimalarial drugs in Ghana has not been comprehensively studied. The objective of the study was to evaluate the effectiveness of dihydroartemisinin-piperaquine as an additional first-line treatment of uncomplicated malaria in Northern Ghana. This paper presents the clinical and parasitological outcomes in the treatment of uncomplicated malaria using dihydroartemisinin-piperaquine in the routine health system.

\textbf{METHODS}

\textbf{Study site and settings}

The study was conducted in the Kassena-Nankana districts of northern of Ghana located on latitude 10° 30’ and 11° 00’ N and longitude 1° 00’ and 1° 30’ W of the Sahelian Savannah.\textsuperscript{12} The area is characterized by a short rainy season and a prolonged dry season from October to March. The Navrongo Health and Demographic Surveillance System monitors health and population dynamics of the area and facilitated the evaluation of the study.\textsuperscript{12} Malaria transmission in the area has been described as hyperendemic with distinct seasonal pattern with peak of transmission following the major rains and the dry season having low rates of infection.\textsuperscript{13-15} The health system of the area includes one referral hospital located in Navrongo the district capital and eight health centres which provide secondary curative and preventive health care. There are about thirty community-based health planning and services clinics located in various communities providing primary health care services and carrying out maternal and child health services. There are three private clinics, two pharmacy shops and over fifty drug and chemical shops.

\textbf{Study design and population}

This was a health system research study involving patients attending the district hospital located in the Navrongo municipality between September 2014 to September 2015. All patients reporting to the hospital during the period with symptoms and signs suggestive of malaria were eligible for inclusion. The presence of malaria parasites was detected by rapid diagnostic test and then confirmed by microscopy before written informed consent documentation. Patients were enrolled after microscopic confirmation of parasitaemia.

The study had two arms (supervised and unsupervised) and participants enrolled into one of the two arms systematically until the study completion. The supervised arm was designated group S and the unsupervised group as group U. Treatment allocations consisting pieces of paper were generated half of them labelled S (supervised arm) and the remaining half labelled U (unsupervised arm). Each piece of the labelled paper was sealed in an opaque envelope and stored in a locked cabinet at the hospital. When a patient was enrolled and was ready to receive treatment, the cabinet was opened by the
investigator and the available envelope was picked and opened to determine the treatment arm to which the patients were to be assigned. This procedure was continued sequentially until the study completion. In the supervised arm of the study, all treatment doses of the study drug were administered to the patient under direct observation in the hospital by a study team member and in the unsupervised arm only the first treatment doses were given to the patients under supervision at the hospital whilst the remaining medications were given to patients to take home after they had been instructed on how to administer the treatment by a study team member.

Study participants and selection criteria

Patients were enrolled into the study only if they met the following selection criteria; clinical diagnosis of uncomplicated malaria, positive malaria test by rapid diagnostic tests at screening and confirmation by microscopy, written informed consent, aged ≥6 months and weight ≥5 kg, capability of taking an oral medication and resident in the study area for at least 2 months following enrolment. Potential study participants were excluded from the study if they did not meet any of the selection criteria.

Written informed consent was obtained from all study participants. Parental consent for patients aged <18 years and assent from children 12-17 years were obtained before enrollment into the study. Each enrolled participant was followed-up for a period of 42 days from the day of enrollment. All participants had scheduled visits on day 3, 7, 14, 21, 28, 35 and 42 and on any day of ill health within the stated period. Additional visits were scheduled for patients in the supervised arm on days 1 and 2 for their treatment doses. On each of these scheduled visit days, thin and thick blood smears were prepared for malaria parasite detection and quantification. In addition, haemoglobin concentrations were measured using HemoCue® Hb 301 photometer, and any reported signs and symptoms were recorded.

Study drugs

The treatment drug was dihydroartemisinin-piperaquine (Duo-Cotecxin™, manufactured by Zhejiang Holley Nanhu Pharmaceutical Company limited China; Lot Number 131121; date of manufacture 12/11/2013 and date of expiry 11/2015) that was in the market and being prescribed was used in the study. Treatment doses of dihydroartemisinin-piperaquine (Duo-Cotecxin™) were as follows: 20/160 mg (dihydroartemisinin/piperaquine) children dose was given as one tablet per day for those 5 kg to <10 kg; two tablets per day for those 10 kg to <20 kg and for the adults the dosage was 40/320 mg (dihydroartemisinin/piperaquine) administered as two tablets per day for those between 20 kg to <40 kg and 3 tablets per day for those ≥40 kg and all the treatment doses were given once daily for three days. The non-artemisinin agent piperaquine is an oral active bisquinoline that is structurally similar to chloroquine. Both piperaquine and chloroquine have similar targets through the inhibition of the heme-digestion pathway in the food vacuole of the parasite.

