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Clinical Outcomes of the Pharmacotherapy of Cerebral Malaria among Children in a Nigerian Resource-Limited Facility

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Abstract

In resource-limited facilities with a high burden of Cerebral Malaria (CM), it is necessary to identify the pharmacotherapeutic interventions with the best clinical outcomes to reduce morbidity and mortality of the disease. This study aimed at evaluating the clinical outcomes of the pharmacotherapy of CM among children admitted in the Emergency Paediatric Unit (EPU) of Specialists Hospital Sokoto, Nigeria. A Prospective longitudinal study design was used to evaluate eligible children aged ≤ 5 -years and admitted with CM in the facility between July and September 2016. The treatment was based on WHO 2015 guideline for the management of severe malaria. The outcomes of treatments: Blantyre Coma Scale (BCS) score, temperature, and some prognostic information were documented in a structured data collection form from 0 to 96th hours of their admission. The data were analysed using descriptive, T-test, ANOVA and correlation statistics at $p < 0.05$. The result shows that the average age of the 60 patients evaluated was 3.2 ± 1.5 years. Patients treated with IV-Quinine were observed to have better improvement of BCS score, a better decline in body temperature, higher discharge rate, a lower risk of neurological sequelae and death but with longer duration of hospital stay compared to those on IV-Artesunate. Patients on antibiotics especially ceftriaxone, and diazepam had better improvement in BCS score and decline in their body temperature. In conclusion, patients treated with drug combinations containing IV-Quinine antimalaria, ceftriaxone antibiotic and diazepam had better clinical outcomes. Despite the WHO's recommendation of IV-Artesunate as the first-line antimalaria for the treatment of CM due to its advantages, clinicians should still consider IV-Quinine as a very good option.

Key Words: Cerebral malaria; clinical outcomes; malaria in children; pharmacotherapy; prognosis.

Introduction

Severe malaria, unlike uncomplicated malaria, is associated with clinical and/or laboratory evidence of vital organ dysfunction (WHO, 2015). It is mostly caused by *Plasmodium falciparum* parasite especially in the sub-Saharan region (WHO, 2015). Features of severe malaria include multiple convulsion, impaired consciousness,

severe anaemia, renal failure etc. Cerebral malaria is the form of severe malaria that affects the brain. It is associated with seizures, encephalopathy, neurological complications and death (WHO, 2015).

According to World Health Organisation (WHO), as of 2017, Africa has 92% (out of 219 million) and 93% (out of 435, 000) of

malaria cases and death respectively (WHO, 2018). Children under the age of 5 years are the most vulnerable, accounting for 61% (266, 000) of global malaria deaths in 2017 (WHO, 2018). This death is mostly as a result of cerebral malaria. Survivors of cerebral malaria are mostly presented with a wide range of complications like neurological sequelae (Idro *et al.*, 2010).

Several studies conducted in Nigeria reported that severe malaria, which predominantly affects children under the age of 5 years, was the most common cause of emergency visits resulting to high morbidity and mortality (Ibeziako & Ibekwe, 2002; Jiya *et al.*, 2008; Adeboye *et al.*, 2011; Okechukwu & Nwalozie, 2011; Abhulimhen-Iyoha & Okolo, 2012).

Management of patients with cerebral malaria involves the use of parenteral antimalarials, broad-spectrum antibiotics, adjuvant therapy targeting some conditions presented by the patients and other supportive measures (WHO, 2012, 2015).

Several studies were conducted on the clinical outcomes of patients on different antimalarial drugs, especially Artesunate and Quinine. Some studies reported no difference in the outcomes of patients on IV Artesunate compared to those on IV Quinine (Jones *et al.*, 2007) while others prioritise the use of IV Artesunate (Dondorp *et al.*, 2010; Sinclair *et al.*, 2012; Keene *et al.*, 2018; El Ket *et al.*, 2019).

Nigerian studies on the outcomes of different drugs among adults or children with cerebral (or severe) malaria appear to be limited. However, Aguwa *et al* (2010) reported that parenteral Quinine and Artemether were equally effective (Aguwa *et al.*, 2010). In the

same year, a clinical trial conducted in many African countries, including a centre in Nigeria showed that Artesunate was superior to quinine (Dondorp *et al.*, 2010).

However, these studies did not consider the effect of other pharmacotherapeutic agents on the outcomes of the patients evaluated. Also, the studies were conducted in an ideal situation, without resource limitation. Hence, all the medications, as well as relevant laboratory investigations required for diagnosis and/or monitoring treatment progress were available.

Furthermore, there is a need for periodic evaluation of treatment effects of available therapeutic agents especially in resource-limited settings where laboratory investigations are either not always available, accessible or affordable by the patients. This will ensure that clinicians are more aware of the expected outcomes of almost every available treatment option that shall eventually improve patients' outcomes.

In this study, the clinical outcomes of the pharmacotherapy of cerebral malaria among children admitted in the Emergency Paediatric Unit (EPU) of Specialists Hospital Sokoto, Nigeria were evaluated.

Methods

Study Design and Setting

A prospective longitudinal study design was used for this study. The study was carried out at Specialists Hospital Sokoto. The hospital is a 500-bed capacity health care facility located in Sokoto State, North-western Nigeria. The tertiary health care facility, owned by the state government, also serves as a secondary health care setting for people within and around Sokoto metropolis.

