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Assessment of Pre-Referral Treatment of Severe Malaria Among Children Seen at a Referral Health Facility in South-Western Nigeria

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ABSTRACT

Background: In settings where intravenous artesunate and supportive care cannot be guaranteed, timely and efficient administration of pre-referral antimalarial is crucial. The study aimed to determine the prevalence of pre-referral treatment of severe malaria, the type of pre-referral antimalarial given, and to determine the relationships between pre-referral treatment and outcomes of childhood severe malaria at a referral health facility.

Methods: This is a retrospective cross-sectional study which involved the review of clinical admission of children aged 1month to 15 years, referred from a health-facility due to suspected severe malaria and who had parasitological evidence of plasmodium falciparum. Diagnosis of severe malaria was made based on clinical features consistent with the World Health Organization (WHO) criteria.

Results: 109 medical records were reviewed. the children had a median (IQR) age of 2.0 (4.25) years. The subjects were predominantly male; 59 (54.1%). Forty-six (42.2%) received pre-referral antimalarial, intramuscular artemether was the most common pre-referral antimalarial drug recorded in 33 (30.3%) of the participants. None received rectal artesunate as a pre-referral antimalaria drug. Severe anaemia, prostration and cerebral malaria were the most frequent components of severe malaria occurring in 26 (23.9%), 24 (22.0%) and 23 (21.1%) participants respectively. Six (5.5%) of the participants died and all of them did not receive pre-referral antimalarial treatment There was a statistically significant relationship between pre-referral antimalarial treatment and disease outcome p= 0.024 as none of the children who died from severe malaria received pre-referral treatment.

Conclusions: The proportion of children with severe malaria who received pre-referral antimalarial was 42.2%. Intramuscular artemether was the most common pre-referral antimalarial given. Pre-referral antimalaria treatment reduces mortality associated with severe malaria in children.

Key words: Pre-referral Treatment, Childhood, Severe Malaria, Disease Outcome.

1. INTRODUCTION

Malaria is an infectious disease caused by the plasmodium species and it is transmitted through the bite of infected mosquitoes. Plasmodium falciparum is almost exclusively the cause of severe malaria and can lead to death.[1,2] Despite the ongoing global malaria control programme, severe malaria is still one of the leading causes of morbidity and mortality in children. Interventions such as indoor residual insecticidal spraying, use of long-lasting insecticide bed nets, prompt treatment with an effective anti-malarial and malaria vaccine for young children have the potential to reduce the burden of the disease.[3,4] Regrettably in 2022, according to the World Health Organization, Nigeria accounted for 38.5% of global malaria deaths in children aged less than 5 years. Children are at higher risk of developing the severe form of malaria because they have little effective immunity.[3] Earlier study reports that severe malaria accounted for about 21% of all malaria cases seen in children at a tertiary hospital.[5] The burden of severe malaria in children is a notable public health concern.

Severe malaria is a medical emergency, it is defined by clinical or laboratory evidence of organ dys-

function in the presence of P. falciparum asexual parasitaemia.[2,6] After a rapid clinical assessment and confirmation of diagnosis where feasible, immediate commencement of treatment with parenteral medication is necessary.[6] Intravenous Artesunate is the first treatment of choice for severe Plasmodium falciparum malaria.[6] However, in settings where effective antimalarial treatment, and supportive care cannot be guaranteed, it is expected that an initial (pre-referral) treatment be given to children with severe malaria before transferring the child(ren) to a higher level of healthcare where adequate post-referral case management can be provided.[6,7]

The Pre-referral treatment is an important strategy aimed at stabilizing the child's condition before transfer, thereby reducing disease morbidity, reducing childhood mortality and improving overall child health. The WHO recommends the pre-referral (single-dose) treatment options for children in descending order of preference, as intramuscular artesunate, intramuscular artemether and intramuscular quinine, however, where intramuscular injections are not available, children under 6 years should be administered a single dose of rectal artesunate.[6] The child should thereafter be transferred immediately to an appropriate health facility where the full treatment consisting of injectable antimalarial and oral artemisinin-based combination therapy (ACT) can be provided.

