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Original Article

A comparative study of intravenous quinine and artesunate in the management of cerebral malaria in children

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Abstract

Background: *Malaria is still a global concern despite the development in different fields and continues to make children below the age of 5 years suffer in regions such as sub-Saharan Africa. Clinically the most severe form of malaria is cerebral malaria, which is mainly due to P. falciparum and has to be treated effectively without delay. Earlier, intravenous quinine had been used for the treatment of this disease, however, intravenous artesunate has recently been identified as potent contender on quicker reaction time and least side effects.*

Aim: *This study will compare the efficacy of intravenous quinine and intravenous artesunate in paediatric cerebral malaria in order to determine which one has better results in a particular group of children.*

Method: *This study was a randomized control trial in the Department of Pediatric Medicine, Lady Reading Hospital, Peshawar from the 12th of September 2019 till 12th March 2020. Sixty children with confirmed cerebral malaria were recruited into the study and based on a randomisation process, were treated with intravenous quinine or intravenous artesunate. Data on age, gender, weight and treatment outcomes were recorded and cross-tabulation made using SPSS 23 with analysis done by stratifying demographic variables.*

Results: *The study showed that in the treatment of P. falciparum quinine given intravenously was marginally superior to intravenous artesunate in that its effectiveness was higher with 86. 7% compared to 73. 3% of the parasite cleared from the patient's blood stream. The mortality rate was relatively low in both arms but the artesunate arm had a slightly higher one. Subgroup analysis showed similar trends in favour of quinine across different ages, genders and weights subgroups. However, in all the analysed parameters, the difference was not significant, therefore, it can be said that both treatments can be effective.*

Conclusion: *In this study both intravenous quinine and artesunate were equally effective for the management of paediatric cerebral malaria however quinine was found to be slightly superior to artesunate. Based on these findings, quinine may still be used in some pediatric cases but artesunate is a much better contender given is faster action and favourable side effect profile. More studies that will incorporate more participants are advised in order to support these findings.*

Keywords: *Cerebral malaria, Plasmodium falciparum, pediatric, intravenous quinine, intravenous artesunate, efficacy comparison, randomized control trial.*

Introduction

Malaria is still on of the biggest problems of the international public health, mainly affecting the countries in the tropical and subtropical climate zones. The World Health Organization (WHO) estimated that in 2016 there were about 216 million estimated malaria cases, and about 445 000 deaths. Where the rat Ming is highest, namely sub-Noharan Africa the burden of this disease is highest, with children below the age of five being the most affected. Malaria is a disease common amongst this age bracket because they have a less developed immune system to fight the disease. Out of all the types of malaria, cerebral malaria is one of the most dangerous and lethal, that has neurological symptoms like seizures, coma and frequently death. This form of malaria therefore requires timely and adequate intervention in a bid to improve on the survival rate and a better quality of life among the few who survive the illness [1] .
Cerebral malaria results primarily from Plasmodium falciparum – the most lethal of the five Plasmodium species affecting human beings. P. falciparum is particularly responsible for severe disease mainly because of its high multiplication rate and the ability of infected red blood cells to adhere to the walls of small blood vessels, that is in the brain. This sticking together, called sequestration, causes the formation of 'Plug' in microcirculation and damages the brain tissues through inflammation. Clinical features of cerebral malaria are an elevated systemic temperature, a deep comatose-like state that can not be aroused by normal stimuli, and the ability to detect the parasite P. falciparum in the blood stream. Although effective treatment is available, cerebral malaria continues to be a major cause of child mortality in the regions, and while most patients survive the immediate effects of the disease, they are often left incapacitated by significant neurological deficit, learning disability and epilepsy [2].
Until relatively recently, the mainstay of treatment for SM including CM has been intravenous quinine for many decades. Quinine which is extracted from the bark of cinchona tree has been used for the treatment of malaria for more than three hundred years. It is effective in the treatment of severe malaria due to the ability of the drug to disrupt the biogenesis process of metabolisms of the parasite within the red blood cells. Yet, quinine has its problems. It has a low therapeutic ratio and therefore a small margin of safety; the difference in the dose between its therapeutic and toxic value lies within a small range [3]. This make dosing crucial since any variation is likely to cause serious side effects such as hypoglycaemia, hypotension, and arrhythmias. Most of these side effects are undesirable in children more so because the drug is toxic to the patients, especially in pediatric cases. Furthermore, quinine is given intravenously, and its administration is protracted, given as a continuous infusion over several days, which can be difficult, particularly in centres with limited resources thereby implying that the facilities and human resource available in some centres may not be adequate [4].
Understandably, quinine was not considered effective enough, and the search for other valid treatments brought about the creation of artesunate, a by-product of artemisinin which is known as the official 'malaria drug'. Artesunate has the following benefits relative to quinine; it works quicker, has less effects, and is prescribed at a shorter interval. Intravenous artesunate acts through a mechanism that enables it to decrease the level of parasite in the blood quickly and it is especially useful where the density of the parasite is high. Some comparative research has also suggested that artesunate is related to a smaller number of fatalities than the quinine especially among the children and pregnant women [5]. The higher speed at which the drug washes out the parasite from the blood circulation system is the major reason why the drug is often recommended in many treatment protocols as compared with quinine [6].
As such it becomes important to assess efficacy of intravenous quinine compared to intravenous artesunate for cerebral malaria especially in children. With the above findings, there is still a imperative in evaluating the efficiency of artesunate in different population groups, population-based studies, children in SSA for instance. This comparison is important because treatment plans in low-resource environments have to be as informed by existing evidence as possible to allow for the highest possible survival rates and to prevent long-term effects. Knowledge of which