Study Population

Children admitted with cerebral malaria within the study period were used for this study. The choice of the population was due to the fact that cerebral malaria, which mainly affects children under the age of 5 years in this sub-Saharan region has a very high fatality (WHO, 2018).

Eligibility Criteria

The eligibility criteria for the study were: children less than or equal to 5 years of age, clinically diagnosed by a team of experienced physicians to have cerebral malaria (with or without comorbidity) and admitted in the Emergency Paediatric Unit (EPU) of the hospital. Children aged above 5 years or those with other forms of severe malaria were excluded from the study.

Data Collection

Period of the Data Collection

The data were collected in the year 2016, during the raining season, when the rainfall was at its peak (July to September). The choice of the period was because malaria and hence severe/cerebral malaria cases are mostly observed in that season.

The instrument for the Data Collection

The data were collected in a data collection form designed based on the WHO guideline for the management of Severe Malaria (WHO, 2012, 2015). The instrument captures patients' baseline sociodemographic and clinical characteristics, medications and treatment monitoring parameters as well as outcomes of treatment.

Patients' Recruitment

Parents of all eligible patients admitted in the EPU of the hospital were approached by a trained research assistant. Information on the research was introduced to them. The

children of those who agreed to participate in the study and gave their verbal consent were recruited. A total of 60 patients were recruited and evaluated.

Treatment

Recruited patients were treated by the hospitals' caregivers (physicians, pharmacists, nurses) based on the WHO guideline for the management of Severe Malaria (WHO, 2012, 2015). Each patient was treated with intravenous (IV) fluid (4.3% Dextrose Saline with 50% dextrose as required), IV antimalarial (Artesunate or Quinine), and IV broad-spectrum antibiotics (Ceftriaxone, Cefuroxime, Metronidazole, Chloramphenicol, or Crystalline Penicillin) with or without parenteral Anticonvulsant (Diazepam), depending on whether the patient had convulsion or not. The WHO and British National Formulary (BNF 71) recommended doses were used for each drug category (WHO, 2012, 2015; BNF, 2016). Only the brands of drugs approved by the hospital were used. Patients' hyperpyrexia was managed with periodic tepid sponging.

Outcomes

The outcomes of treatment were obtained from physicians' assessments, patients' observation and patients' case files. The intermediate outcomes were the Blantyre Coma Scale (BCS) score (Molyneux *et al.*, 1989; Newton *et al.*, 1997; Taylor, 2009) and temperature of the patients, monitored at 0, 6, 12, 24, 48, 72 and 96 hours. The BCS of the patients was graded between score 5 (fully conscious) and score 0 (nonresponsive). The final outcomes of the patients which were: duration of hospital stay, the proportion of patients that were discharged, referred with neurological sequelae, referred with other conditions, declined further treatment and dead were collected and documented.

Ethical Consideration

The ethical approval for this study was sought and obtained from the Health Research and Ethics Committee of Specialists Hospital Sokoto. Verbal consent was obtained from the patients' parents. The confidentiality of the patients and the data obtained were maintained.

Data Analysis

The data collected were coded and entered into version 20 of the IBM Statistical Product and Service Solutions (SPSS) for analysis. Descriptive, students' T-test, one way ANOVA, cross-tabulation and Pearson correlation statistical analyses were appropriately used to analyse the data. Level of significance for inferential statistics was set at $p < 0.05$.

Trends of changes (percentage changes) in the BCS scores and body temperature readings of the patients throughout their treatment periods were compared using charts. The comparison was based on patients' treatment with different antimalaria (IV artesunate or IV quinine), antibiotics (IV ceftriaxone or others) and whether they were treated with diazepam (only for patients with multiple convulsion) or not.

Results

Sociodemographic and Baseline Clinical Characteristics of the Patients

The average age, body weight and body mass index (BMI) of the 60 patients evaluated were 3.2 ± 1.5 years, 11.6 ± 4.2 Kg and 13.9 ± 3.0 Kg/m² respectively. Most of the patients were male (58.3%) and underweight (93.3%) (Table 1).

Patients' average duration of illness before admission was 4.7 ± 5.8 days. Clinical features of cerebral malaria observed among

these patients were prostration ($n = 60, 32.3\%$), impaired consciousness ($n = 59, 31.7\%$), multiple convulsions ($n = 47, 25.3\%$), and respiratory distress ($n = 20, 10.7\%$), with each patient presenting with an average of 3.2 ± 0.6 features.

Their average baseline BCS score, Temperature (T), Pulse Rate (PR), Respiratory Rate (RR) and Pack Cell Volume (PCV) were 0.8 ± 0.9 , 37.4 ± 0.9 °C, 106.2 ± 17.6 b/m, 29.4 ± 7.5 c/m and $21.8 \pm 9.1\%$ respectively. There was an attempt to treat most (65%) of the patients before admission.

Treatments Received by the Patients

Most of the patients were treated with Artesunate + Ceftriaxone + Diazepam (43.3%), Artesunate + CPC/Xpen + Diazepam (13.4%) and Artesunate + Ceftriaxone (8.3%) combinations as shown in Table 2. In addition to the medications, all the patients were given 4.3% Dextrose Saline and Dextrose Water. Only 4 out of the 60 patients were not given multivitamins and/or supplements after recovery. Fourteen (23.3%) patients received packed cells transfusion.