Sample-size estimation

This was a pilot study and the sample size were based on the probable frequency of an adequate clinical and parasitological response (ACPR) by day 42 but there is no data available from the district or in country indicating what proportion of the participants might be treatment failures. We therefore assumed that about 10% of the participants would be treatment failures by day 42 and that about 5% of those enrolled would be lost to follow-up. It was then estimated that, with a 95% confidence level, enrolment of 200 patients would yield adequate precision for the study.

Data processing and analyses

Data was double entered and cleaned using Epidata and exported into Stata for analysis. Stata 12.1 (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA) was the statistical tool used to analyses the study data. We used descriptive statistics to summarize the numbers and proportions of the baseline characteristics. Ages of patients were captured as continuous variables and other variables captured as categorical variables. Statistical methods used to compare groups for primary and secondary outcomes were parametric and tests chi squared and t-test. Both evaluable and ITT analyses were employed to determine the treatment outcomes. In the evaluable analysis, only patients with complete follow up data were included in the denominator. In the ITT analysis patients lost to follow up were considered as treatment failure. Primary outcome measures parasite clearance assessed on day 28 and 48 post enrolment. Secondary outcome measures were fever clearance on day three and hemoglobin on day 28, Treatment outcomes were classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and ACPR using a modification of the World Health Organization guideline. No interim analyses were undertaken.

Ethical clearance for the study was obtained from the Navrongo Institutional Review Board before the commencement of the field activities of the project.

RESULTS

Participant characteristics

A total of 263 patients with acute febrile illnesses were screened for inclusion into the study. Of this number, 73.8% (194/263) met the study selection criteria and were enrolled (Figure 1). The detailed background characteristics of the enrolled patients are presented in Table 1. About 51% (98/194) of the participants were enrolled into the supervised and 49% (96/194) into the
unsupervised arms of the study. The overall study completion rate was 93.3% (181/194); supervised 92.9% (91/98) and the unsupervised 93.8% (90/96). The total median age of participants was 6.7 years (IQR 4.2-11.0; range 0.75-57.5) with females constituting 54.1% (105/194) of the total enrolled; 59.2% (58/98) in the supervised arm and 49.0% (47/96) in the unsupervised arm. The proportion of patients aged <5 years was 34.7% (34/98) in the supervised arm compared to 32.3% (31/96) in the unsupervised arm. The median weight and height of the enrolled participants were 20.0kg (IQR 14.0-30.0; range 6.0-71.0) and 120 cm (IQR 103-139; range 49.0-170) respectively.

Clinically, the respective mean±SD of axillary temperature and haemoglobin concentration of participants at enrolment were, 37.6±1.0°C and 11.1±1.7 g/dl. Overall geometric mean parasite density was 11,098 (95% CI 8223, 14978) parasites per microliter (/µl) of blood; 12519 (95% CI 8584, 18258) in the supervised arm and 9814 (95% CI 6113, 15756) /µl in the unsupervised arm. The reported prevalence of fever within the previous two weeks was 26.8% (52/194) and was comparable in the two arms. Of the number, 46.2% (24/52) sought health care in the last two weeks for a febrile illness. Bednet usage was high, with 75.8% (147/194) of the patients reported of having slept under a bednet the previous night prior to enrolment; supervised arm (64.3%) and unsupervised arm (87.5%). Overall, 67.5% (131/194) of the patients reported IRS of their homes; supervised arm, 68.4% (67/98) compared to the unsupervised arm, 66.7% (64/96). In all about 25% (48/194) of participants took medication in the last two weeks for the treatment of fever and about 8.0% (15/194) took herbal preparation for the treatment of acute illnesses.