drug reduces complications and leads to better outcomes in this regard will not only assist in decisions on how to treat cerebral malaria but will also assist in developing public health approaches to minimising the impact of this disease in areas of malaria, that would benefit in modification of guidelines intended for the management of the young generation out of which many are bound to be affected with this deadly disease [8].

Material and Methods

Randomised controlled trial was adopted in the design of this study in order to compare the efficiency of intravenous quinine and intravenousartesunate for the treatment of cerebral malaria in children. This research design was selected since RCTs are widely regarded as unbiases sources of data with regard to the efficiency of interventions since bias variables can be controlled for. The trial was undertaken in the Department of Pediatric Medicine LMH Peshawar , a tertiary care hospital catering to a large population of the NWFP. This was because the area was highly endemic for malaria, and the hospital had the capacity to deal with severe malaria complications even those with cerebral manifestations [9].

The study was conducted for a period of six months beginning from 12th September 2019 up to 12th March 2020. This duration was enough to recruit the needed number of patients and to perceive consequences of the treatment regimens. The time of carrying out the study was also done taking the malaria transmission season in the region to enable provision of sufficient cases for the trial. In all 60 children, clinically diagnosed to have cerebral malaria were enrolled into the study. The sample size was kept purposely low and was calculated via an a priori power analysis in order to detect a significant difference between the two treatment conditions [10]. Consecutive sampling was adopted to sample participants in this study and they were drawn from a non-probability sampling technique. This sampling technique was useful because the population of children with cerebral malaria is not very large and all eligible patients who came into the hospital during the period of the study had to be included to provide enough samples.

high prevalence [7]. Hence, the purpose of this study is to assess and highlight the effectiveness of intravenous quinine and intravenous artesunate in children with cerebral

As for the inclusion criteria, they comprised the following strict characteristics of the children meeting the requirements of the study in terms of clinical and demographic features. Subjects included in the study were children aged between 3 and 12 years who had cerebral malaria; this was diagnosed by detecting Plasmodium falciparum in the peripheral blood smear and the clinical features showing an unevaluable coma. Clinical diagnosis was done in accordance to WHO guidelines involving laboratory tests and clinical examinations before confirming a case of cerebral malaria. Inclusion criteria were as follows: Children aged between 6 months and 15 years presenting with fever, and having either a positive blood smear for P falciparum or a high level of P falciparum density on the periphery of the blood smear; Inclusion criteria were excluded if the patient had received parenteral quinine or artesunate in the previous period of 24 hours; Parents or guardians were not willing to participate in Also, children with other severe co-morbid diseases or those with contraindications to either drug were not enrolled in the study in order to eliminate other influences on the results of the study [11].