Outcomes of Treatments Received by the Patients

The BCS and temperature of the patients monitored from baseline (0 hours) to 96th hour of treatment initiation and compared based on different medications given are shown in table 3. The baseline BCS and temperature of patients on different antimalarial drugs were statistically the same using one way ANOVA at $p < 0.05$. Similarly, baseline BCS and temperature of patients treated with different antibiotics and anticonvulsants were statistically the same using T-test at $p < 0.05$.

Effect of IV Artesunate and IV Quinine on the BCS Score and Temperature of the Patients

Figure 1 showed the plot of percentage changes in the BCS and temperature of patients on different antimalarial drugs with respect to the baseline value. In figure 1a, patients on IV Quinine had better improvement in BCS score (recovery) compared to patients on other antimalarials. Patients initially treated with IV Artesunate then later switched to IV Quinine after 24 hours had a slightly higher percentage improvement in their BCS scores from 48 hours than those on IV Artesunate alone. With respect to temperature changes, patients on IV Artesunate had a faster rate of decline in their body temperature in the first 24 hours of treatment initiation compared to their counterparts on other antimalarial drugs. However, patients on IV Quinine had a better decline in their body temperature from 48 hours of treatment initiation.

Effect of Different Parenteral Antibiotics on the BCS Score and Temperature of the Patients

Patients treated with Ceftriaxone were compared with patients on other antibiotics (Chloramphenicol + Crystalline Penicillin or Cefuroxime + Metronidazole). Figure 2a and 2b showed that patients on Ceftriaxone respectively had better improvement in their BCS scores and better decline in their temperature compared to patients on other antibiotics.

Effect of Anticonvulsant (IV Diazepam) on the BCS Score and Temperature of the Patients

The result also showed that patients that presented with multiple convulsions and treated with IV diazepam had better improvement in BCS scores (Figure 3a) and

better decline in body temperature (Figure 3b) compared to patients that were not treated with IV diazepam.

Duration of Hospital Stay and Final Outcomes of the patients

The average duration of hospital stay of the patients in the facility was observed to be 4.8 ± 2.8 days (Table 4). Pearson's correlation analysis showed that duration of illness before admission ($r = 0.361, p = 0.006$), number of skipped antimalarial doses ($r = 0.323, p = 0.015$) and number of other medications ($r = 0.399, p = 0.002$) significantly and positively affects patients' duration of hospital stay. It was observed that patients managed with IV Artesunate had the shortest (4.2 ± 2.4 days) duration of hospital stay while patients on IV Quinine (6.2 ± 3.5 days) had the longest. Patients on different antibiotics and those treated and not treated with diazepam had similar duration of hospital stay.

Out of the 60 patients, 35 (58.3 %) were successfully discharged, 9 (15 %) referred to other facilities with neurological sequelae, 7 (11.7 %) referred to other facilities with other conditions, 3 (5 %) declined further treatment while 6 (10 %) were dead.

Crosstabulation of different drugs against the final status of the patients shows that all except one of the 6 patients initially treated with IV Quinine were discharged successfully. Conversely, all except one of the referral cases with neurological sequelae or other conditions as well as all death cases were among patients treated with IV Artesunate or IV Artesunate switched to IV Quinine.

The final outcomes of patients on different antibiotics, as well as that of patients treated with or without diazepam, were similar.

Table 1: Sociodemographic and clinical characteristics of the patients, N=60

Variable	Frequency (%)
Gender	
Male	35 (58.3)
Female	25 (41.7)
Total	60 (100)
Categorised BMI	
Underweight	56 (93.3)
Normal Weight	3 (5.0)
Overweight	1 (1.7)
Total	60 (100)
Monthly Income of the Guardian (NGN) (1 USD = 365 NGN)	
Less than 10, 000	13 (21.7)
>10, 000 - 50, 000	29 (48.3)
>50, 000 - 100, 000	16 (26.7)
>100, 000	2 (3.3)
Total	60 (100)
Level of Education of the Guardian	
Primary/Islamic Education	13 (21.7)
Secondary School	18 (30.0)
Post-secondary School	29 (48.3)
Total	60 (100)

Table 2: Combination of Medications Used in the Facility, N = 60

Combination of Medications	Frequency (%)
Artesunate + Ceftriaxone + Diazepam	26 (43.3)
Artesunate + CPC/Xpen + Diazepam	8 (13.4)
Artesunate + Ceftriaxone	5 (8.3)
Artesunate <i>switched</i> to Quinine + Ceftriaxone + Diazepam	5 (8.3)
Quinine + Ceftriaxone + Diazepam	4 (6.7)
Artesunate + Cefuroxime + Metro	3 (5.0)
Artesunate <i>switched</i> to Quinine + Ceftriaxone	3 (5.0)
Quinine + CPC/Xpen + Diazepam	2 (3.3)
Artesunate <i>switched</i> to Quinine + CPC/Xpen + Diazepam	2 (3.3)
Artesunate + CPC/Xpen	1 (1.7)
Artesunate <i>switched</i> to Quinine + CPC/Xpen	1 (1.7)
Total	60 (100)

CPC = Chloramphenicol; Xpen = Crystalline Penicillin; Metro = Metronidazole

Table 3: Blantyre Coma Scale scores and Temperature of patients treated with different medications; monitored throughout treatment periods