Figure 1: Flowchart for overall study screening, recruitment and enrolment.
Table 1: Background characteristics of all study participants at enrolment.

| Description                                      | Supervised arm (n=98) | Unsupervised arm (n=96) |
|--------------------------------------------------|-----------------------|-------------------------|
| Female, n (%)                                    | <5 (50.0)             | ≥5 (49.0)               |
| Median age (years), range                         | 3.8 (1.3-4.8)         | 9.6 (5.0-32.2)          |
| Median weight, kg (range)                        | 13.5 (6.0-20.0)       | 25.6 (11.0-65)          |
| Median height (cm) (range)                       | 97.0 (57.0-122)       | 133 (100-166)           |
| Temperature (°C), mean±(SD)                      | 37.8 (1.0)            | 37.5 (1.0)              |
| Temperature ≥37.5 °C, n (%)                      | 19 (55.9)             | 30 (46.9)               |
| Hb (g/dl), mean±SD                               | 10.4 (1.7)            | 11.7 (1.4)              |
| Geometric mean parasite density/µl               | 16791                 | 10711                   |
| Indoor residual spray of homes, n (%)            | 26 (76.5)             | 41 (64.1)               |
| Sleeping under bed net, n (%)                    | 29 (85.3)             | 34 (53.1)               |
| History of fever within last two weeks, n (%)    | 8 (23.5)              | 16 (25.0)               |
| Sought health care in last two weeks for a fever, n (%) | 5 (14.7)             | 6 (9.4)                 |
| Took any medication in the last two weeks, n (%) | 11 (32.4)             | 13 (20.3)               |

At enrolment, 97 (50.0%) of the patients had temperature ≥37.5 °C. Other presenting symptoms at enrolment were reported fever (87.6%), headache (65.5%), loss of appetite (58.8%), diarrhoea (51.0%), vomiting (50.5%), chills (45.4%), cough (34.5%) and, general malaise (33.0%). In addition, irritability (3.1%), stomach ache (28.4%), nausea (20.7%), dizziness (17.5%), and fatigue (16.5%), joint pain (12.4%), drowsiness (11.9%), muscle pain (10.8%),
among others were reported. Table 2 presents contributions to total presenting symptoms at enrolment by study arm.

**Participant withdrawals**

The number of enrolled participants who were withdrawn from the study prior to achieving an endpoint was 13 (6.7%). Seven were in the supervised and six in the unsupervised arms of the study. About 62% (8/13) of the withdrawn cases were females and 46% (6/13) of them were under five years of age. A total of nine withdrawals (69.3%) took place before day 28; six from the unsupervised arm and 3 from the supervised arm. Four patients all in the supervised arm of the study were withdrawn from the study after day 28. Seven participants were withdrawn because they travelled outside the study area and therefore were lost to follow up (4 from the unsupervised and 3 from the supervised), three participants (2 females and 1 male) in the supervised arm missed two consecutively scheduled follow-up visits and were thus withdrawn. Two patients, one in each of the study arms took other antimalarial drugs during the study. One female in the unsupervised arm withdrew her consent because she was no longer interested in the study.

**Treatment outcomes**

Table 3 presents the clinical and parasitological outcomes by study arm and duration. Overall, there was no ETF in either arm. One patient had LPF by day 28 in the supervised arm but two was observed in unsupervised arm. One patient had LCF by day 42 in the supervised arm but none in the unsupervised arm. Eleven patients had LPFs by day 42; six of them from the supervised arm and five in the unsupervised arm.

The total day 42 polymerase chain reaction (PCR)-unadjusted ACPR was 93.4% (88.7, 96.5) by evaluable and 87.1% (81.5, 91.4) by intention to treat (ITT) p-value=0.042. The total day 28 PCR-unadjusted ACPR by evaluable was 98.9% (95% CI 94.1, 99.9) in the supervised arm compared to 97.8% (95% CI 92.2, 99.7) among the unsupervised patients. Again, the day 28 PCR-unadjusted ACPR by ITT was 95.9% (95% CI 89.8, 98.8) in the supervised arm compared to 91.7% (95% CI 84.2, 98.3) in the unsupervised arm. Figure 2 compares the day 42 ACPR rates by treatment arms.