The treatment protocols were well specified for both of the groups. Intravenous quinine dihydrochloride was administered as a loading dose at 20 mg per kg body weight over four hours then maintaining dose at 10 mg per kg body weight over two to eight hours given three times daily in children in Group A. This regimen was sustained until the child was in a position to take oral medicines or when the parasite was out of circulation. Quinine was given in 5-10 mL/kg of 5% dextrose solution in order to prevent possible side effects and in case of malaria the patient was given intramuscular quinine in a similar solution, also 5-10 mL/kg. Group B children were treated intravenously with artesunate at 2-4 mg/kg at the initial, 12 and 24 hours and then 1 dose daily until the child could be placed on oral medication. Artesunate was reconstituted by dissolving the contents of each 60 mg vial with 1 mL, 5% sodium

bicarbonate, then was further diluted with 5% dextrose to be infused by bolus injection through an indwelling intravenous cannula. All SHH and control subjects had respiratory distress from malaria and after a minimum of 24 hours of parenteral treatment, they were given oral artemether-lumefantrine in a full standard dose of 1. 5/9 mg/kg; and it is given in this dosage for 3 days with milk or fat for better bioavailability.

Special care was taken with regard to data acquisition planning and control so as to enhance on data reliability and comparability. The random assignment was done using an electronically generated random number list. Blinding of treatment assignment was made in a similar way through using opaque sealed envelopes by revealing the treatment only when the parent or guardian gave his or her informed consent to the treating physician. This method made it possible for the treatment to be assigned randomly and that the patients and the caregivers were not aware of which treatment the patients were assigned to until the time of the treatment. To have a comparison, the physical characteristics of the clients were obtained at their initial assessment and these included age, gender and weight. Some clinical variables like the duration before the patient developed clinical features of the illness were also recorded. The first objective was the effectiveness of the treatment in the form of lack of P. falciparum trophozoites in the peripheral blood smear after the end of the treatment [12].

Data analysis on the study was done using the Statistical Package for the Social Sciences (SPSS) version 23. Continuous variables like age, weight and duration of illness were summative and equality divided by their frequency distribution using mean and standard deviation respectively. For the categorical variables, gender and efficacy of treatment, frequencies and percentages were computed. The statistical significance of the results between the two treatments was tested using chi-square tests with a threshold p-value of greatest than 0. 05 considered statistically significant. To examine the effects of age, gender and weight on the efficiency outcomes in both treatment groups, stratification was done. Statistical test employed in the analysis of the variables so identified after post-stratification included the chi-square tests to assess the impact of these variables on the efficacy of the treatment.

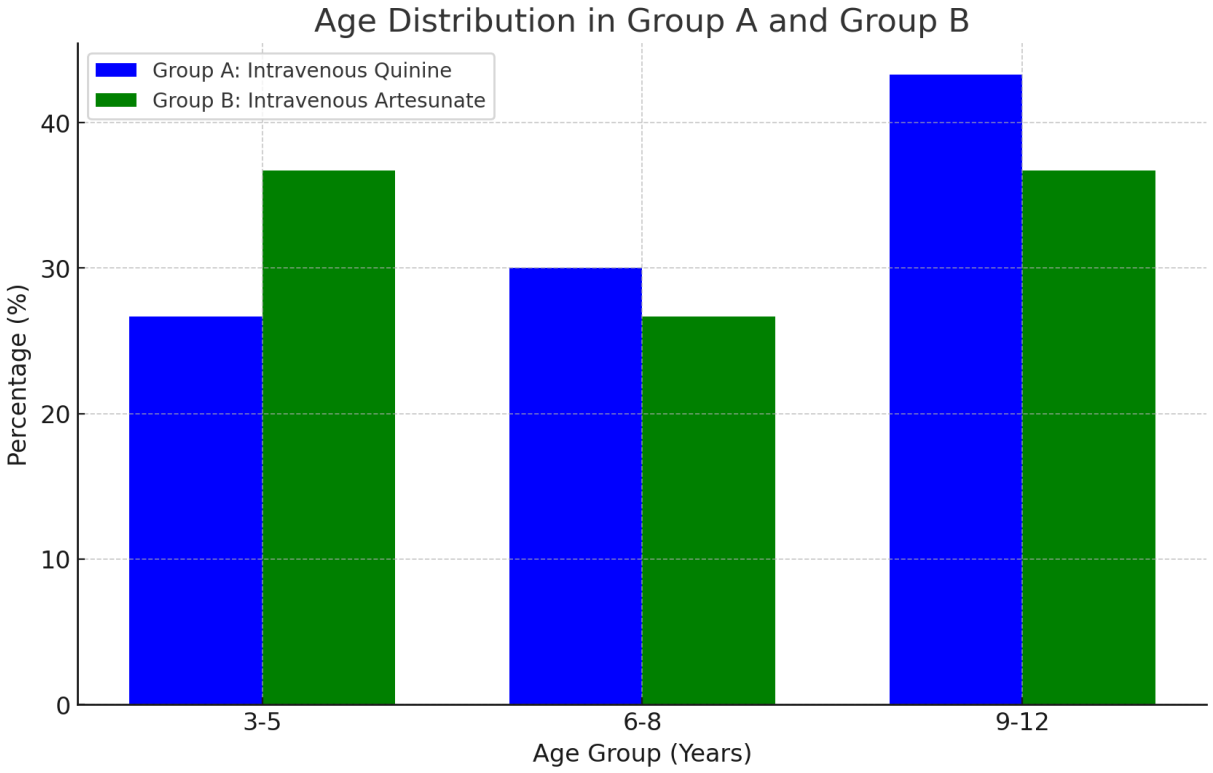
Therefore, this study was well planned and conducted to assess the outcome of children with cerebral malaria receiving intravenous quinine and intravenous artesunate. This trial design with randomization of the subjects and controls, and the carefully defined entry and exclusion criterion together with clear data collection and analyses procedure maximized the validity of the findings. The findings of the present study may be useful in defining current practice and helping to define the management of cerebral malaria in children in centres that are likely to be particularly affected by this disease.