Variables	Monitoring Periods (Hours)						
	0	6	12	24	48	72	96
BCS Scores (0-5)							
<i>Antimalaria</i>							
IV Artesunate	0.8±0.9 ^b	1.7±1.1	2.0±1.3	3.3±1.0	3.6±1.0	3.8±0.9	3.8±1.0
IV Quinine	0.3±0.8 ^b	1.6±1.8	1.8±1.8	3.2±1.7	3.7±1.4	3.8±1.0	3.7±1.5
Artesunate→Quinine	0.6±0.7 ^b	2.2±1.5	1.0±1.4	2.1±1.6	3.1±1.5	3.4±1.4	3.3±1.5
<i>Antibiotic</i>							
IV Ceftriaxone	0.7±0.8 ^c	1.8±1.2	1.9±1.4	3.2±1.3	3.6±1.1	3.7±1.1	3.7±1.3
Others *	0.9±1.0 ^c	1.8±1.2	1.8±1.3	2.9±1.5	3.3±1.2	3.8±0.8	3.7±0.7
<i>Anticonvulsant^a</i>							
IV Diazepam	0.7±0.3 ^c	2.0±0.7	1.9±0.2	2.9±0.4	3.5±0.4	3.8±0.2	3.8±0.6
No IV Diazepam	0.8±0.5 ^c	1.4±0.5	2.0±0.8	3.0±1.3	3.5±1.0	3.7±0.7	3.7±0.7
Temperature (^oC)							
<i>Antimalaria</i>							
IV Artesunate	37.4±1.0 ^b	37.1±0.8	36.9±0.7	36.8±0.6	36.7±0.5	36.6±0.5	36.7±0.5
IV Quinine	37.6±1.1 ^b	37.7±0.9	37.4±1.2	37.3±0.7	36.6±0.5	36.6±0.4	36.7±0.2
Artesunate→Quinine	37.2±0.8 ^b	37.3±0.9	37.0±0.7	37.1±0.8	36.9±0.6	36.9±0.6	36.8±0.5
<i>Antibiotic</i>							
IV Ceftriaxone	37.5±1.0 ^c	37.3±0.8	37.0±0.7	37.0±0.8	36.7±0.6	36.7±0.5	36.7±0.5
Others *	37.0±0.7 ^c	36.9±0.7	37.0±0.8	36.7±0.4	36.7±0.5	36.5±0.4	36.6±0.3
<i>Anticonvulsant^a</i>							
IV Diazepam	37.2±0.5 ^c	37.1±0.4	36.9±0.5	36.8±0.4	36.6±0.3	36.5±0.2	36.7±0.1
No IV Diazepam	37.2±0.4 ^c	37.2±0.8	37.2±0.5	37.1±0.3	37.1±0.3	36.9±0.5	36.9±0.2
* Chloramphenicol+Crystalline Penicillin or Cefuroxime+Metronidazole; ^a Patients presented with multiple convulsion were treated with diazepam; Artesunate→Quinine = Artesunate switched to quinine after 12 hours; BCS = Blantyre Coma Scale; ^b patients had statistically the same baseline BCS or Temperature within the respective groups using one way ANOVA at $p<0.05$; ^c patients had statistically the same baseline BCS or Temperature within the respective group using student's T-test at $p<0.05$							

Figure 1: Effect of Antimalaria on Blantyre Coma Scale (BCS) Score Improvement and Temperature Decline

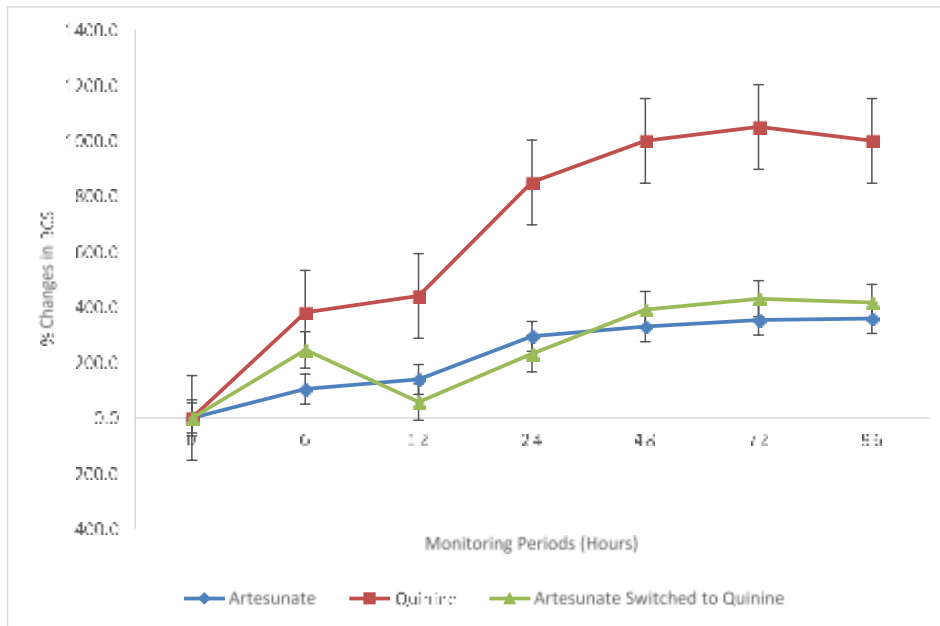


Figure 1a: Improvement in the BCS Score of patients on Artesunate, Quinine or Artesunate switched to Quinine