In children, the deaths from severe malaria are a result of pathophysiological derangements, [6,8,9] and the risk of death is greatest in the first 24 hours, hence stabilizing, prompt treatment and prevention of further deterioration are important in the management of severe malaria.[6,10,11] Timely and efficient administration of pre-referral treatment can prevent further deterioration and improve disease outcomes among the patients. However, we do not know about the practice of pre-referral antimalaria treatment and the impact of pre-referral antimalaria treatment on disease severity and outcome especially among children (a high-risk group) with severe malaria in Osogbo, Nigeria. To optimize community-based healthcare efforts in the management of childhood severe malaria, there is a need to assess the practice of pre-referral antimalarial treatment. The study therefore aimed to determine the prevalence of pre-referral treatment of severe malaria, the type of pre-referral antimalarial given, the pattern of presentation and to determine the relationships between pre-referral treatment and outcomes of childhood severe malaria at a referral health facility in south western Nigeria.

2. METHODOLOGY

2.1 Study Area

The study was conducted at a tertiary hospital in Nigeria. The hospital serves as a referral center to private, primary and secondary health care facilities in and around the city, including neighbouring states.

2.2 Ethical Consideration

Institutional ethical clearance was obtained from the UniOsun Institutional Review Board with protocol number UNIOSUNHREC2024/002B. Patients' information was kept confidential.

2.3 Study Design

This is a hospital-based cross-sectional retrospective study. It involved the review of clinical admission records from January 2021 to December 2023, focusing on children aged 1month to 15 years who had been to a health facility whom had referral notes and were referred on account of suspected severe malaria with parasitological evidence of plasmodium falciparum (at the referral; study centre). The diagnosis of severe malaria was made and documented by the attending physician, the diagnosis was validated by the researchers using the WHO criteria which was based on clinical features consistent with any of the following criteria (cerebral malaria, severe malaria anaemia, multiple convulsions, prostration, hypoglycaemia, acidosis, renal impairment, shock, pulmonary oedema, hyperparasitaemia, jaundice and significant bleeding) occurring in the absence of an alternative cause and in the presence of parasitaemia of the asexual form of P. falciparum.6 Children with severe malaria who had not been previously seen at any facility and/or without a referral letter were excluded. Children with severe malaria, who had other forms of diagnoses (infection with or without positive blood culture) were also excluded.

The study proforma was filled by the researchers using the information extracted from the patient's medical records.

The primary outcome of the study was the proportion of children with suspected severe malaria who received pre-referral antimalaria treatment i.e., a single-dose antimalarial treatment given prior to patient's referral. The secondary outcome was treatment outcome which included: survived without sequelae, survived with sequelae, discharge against medical advice and death. Outcome was determined at the point of discharge or death.

2.3 Clinical Definitions

Severe falciparum malaria: was defined based on WHO diagnostic criteria; as one or more life threatening complications occurring in the absence of an identified alternative cause and in the presence of P. falciparum asexual parasitaemia.[6]

Pre-referral malaria treatment: initial antimalaria treatment with any of intramuscular artesunate, rectal artesunate, intramuscular artemether and intramuscular quinine given to children with suspected severe malaria before transferring to a health facility where the full treatment can be provided.[6]

2.5 Data Collection Methods

The researcher and three doctors who had been trained on the audit procedure were involved in data collection. All the medical records (case notes) of children 1 month to 15 years admitted with the diagnosis of severe malaria were retrieved from the medical records of the hospital and reviewed. The data were collected using the study proforma and anonymized. The proformas were filled by the researchers; using the information extracted from the patients' medical records. Data obtained include the child's demographic characteristics (age, sex, parental occupation and parental highest level of education). The socio-economic classification was based on rank assessment of parental occupation and the level of education. The participants were classified into the upper class (I and II) middle class (III and IV) and lower class (V and VI) Symptoms of illness, place of referral, pre-referral antimalaria treatment given, type of severe malaria, malaria test(s), malaria treatment including supportive treatment administered and disease outcome were documented. Diagnosis of malaria was confirmed from the medical record by the identification of a positive microscopic test and or positive rapid diagnostic test for P. falciparum. The subjects were classified as having severe malaria based on clinical and/or laboratory findings according to WHO.6