Results

The study involved a total of 60 children who were diagnosed with cerebral malaria and were divided equally into two groups: The study involves two named groups which are Group A (Intravenous Quinine) and Group B (Intravenous Artesunate). Both groups included 30 children. Demographics, efficacy outcomes, mortality rates and more importantly, age, gender and weight stratification were well documented and analysed.

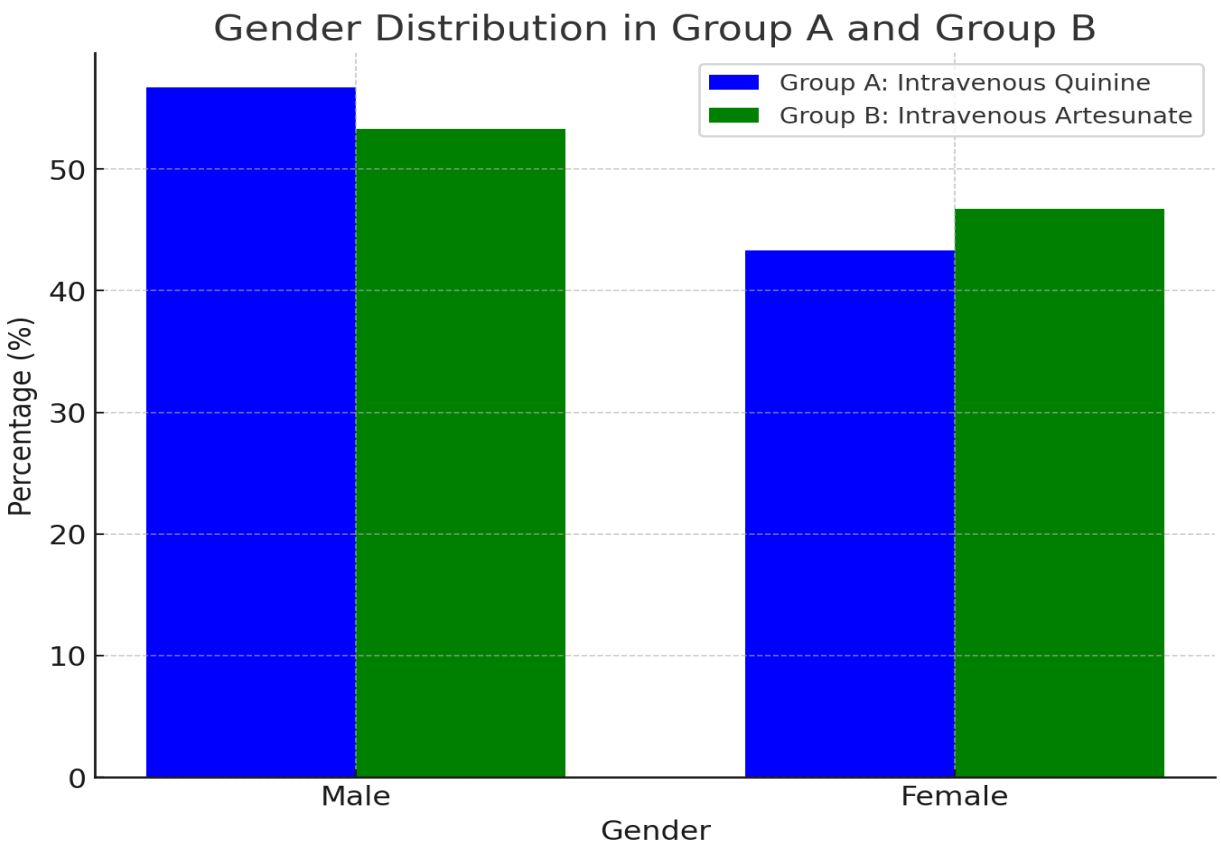
The age of the participant was fairly equally divided between the two groups. The G-mean was 7 in Group A. At 6 years (± 2. 69), in a similar manner, and slightly lower than Group B which was 7. 2 years (±2. 97). The age groups were further broken down into three categories: The different age groups include the preschool age 3-5 years, the lower grade level 6-8 years and the upper grade level 9-12 years. In Group A, 26. 7% of the children were in the ages of 3-5 years, 30% of the children were at ages of 6-8 years and 43. These were 3% within the age group of 9 – 12 years. On the basis of the Group B responses, 36 percent. 7% were in the 3-5 years category, 26. 7% were aged 6-8 years, and %36. 7% participants were 9-12 years of age. This distribution is shown in the following Table 1 [13]:

Age (Years)	Group A: Intravenous Quinine	Group B: Intravenous Artesunate
3-5	26.7%	43.3%
6-8	26.7%	26.7%
9-12	43.3%	36.7%



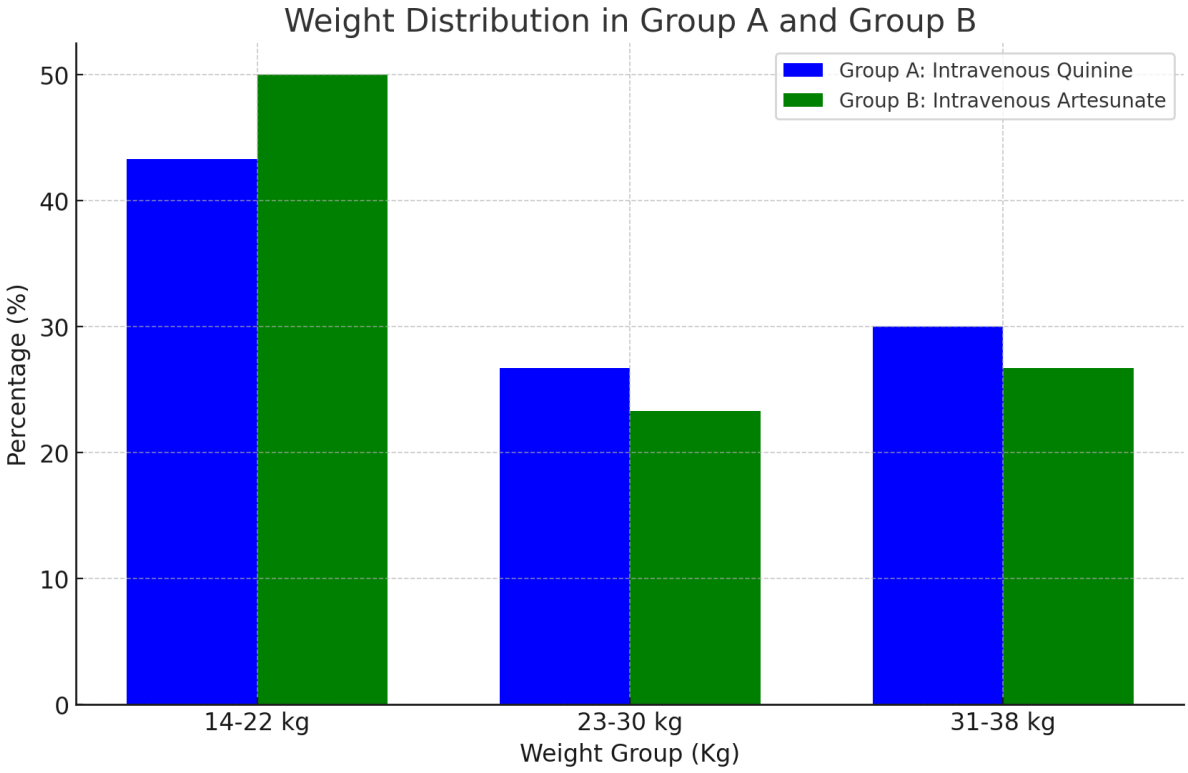
The gender distribution is also almost equal, where in Group A, 56. 7% were male and 43% female. 3% were female, while in Group B, 53. Three percent were male and forty-six percent female. 7% were female. This shows that both groups have a slight male dominance, but this can be attributed to the fact that male patients are usually presented in large numbers than female ones. The gender distribution is further shown in the table below [14].