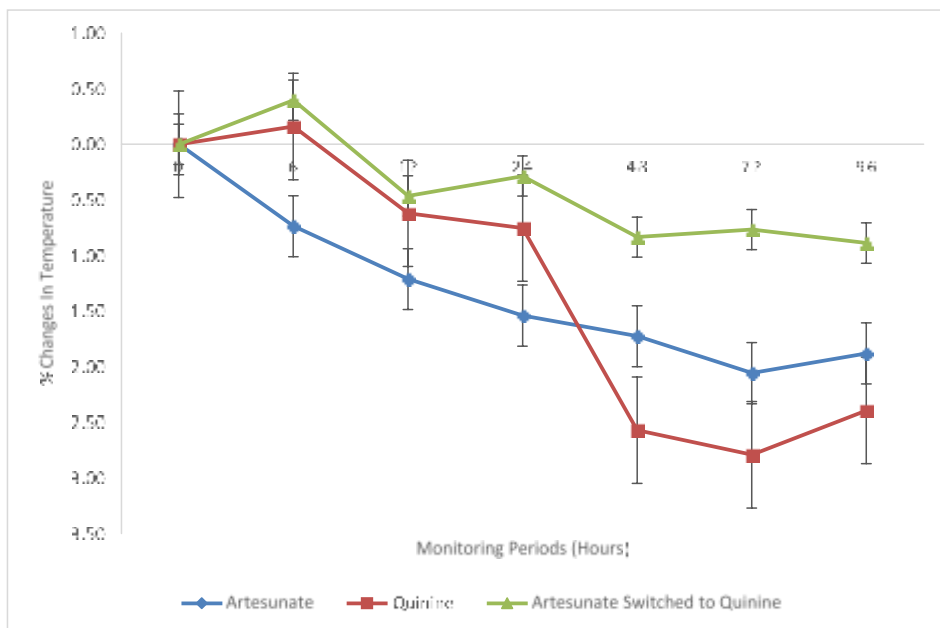


Figure 1b: Decline in body Temperature of patients on Artesunate, Quinine or Artesunate switched to Quinine

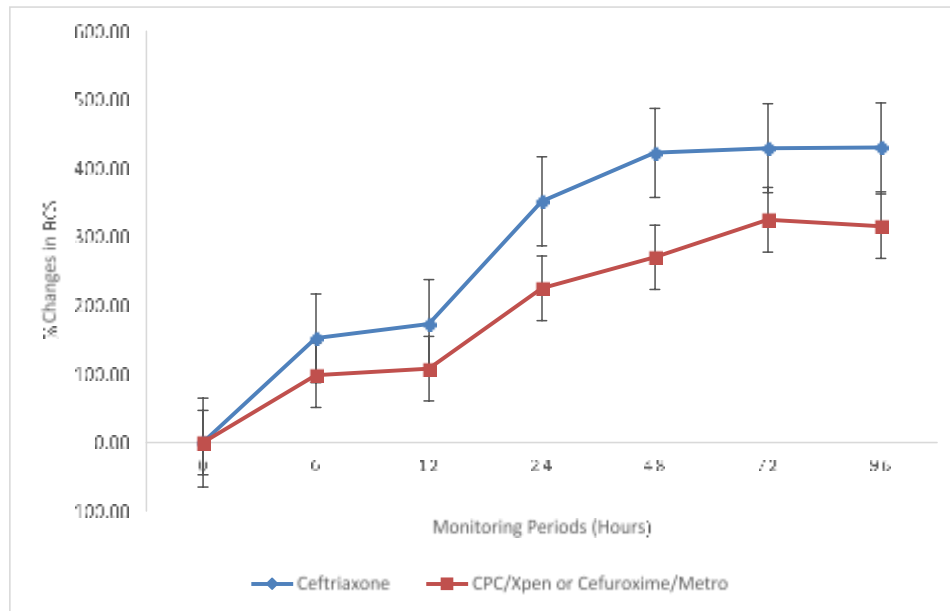


Figure 2a: Improvement in the BCS Score of patients on Ceftriaxone versus those on Chloramphenicol + Crystalline Penicilline or Cefuroxime + Metronidazole

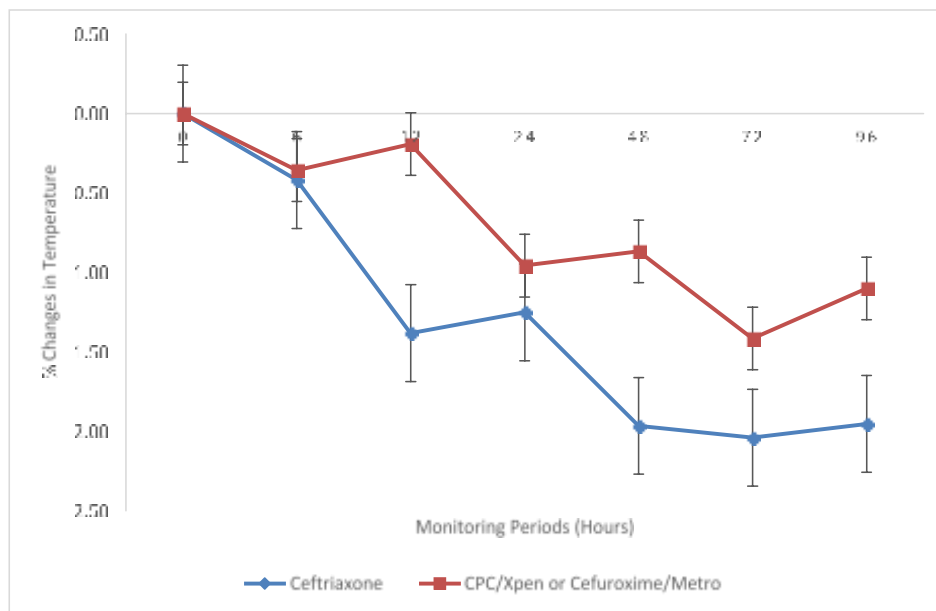


Figure 2b: Decline in body Temperature of patients on Ceftriaxone versus those on Chloramphenicol + Crystalline Penicilline or Cefuroxime + Metronidazole