All the participants received standard care for severe malaria in line with WHO recommendation.[6]

2.6 Data Management and Analysis

The data was entered into a personal computer and was analyzed using IBM Statistical Package for Social Sciences (SPSS) version 25.0. The demographic characteristics of the children were summarized using descriptive statistics. The participants' age was presented using median (IQR) because the data was skewed. Proportions and percentages were determined for children with severe malaria who received pre-referral antimalarial treatment, type of pre-referral treatment given, place of referral and disease outcome. The relationship between pre-referral treatment and disease outcome was determined using the Pearson chi- square test. Statistical significance was established when the "p- value" was < 0.05.

Availability of Data

The data supporting the findings of this study are openly available on Zenodo at https://doi.org/10.5281/zenodo.14602466.

3. RESULTS

A total of 3156 patients were admitted to the Children's Emergency Unit during the study period. One hundred and forty-five patients were admitted for severe malaria, however, only a total of 134 (92.4%) case records were retrieved, of which 109 (81.3%) patients met the study criteria and were studied.

3.1 Socio-Demographic and Referral Characteristics of the Participants

The age-group 1 month to 5 years accounted for 76.1% of the subjects. The median (IQR) age was 2.0 (4.25) years. There were 59 (54.1%) males, while 59 (54.1%) children belonged to the middle socio-economic class. The most common source of referral was private facilities and this accounted for 49.5% of the children. This is shown in Table 1.

Table 1: Socio-Demographic and Referral Characteristics of the Participants

Variables	Frequency (n=109)	Percentage (%)
Age		
1Month – 5 Years	83	76.1
6 – 10 Years	19	17.4
11 – 15 Years	7	6.4
Sex		
Male	59	54.1
Female	50	45.9
Socio-economic Status		
Upper	31	28.4
Middle	59	54.1
Lower	19	17.4
Source of Referral		
Primary Health Centre	32	29.4
Private Hospital	54	49.5
General Hospital	23	21.1
Received Pre-referral Antimalaria Treatment		
Yes	46	42.2
No	63	57.8
Pre-referral Drug Treatment		
Intramuscular Artesunate	13	11.9
IMntramuscular Artemether	33	30.3
Rectal Artesunate	0	0.0
Quinine	0	0.0
None	63	57.8

Table 2: Pattern of Severe Malaria Among the Participants

Features of Severe Malaria	Frequency (n=109)	Percentage (%)
Severe Anaemia	26	23.9
Prostration	24	22.0
Cerebral Malaria (CM)	23	21.1
Multiple Convulsion	16	14.7
Hyperparasitaemia	6	5.5
Acidosis	6	5.5
AKI*	4	3.7
Hypoglycaemia	2	1.8
CM and Anaemia	2	1.8

*AKI = Acute Kidney Injury

Forty-six (42.2%) received pre-referral antimalaria treatment. Intramuscular artemether was the most common pre-referral antimalaria drug administered to 33 (30.3%) children. None of the children received rectal artesunate or quinine as pre-referral antimalaria drug (Table 1)

Table 3: Duration of Hospital Stay and Outcome of Disease in the Participants

Variables	Frequency (n =109)	Percentage (%)
Duration of Hospital Stay (Days)		
<1	4	3.7
1 – 3	43	39.4
4 – 7	33	30.3
>7	29	26.6
Outcome		
Survived Without Sequelae	97	89.0
Survived With Sequelae	5	4.6
Death	6	5.5
DAMA	1	0.9

Note: Children who survived with sequelae =5 (loss of neck control;2, visual impairment;2, spastic disorder;1) n= number of children

3.2 Pattern of Severe Malaria Among the Participants

Severe anaemia, prostration and cerebral malaria were the most frequent components of severe malaria occurring in 26 (23.9%), 24 (22.0%) and 23 (21.1%) children respectively, while hypoglycaemia and acute kidney injury were the least common observed in 1.8% and 3.7% respectively. This is shown in Table 2.