**Table 3: Treatment outcome by age groups.**

| Outcome   | Supervised arm | Unsupervised arm |
|-----------|----------------|------------------|
|           | Day 28 N (%)   | Day 42 N (%)     | Day 28 N (%)   | Day 42 N (%)     |
| Total enrolled | 98 (98) | 96 (96) | 95 (90) | 90 (90) |
| Withdrawn   | 3 (7) | 6 (6) | 0 (0) | 0 (0) |
| Completed   | 95 (91) | 90 (90) | 0 (0) | 0 (0) |
| ETF         | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| LCF         | 0 (1) | 0 (0) | 0 (0) | 0 (0) |
| LPF         | 1 (6) | 2 (5) | 1 (2) | 5 (5) |
| Total failures | 1 (7) | 2 (5) | 1 (2) | 5 (5) |
| Total cured  | 94 (84) | 88 (85) | 91 (96) | 91 (88.5) |
| % ACPR (ITT) | 95.9 | 85.7 | 91.7 | 88.8 |
| % ACPR (evaluable) | 98.9 | 92.3 | 97.8 | 94.4 |

\(^a\)=ACPR.
Table 4: Mean haemoglobin concentration (SD) by age and treatment arm.

| Follow up days | Supervised arm | Unsupervised arm |
|----------------|----------------|------------------|
|                | <5             | ≥5              | Total         | <5             | ≥5              | Total         |
| Day 0          | 10.4 (1.7)     | 11.7 (1.4)      | 11.2 (1.6)    | 10.0 (1.8)     | 11.5 (1.7)      | 11.0 (1.9)    |
| Day 3          | 9 (1.6)        | 10.1 (1.5)      | 9.7 (1.6)     | 8.7 (1.9)      | 10.2 (1.8)      | 9.7 (2.0)     |
| Day 14         | 10.1 (1.2)     | 10.9 (1.4)      | 10.6 (1.4)    | 10 (1.5)       | 10.9 (1.9)      | 10.6 (1.8)    |
| Day 28         | 10.9 (1.0)     | 11.4 (1.1)      | 11.2 (1.1)    | 11 (1.2)       | 11.5 (1.4)      | 11.4 (1.3)    |
| Day 42         | 10.9 (1.5)     | 11.7 (1.2)      | 11.4 (1.3)    | 10.5 (1.5)     | 11.7 (1.7)      | 11.4 (1.7)    |

Overall, the day 28 PCR-unadjusted ACPR in children less than 5 years was 100% in both the supervised and unsupervised arms of the study. The day 28 PCR unadjusted ACPR was 98.4% in the supervised and 96.8% in the unsupervised arms in patients 5 years or older by evaluable analysis, p=0.56. The day 42 PCR-unadjusted ACPR by evaluable analysis in children less than 5 years was 90.6% and 96.4% in the supervised and unsupervised arms of the study, p=0.37. The day 42 ACPR in patients 5 years or older was 93.2% and 93.5% respectively in the supervised and unsupervised arms of the study by evaluable analysis, p=0.95.

By ITT the day 28 PCR-unadjusted ACPR in children less than 5 years was 97.1% in the supervised and 90.3% in the unsupervised arms, p=0.25. The day 28 ACPR in patients 5 years or older by ITT was 95.3% in the supervised arm and 92.3% in the unsupervised arm of the study, p=0.48. The day 42 PCR-unadjusted ACPR by intention to treat analysis in patients aged less than 5 years was 85.3% in the supervised and 87.1% in the unsupervised arms. The day 42 ACPR by ITT in patients 5 years or older was 85.9% in the supervised and 89.2% in the unsupervised arms of the study.

**Haemoglobin concentration**

The haemoglobin concentration changes for both the supervised and the unsupervised arms were similar (Table 4). At baseline the total mean haemoglobin concentration for the supervised arm was 11.2 g/dl, this declined to 9.7 g/dl on day 3 following treatment and increased to 11.4 g/dl by day 42 making a gain of about 0.2 g/dl. For the unsupervised arm, the total mean haemoglobin concentration was 11.0 g/dl at baseline, decreasing to 9.7 g/dl on day 3 before increasing to 11.4 g/dl on day 42 making a gain of 0.4 g/dl over the baseline haemoglobin concentration. Haemoglobin recovery in the under five years old were more sensitive to treatment than in older patients. From Table 4 the haemoglobin concentration increased by 0.5 g/dl from day 0 to day 42 in children aged less than five years in both treatment arms. Additional details are presented in Table 4.

**Fever resolution**

The patterns of fever resolution for both the supervised and unsupervised arms were similar (Figure 3). Fever resolution was fast; by day 3 of follow up, 99.0% of patients in the supervised arm compared to 95.8% in the unsupervised arm achieved fever clearance. Interestingly, by day 7 of follow up; all patients in the unsupervised and supervised arms of the study had complete fever resolution except two patients in the unsupervised arm whose fever persisted beyond day 7.
DISCUSSION

The increasing numbers of new artemisinin combination treatments in the routine health care delivery systems create the need for information on their performance. The study examined the effectiveness of dihydroartemisinin-piperaquine as a third first line antimalarial in the routine health care system of Northern Ghana.