Figure 2: Effect of Antibiotics on Blantyre Coma Scale (BCS) Score Improvement and Temperature Decline

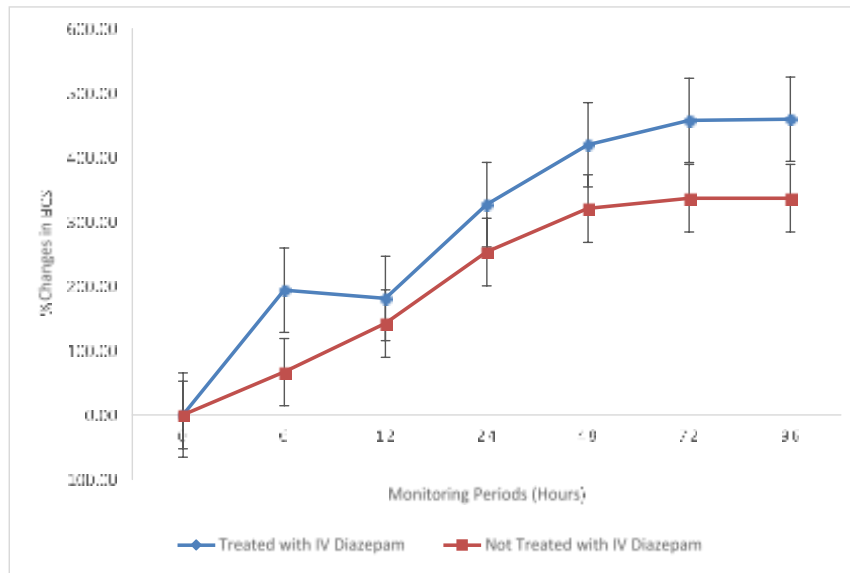


Figure 3a: Improvement in the BCS Score of patients treated with or without IV Diazepam based on the presence or absence of Multiple Convulsion

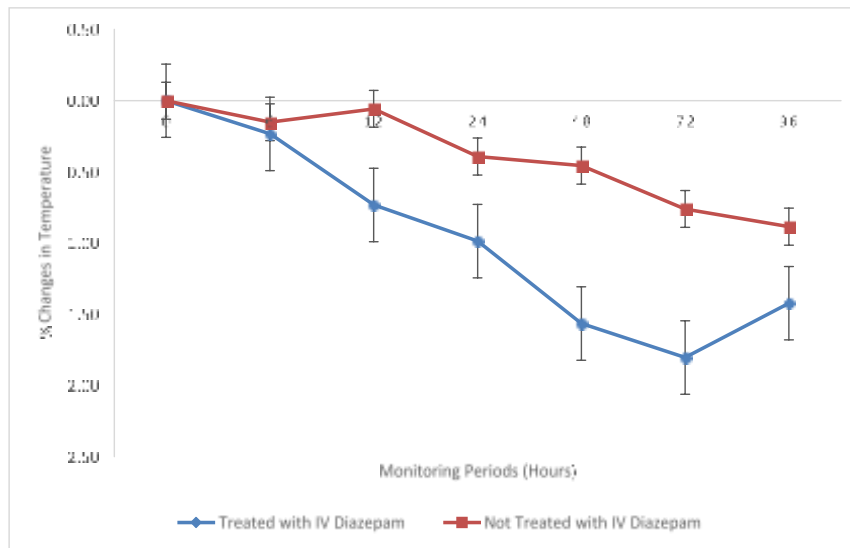


Figure 3b: Decline in body Temperature of patients treated with or without IV Diazepam based on the presence or absence of Multiple Convulsion

Figure 3: Effect of Diazepam on Blantyre Coma Scale (BCS) Score Provement and Temperature Decline