3.3 Duration of Hospital Stay and Outcome of Disease

Forty-three (39.4%) of the participants were on admission for 1-3 days. Six (5.5%) of the all the children with severe malaria died. (Table 3)

3.4 Relationship Between Pre-Referral Treatment and Out-Come

All the children who received pre-referral antimalaria treatment survived (Table 4) This was statistically significant p= 0.009.

Table 4: Relationship Between Pre-referral Treatment and Outcome

Outcome	Pre-referral treatment (n=109)		Test statistics	P-value
	Yes (%)	No (%)		
Survived	46 (44.7)	57 (55.3)	$\chi 2 = 6.833$	0.009
Death	0 (0.0)	6 (100.0)		

4. DISCUSSION

This study shows that 42.2% of the children with severe malaria received pre-referral antimalaria treatment. The most common pre-referral antimalaria drug was intramuscular artemether followed

by intramuscular artesunate. Although intramuscular artesunate is the most preferred pre-referral intervention for malaria,[6] more participants received intramuscular artemether. This finding may suggest that artemether is more readily available or that the healthcare workers in the study community either find artemether easier to administer as it does not require reconstitutions compared to intramuscular artesunate. The use of artemether in this study is still consistent with WHO recommendation that in settings where intramuscular artesunate is not available, intramuscular artemether still remains a viable alternative.[6] Randomized trials in children comparing intramuscular artesunate and artemether as pre-referral treatment of severe malaria is not available. An earlier study done in adult patients in Vietnam showed that the median times to fever and time of parasite clearance were similar, nevertheless, intramuscular artesunate has considerable pharmacokinetic benefit over artemether in the treatment of severe falciparum malaria.[12] Artesunate is a water soluble drug and it is absorbed more rapidly when compared to artemether which is an oil-based drug whose absorption may fluctuate particularly among patients who are hypotensive or in shock.[12] This highlights the effectiveness of intramuscular artesunate as a first-line antimalarial drug. A previous study that compared artemether and artesunate injections to quinine showed that artemether shortens the time of parasite clearance and fever clearance[13] and artesunate reduced the death of severe malaria in African children by 22·5%.[14]

Other pre-referral treatment options such as rectal artesunate was not available in the community at the time of this study hence none of the participants received it. This finding is comparable with a previous Nigerian study done in 2019 after the introduction of rectal artesunate, it was observed that only 0.8% of the participants ever received rectal artesunate, with only a slight increase to 1.2% towards the end of 2021.[15] The use of rectal artesunate as a pre-referral treatment is not popular despite it being in the national guideline.[16] Pre-referral rectal artesunate for severe malaria has been reported as an effective malaria intervention particularly among children younger than 6 years whose access to malarial injections will take several hours.[17]

The common features of severe malaria among the studied children were severe anaemia, prostration and cerebral malaria. This pattern of presenting features is comparable with earlier Nigerian and Ghanaian studies who reported severe anaemia, respiratory distress, prostration and cerebral malaria as the common features in their cohort.[8,9,11] Severe anaemia and cerebral malaria have been reported to be common in areas hyperendemic for malaria such as Nigeria.[18] Although the causes of anaemia are multifactorial, the increased prevalence of severe anaemia in this study may be related to the increased number of children less than 5 years, it has been shown that severe malarial anaemia occurs more frequently in younger children.[11] Anaemia from nutritional deficiencies is common in this age group, the effect of malaria episode(s) will further worsen anaemia in these children. Malaria infestation causes an acute reduction in haemoglobin as a result of haemolysis of both the parasitized and non-parasitized red blood cells, also, there is bone marrow dyserythropoiesis which further worsens the anaemia.[18]