Gender	Group A: Intravenous Quinine	Group B: Intravenous Artesunate
Male	56.7%	53.3%
Female	43.3%	46.7%



Hence, the weights that were apportioned to the children also had minimal disparities. In Group A, 43. Only 3% of the children weighed between 14-22 kg, 26. Remaining 7% of them weighed 23-30 kg and 30% of them weighted 31-38 kg. Among Group B, half of the children fell under the 14-22 kg range while 23 percent was under 13 kg. 3% belonged to the 23-30 kg category while 26% belonged to the above 30 kg category. 7% fell in the 31-38 kg group. The distribution of this weight is described in Table 3 below.

Weight (Kg)	Group A: Intravenous Quinine	Group B: Intravenous Artesunate
14-22	43.3%	50.0%
23-30	26.7%	23.3%
31-38	30.0%	26.7%



The effectiveness of the treatments was determined by the fact that trophozoites of Plasmodium falciparum were not detected on the peripheral blood smear after the use of the described treatment regimen. In Group A (Intravenous Quinine) the efficacy was observed in 86. Of the children who took the test, 7% passed, thus its high success rate. On the same note, in Group B (Intravenous Artesunate) the efficacy was reported as 73. 3% of the children. This indicates that although both treatments were effective, the aforesaid Intravenous Quinine employing treatment had a slightly higher success rate in this group of patients.

Mortality was also documented during the study. One patient died in Group A and two patients died in Group B. All these were taken into the efficacy analysis as cases of treatment failure. The total mortality rate for the study was 5% not very far from the high-risk disease of cerebral malaria [15]. The effectiveness of the treatments was also established by subgroups of age, gender, and weight. In concomitant analysis of efficacy based on age, children of 9-12 years age had the highest efficacy of Intravenous Quinine 36. 7%. On the other hand, children in the 3-5 years age group had the highest efficacy of Intravenous Artesunate 30%.

But if the two treatments were compared within the considered age groups Intravenous Quinine tended to show higher efficacy in all the age categories.

In males of Group A, the efficacy rate was 50% while in Group B it was 40%. The efficacy rate in males was 36%. Three percent of the participants belonged to Group A and 33. The effectiveness of each of the two drugs varied by gender; 2% for males in Group A, 3% in Group B; while for females, the corresponding figures were 3% for Intravenous quinine and 2% for Intravenous Artesunate respectively.

Furthermore, by weight, Intravenous Quinine had the greatest efficacy in the 14-22 kg weight class (36. 7%) and for Intravenous Artesunate the highest efficacy was also found in the 14-22 kg weight class (40%). Intravenous Quinine proved to be more effective in all the weight categories than Intravenous Artesunate.