Table 4: Final outcomes of patients treated with different medications

Antimalarial Medication	Duration of Hospital Stay (Days) (Mean \pm SD)	Patients' Final Status – n (%)					Total Number of Patients
		Discharged Successfully	Referred with Neurological Sequelae	Referred with Other Conditions	Declined Further Treatment	Dead	
Antimalaria							
IV-Artesunate	4.2 \pm 2.4	24 (55.8)	6 (14.0)	7 (16.2)	3 (7.0)	3 (7.0)	43 (100.0)
IV-Quinine	6.2 \pm 3.5	5 (83.3)	1 (16.7)	-	-	-	6 (100.0)
Artesunate \rightarrow Quinine	5.6 \pm 3.4	6 (54.5)	2 (18.2)	-	-	3 (27.3)	11 (100.0)
<i>Total</i>	4.8 \pm 2.8	35 (58.3)	9 (15.0)	7 (11.7)	3 (5.0)	6 (10.0)	60 (100.0)
Antibiotic							
Ceftriaxone	4.6 \pm 2.8	24 (57.1)	6 (14.3)	4 (9.5)	3 (7.1)	5 (12.0)	42 (100.0)
Others*	4.8 \pm 2.8	11 (61.1)	3 (16.7)	3 (16.7)	-	1 (5.6)	18 (100.0)
<i>Total</i>	4.8 \pm 2.8	35 (58.3)	9 (15.0)	7 (11.7)	3 (5.0)	6 (10.0)	60 (100.0)
Anticonvulsant ^a							
Treated with Diazepam	4.8 \pm 2.5	28 (59.6)	7 (14.9)	5 (10.6)	2 (4.3)	5 (10.6)	47 (100.0)
Not Treated with Diazepam	4.3 \pm 3.6	7 (58.3)	2 (15.4)	2 (15.4)	1 (7.7)	1 (7.7)	13 (100.0)
<i>Total</i>	4.8 \pm 2.8	35 (58.3)	9 (15.0)	7 (11.7)	3 (5.0)	6 (10.0)	60 (100.0)

IV=Intravenous; *Chloramphenicol+Crystalline Penicillin or Cefuroxime+Metronidazole; ^a Patients presented with multiple convulsion were treated with diazepam; Artesunate \rightarrow Quinine = IV Artesunate Switched to IV Quinine after 12 hours.

Discussion

The result of this study shows that the patients evaluated were approximately three-years-old, reflecting the population choice of this study which is children that are not more than five-years-old. Most of the patients were also observed to be underweight which could reflect the effect of the disease on the patients or the low socioeconomic status of the people in this region. Majority of the patients belong to the male gender. This could mean that a male child is more susceptible to cerebral malaria in this region. A similar study conducted in this region reported a similar

finding (Abdullahi *et al.*, 2009). The fact that the parents of the patients were observed to be low-income earners with the highest level of education being Secondary Education reflects the low economic status and low literacy level of the people in this region (Countrymeters, 2020).

The patients were reported to have spent about five days with their current illness, most of which were given a home-based treatment before they were brought to the hospital with the severe form of the disease. Delay in hospital visit must have contributed

to worsening the disease state while the home-based treatment was more likely to be inappropriate which also must have contributed to worsening the patients' condition. This exposes the need for public enlightenment on the dangers of delaying hospital visitation especially with regards to children's ailments, in a malaria-endemic area like this sub-Saharan country. Some studies have reported the link between home-based malaria management and poor patients' outcomes like increase in mortality (Hopkins *et al.*, 2007; Orimadegun *et al.*, 2008).

Each patient was observed to present with approximately three features of cerebral malaria. The most common features were prostration, impaired consciousness, multiple convulsions and respiratory distress. A study previously conducted in this region of Sokoto reported similar findings (Jiya *et al.*, 2008). Other baseline clinical features of the patients were low BCS score, elevated temperature and low PCV. These are among the clinical consequences of severe (cerebral) malaria which were reported in several studies to be associated with poor prognosis and higher mortality (Rahman *et al.*, 2001; von Seidlein *et al.*, 2012). The clinical features observed among these patients on admission show the need for emergency and 'aggressive' approach in managing these patients with the best possible therapeutic alternatives to minimise the morbidity and mortality of the disease.

Majority of the patients in this setting were observed to be treated with Artesunate + Ceftriaxone + Diazepam combination. This could be because of physicians' experience, or most likely, because of WHO recommendations for the treatment of cerebral malaria (WHO, 2012, 2015). In the recommendations, IV Artesunate was the

preferred antimalaria, broad-spectrum antibiotic like the ceftriaxone as well as parenteral Diazepam (for patients with multiple convulsion) were recommended for this kind of case. Other adjuvants like IV Dextrose Saline and IV Dextrose were used based on the WHO recommendations.

Clinical Outcomes of treatment were observed to vary based on the drugs used. Effects of different drugs on patients' Intermediate Outcomes (improvement in BCS scores and decline in their body temperatures) as well as their Final Outcomes (duration of hospital stay, discharge rate, neurological sequelae and mortality rate) were reported in the results.

Patients treated with IV Quinine were observed to have better improvement in their BCS score and decline in their body temperature compared to their counterparts on IV Artesunate. This could suggest that IV Quinine is a better antimalaria for the treatment of cerebral malaria. However, a large Artesunate-Quinine trial conducted in nine African countries, Nigeria inclusive, suggested that Artesunate has better outcomes including improvement in BCS score (Dondorp *et al.*, 2010). The difference in these findings could be attributed to the development of resistance to Artesunate. This is because, there are growing concerns about the development of resistance to Artemisinin derivatives for the treatment of malaria (Phyo *et al.*, 2018; Tyagi *et al.*, 2018).

Furthermore, it was observed that patients that were initially treated with IV Artesunate then switched to IV Quinine had the worse trends of BCS improvement (before switching to IV Quinine) and temperature decline. This could be because the patients had treatment failure with IV Artesunate,

hence treated as a refractory case with IV Quinine. The apparent treatment failure could be as a result of resistance to Artesunate.