Some children with severe malaria are extremely weak and present with prostration. Malaria with prostration is an important sign which helps to identify those who require monitoring, and prompt treatment to prevent further complications. Prostration may precede impaired consciousness in some patients with cerebral malaria.6 Cerebral malaria is another feature of severe malaria which was reported in 21.1% of the children. This finding is similar to 19.7% reported by Orimadegun et al[11] and 21.6% by Edelu et al[8] but slightly lower than 24.4% reported by Odeyemi et al[5] all in southern Nigeria. The site of study being a referral centre may be partly responsible for the prevalence rate recorded, as severe forms of malaria are often seen in tertiary facilities. Also, children have partial immunity to malaria; many children are therefore at increased risk of cerebral malaria because they have not developed a sufficient level of specific acquired immunity to protect them from the malaria parasite.

The role of pre-referral antimalaria treatment in the management of childhood severe malaria cannot be over-emphasized as it reduces disease morbidity and/or disabilities thereby improving disease outcome.[6] In this study, all the children who died did not receive pre-referral antimalaria treatment. This finding is similar to an earlier study by Ilunga et al[19] who observed that there was a higher fold risk of mortality for children with severe malaria who did not receive pre-referral treatment compared to those who received initial treatment from health centres or hospitals. This demonstrates the benefit of receiving pre-referral antimalarial treatment in children with severe malaria and this has been corroborated by earlier reports which observed that pre-referral antimalarial treatment reduces childhood mortality and improves overall child health.[7,17] The benefit of pre-referral treatment appears to be consistent regardless of the route of administration of the artemisinin-based antimalarial used for the pre-referral treatment. While intramuscular artemether and intramuscular artesunate were used in our study, studies where rectal artesunate was used also revealed similar benefits.[7,17] Intramuscular artesunate achieves therapeutic plasma concentrations like the intravenous artesunate and it induces parasite clearance within hours in patients with severe malaria,[14,17,20] hence; the reason for its recommendation as alternative pre-referral treatment when intravenous artesunate is not feasible. In situation where intramuscular artesunate is not available intramuscular artemether is a safe alternative.

The present study shows that Child mortality from severe malaria is still fairly high. The non-usage of pre-referral antimalaria in the presence of severe disease contribute to the mortality recorded. This finding highlights the importance of pre-referral antimalarial treatment as an intervention necessary to reduce malaria death. There is a need for health workers to ensure that all children with severe malaria who require transfer to a higher facility of care should receive pre-referral antimalarial.[6]

4.1 Conclusion

The study shows that 42.2% of the children with severe malaria received pre-referral antimalaria, with intramuscular artemether being the most common pre-referral antimalarial given. There was no mortality among children with severe malaria who receive pre-referral antimalaria treatment.

4.2 Recommendation

We recommend that pre-referral antimalaria awareness campaigns be done at the community level and the practice should be encouraged by all health care workers in facilities where access to intravenous artesunate and supportive care for severe malaria is unavailable. The use of feedback to the referring centres as a

mean of enhancing good pre-referral malaria treatment practices should be encouraged.

Contributor Roles Taxonomy (CRediT) Statement

OAO; conceptualization, data acquisition, data analysis, validation and writing of initial draft

OSO, OFA and ATO; validation, reviewing and editing the content of the manuscript.

ARG and ATE; data acquisition, validation and reviewing of the manuscript.

Study Limitation

Due to the retrospective nature of the study, the health care workers who referred the patients were not interviewed, this might have helped to determine the reason (s) for their choice of referral drug. The time of administration of pre-referral drug was not documented in the referral notes, this may be useful in determining the effect of timing of antimalarial administration on the disease outcome.

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Conflicts of Interest:

The authors declare that they have no conflict of interest.

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