The results indicate that in terms of dosing and frequency of the treatment the study completion rate was approximately 93.3%; this was similar in the supervised and unsupervised arms of the study. This finding is high and compares well to what have been reported in studies in acute malaria patients.\textsuperscript{17-19} High treatment completion rate is suggestive of drug acceptability given that patients are more likely to default if adverse drug effects are many and intolerable.\textsuperscript{20-22} Treatment completion rates affect safety and efficacy evaluations and drug effectiveness, in this case dihydroartemisinin-piperaquine combination. When patients terminate treatment prematurely or are lost for evaluations during treatment, the result is incomplete estimation of the outcomes and effectiveness.\textsuperscript{20-22}

Evaluable assessment in trials is the extent to which an intervention can be evaluated in a reliable manner but an intention to treat approach offers unbiased comparisons among treatment groups and provides information about the potential population effects. For participants whose response to treatment could be fully measured because complete information was available (evaluable), the study drug was very efficacious and showed no significant difference between the two treatment arms. There were no ETFs in either arms of the study. Again, for the day 28 evaluations, there was no statistically significant difference from the supervised and unsupervised arms. Similar findings were found in the treatment outcome of day 42 evaluable set. The above findings suggest that dihydroartemisinin-piperaquine is efficacious in the study population and setting irrespective of the mode of treatment administration. This collaborates with what has been reported in other settings.\textsuperscript{17-19} The findings have public health significance as they support the study drug as an alternative first line treatment for uncomplicated malaria in Ghana.

Further analyses involve the treatment population that included all patients (intention to treat), regardless of their adherence, study completion or withdrawal from the study. The two treatment arms showed no difference though the percentage treatment outcome for the supervised arm was higher than the unsupervised arm in the analyses set by day 28. At day 42, the percentage treatment outcome for the unsupervised arm was higher than the supervised arm except that this was again not statistically significant.

From the results when compared to the evaluable group the intention to treat group always had lower treatment outcomes for the overall study, the supervised and the unsupervised arms. The findings have public health relevance as they give an indication of how effective the drug could be when administered in the routine health system. Treatment effectiveness in real life is often lower than the efficacy due to inherent weaknesses in health systems and patient behaviour.

From the study results no severe adverse drug effects was observed and the frequency of adverse events reported were consistent with common malaria signs and symptoms.\textsuperscript{17-19} None of the events was deemed causal and there was no significant difference in adverse events reported in the study arms. Moreover, the frequencies of the adverse events were mild in severity, non-serious in nature and consistent with that expected in patients with acute malaria.\textsuperscript{17-19} Again, the total number of withdrawals from the study prior to achieving an endpoint was comparable in the two arms. The withdrawals did not point to any specific trends and appeared to have occurred at
random. Several reasons account for withdrawals in drugs studies, which may relate to personal, health and safety issues. For instance, if a medication causes side effects then a participant who struggles with that will withdraw and if a patient joined a trial to get a current ailment cured then it is most likely they will withdraw if there is no improvement.

Other reasons may be participant relocation, study procedures or misunderstood expectations. Participant withdrawal affect the success of a study and hence any effectiveness of it.23,24 The trends in haemoglobin recovery for both the supervised and the unsupervised arms were similar, so were the patterns of fever resolution for both the supervised and unsupervised arms consistent with findings from previous studies.17,19

**Limitations**

It should be noted that the sample size may have not been sufficiently powered in the study small difference. Moreover, the adverse events may not have been properly assessed particularly in very young children. In addition, we report PCR-unadjusted cure rates, mindful of a margin of error in these estimates without adjustment for recrudescent and new infections.

**CONCLUSION**

In conclusion there was no significant difference in treatment outcomes between the two study arms suggestive that drug effect may be the same regardless the mode of treatment. The effectiveness of dihydroartemisinin piperaquine in Ghanaian health systems in real life may not be significantly lower than the expected efficacy despite the expected weaknesses in health systems. The fixed dose formulation was safe, well tolerated and thus may have better or comparable compliance with the other alternate first-line ACTs available for routine health care in Ghana.

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