The finding of this study also shows that patients that received IV Ceftriaxone in addition to IV Artesunate or IV Quinine had better improvement in BCS score and decline in temperature compare to those on other antibiotics (Chloramphenicol + Crystalline Penicillin or Cefuroxime + Metronidazole). This finding suggests that antibiotics are beneficial to patients with cerebral malaria probably because of the co-existence of bacterial infection among the patients. This is the reason why the WHO recommended the use of broad-spectrum antibiotic empirically (WHO, 2012, 2015) pending the availability of blood culture result which is difficult to obtain in this resource-limited setting. Hence, the finding of this study also suggests that the bacteria infecting children with cerebral malaria in this setting are more sensitive to Ceftriaxone, hence the antibiotic of choice.

Patients that presented with multiple convulsion were treated with IV Diazepam in addition to an antimalaria and antibiotic. These patients were observed to have better improvement in BCS and decline in body temperature compared to those that had no multiple convulsion (not treated with IV Diazepam). This finding shows the importance of Diazepam in the recovery of children with cerebral malaria. Further studies that would investigate the relationship between Diazepam and decline in body temperature shall consolidate the finding of this study.

Notwithstanding the effects of antimalaria, antibiotic and diazepam on the intermediate outcomes (BCS score and temperature) of these patients, the result also shows the

effects of different drugs on the final outcomes (duration of hospital stay, discharge rate, neurological sequelae and mortality rate) of the patients.

The average duration of hospital stay of the patients was observed to be five days. This could be used to predict the expected recovery period of patients with cerebral malaria. Duration of illness before admission was observed to prolong patients' duration of hospital stay. A study conducted in Nigeria also reported a similar finding (Orimadegun *et al.*, 2008). Other factors that prolong patients' duration of hospital stay were the number of skipped antimalarial doses, which could be due to resistance development, and the number of other medications. These factors should be considered in managing children with cerebral malaria to minimise their duration of hospital stay.

Patients treated with IV Artesunate were observed to have a shorter duration of hospital stay compared to those on IV Quinine. This may be due to the faster action of Artesunate, as an artemisinin derivative (Ukwe, 2012). The trend of decline in body temperature of patients on IV Artesunate was observed in this study to be faster in the first 24 hours compared to their counterparts on IV Quinine. This also supports the faster action of IV Artesunate compared to IV Quinine. The shorter duration of hospital stay of patients on IV Artesunate could also be because it is administered for a shorter period than IV Quinine. Some studies reported similar findings (El Ket *et al.*, 2019).

More than half of the patients were observed to be successfully discharged. Others were referred to other facilities with neurological sequelae or other conditions while few of them died. This is a reflection of the

prognosis of cerebral malaria in the facility. The difference in treatments appears to have some effect on the prognosis.

It was observed that patients treated with IV Quinine from the beginning had a higher discharge rate. This is unlike what was reported in some studies that patients on IV Artesunate had a higher discharge rate (Keene *et al.*, 2018), while others reported no difference in the discharge rate of IV Quinine and Artesunate (El Ket *et al.*, 2019). From the design of this study, it is difficult to strongly state that patients on Quinine will always have better discharge tendency than their Artesunate counterparts. However, the finding shows that there is a strong indication that the discharge rate of patients on Quinine could be higher.

Patients initially treated with IV Artesunate were observed to have a higher proportion of those that had neurological sequelae or died compared to their counterparts on IV Quinine. In terms of neurological sequelae, a study reported a similar finding (Sinclair *et al.*, 2012) while some reported having observed no difference (Jones *et al.*, 2007; Dondorp *et al.*, 2010). In terms of mortality, Artesunate was mostly reported to be associated with a lower risk of death (Dondorp *et al.*, 2010; Sinclair *et al.*, 2012; Keene *et al.*, 2018) which is unlike the finding of this study. However, few studies reported no difference in the risk of death between patients on Artesunate compared to those on Quinine (El Ket *et al.*, 2019). Although the finding of this study is not sufficient to establish an absolute superiority of Quinine over Artesunate, Quinine may be a very good option, especially in resource-limited areas. Further studies are required to substantiate this finding.

The result of this study did not show clear differences between the prognosis of patients on different antibiotics and those treated with or without diazepam. This suggests that their effect on treatment is largely on the intermediate outcomes of treatment (BCS score and temperature) rather than the final outcomes. Further studies are required to evaluate the impact of these drugs on the prognosis of the patients.

The limitations of this study include the fact that it is single-centred. A multi-centred study would have provided more information about the treatment outcomes and generalising the findings may have been possible. Also, the decision to administer a particular drug to patients was conveniently done, which partly contributed to a lack of balance in the number of patients on each treatment group. Randomisation would have minimised possible selection bias. However, despite these limitations, some treatment interventions were observed to lead to better patients' outcomes. These findings will help clinicians in making better therapeutic decisions, hence the ultimate goal of this study.

Patients treated with IV Quinine had better recovery from coma (improvement in BCS score), a better decline in body temperature, higher discharge rate, a lower rate of neurological sequelae and mortality rate but with longer duration of hospital stay compared to those on IV Artesunate. Despite the WHO's recommendation of IV Artesunate as first-line antimalaria in the management of cerebral malaria due to its advantages, clinicians should still consider IV Quinine as a very good option. Also, patients on antibiotics especially ceftriaxone, and diazepam had better recovery from coma (improvement in BCS score) and decline in

their body temperature. Longer duration of illness before admission and an increasing number of skipped antimalaria doses, as well as an increasing number of other medications, prolong patients' duration of hospital stay. The finding of this study should be considered in decision making for the management of children with cerebral malaria, in order to increase their survival and wellbeing.

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