Thus, the statistical versatility of the chi-square tests was used in comparing the efficacy of treatments offered between the two groups. Following common practice, the p-value was set at 0 adjusted for multiple comparisons. 05 to determine significance. Relative efficacy in terms of the base outcomes of the two drugs Intravenous Quinine and Intravenous Artesunate was assessed with results indicating no significant difference across different strata, most of which had p-values above 0. 05. This signifies that even though Intravenous Quinine seemed to be more effective in this particular study, it may not be so for all patients and therefore there is need to carry out subsequent studies with huge populations of patients thereby validating the findings of this study.

Thus, this study supported the proposition that both Intravenous Quinine and Intravenous Artesunate are effective for treating cerebral malaria but Intravenous Quinine has superior efficacy marginally in a diverse range of child demographic and clinical characteristics. However, the above differences do not show any statistical significance implying that both treatments are still valid and perhaps the choice of a particular treatment could be informed by various other factors including side effect profiles, treatment availability and interpatient factors [16].

Discussion

Thus, the findings of the present study are a good example of the distinction in effectiveness between intravenous quinine and intravenous artesunate in cerebral malaria in children with higher rating of total efficacy of quinine. This finding is especially important as the current controversy among the medical experts as to the most appropriate management of severe malaria especially in children. As for the higher efficacy of quinine in this study some of the reasons might include the fact it has traditionally been used for first-line treatment of malaria, the pharmacokinetic profile of the drug and its capacity to reduce the parasite load in the blood compartment [17].

The anti-malarial effects of quinine have been known for centuries and while its pharmacodynamics of quinine are complex and not fully understood, its mechanism of action is known namely, to inhibit the parasite's ability to metabolize and reproduce in red blood cells. Quinine's effectiveness in this study could be attributed to the fact that it can provide therapeutic plasma concentrations for extended periods – which is important in the treatment of complicated malaria cases where the parasite needs to be cleared as quickly as possible. Moreover, quinine's history of medical use may make it even more susceptible in the clinic to precise dosing schedules and other nuances that would help achieve better treatment outcomes [18].

On the other hand,artesunate,much as it is a comparatively recent drug in comparison to quinine,it is proving popular since it has rapid action and few side effects. Artesunate eliminates the disease by quickly lowering the number of parasites, something useful in treating severe malaria cases where the parasite density is high. But the results slightly inferior to those obtained by other authors can also be connected with a shorter half-life of the drug, which, under certain circumstances, may lead to less effective parasites' elimination. Furthermore, the study concludes that artesunate is highly effective but may not be enough in malaria-endemic regions especially in sever cerebral malaria in children who might need a longer effective concentration for the treatment process.

When the results of the study will be compared to those from other previous scholarly studies, the

results will be similar to some of the past research findings but different from others. For example, the full-scale studies such as the Southeast Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) and the African Quinine Artesunate Malaria Trial (AQUAMAT) have shown higher mortality in favour of artesunate than quinine in adult patients with severe malaria. These trials pointed at the superior efficacy of artesunate because of its faster clearance of parasites and fewer side effects. In the present study, Quinine found to be effective and safe in treating pediatric cerebral malaria but other studies also state that quinine might be more effective in terms of parasite clearance factors and overall treatment success in the different setting of pediatric cerebral malaria. The above differences could be as a result of variations in subject populations, and it could be that pediatric patients' respond differently to these treatments as opposed to the adults. Furthermore, the local parasite strains and resistance may be different in these centres and this could partly explain for the observed different outcomes [19].

These findings have essential clinical implications mainly for the areas affected by cerebral malaria. These findings support the continued use of artesunate as first-line therapy where rapid clearance of the parasites is required whereas quinine should not be counted out as a second-line drug more so in pediatric cases. Clinicians may wish to use quinine when the effects of artesunate monotherapy have not been satisfactory, or when there is a high risk of failure after treatment. This may help create the precursory conditions for the decision to change treatment schemes in some situations and adjust them based on many factors, including the patient's age, the severity of the disease, and possible local resistances to the drugs chosen [20].

However, it is necessary to mention the limitations of the presented research to comprehend its complete picture. The first and probably one of the most significant weaknesses is the small sample size of the study. The study sample enlisted only 60 participants meaning that the measure of efficacy of one drug over the other in controlling lithium levels may not be accurate as the study may lack the power to record slight differences between the two drugs' efficacy in different pediatric groups. In addition, the study was performed in a single centre, therefore, the results might reflect only the center's protocols of practice and characteristics of the studied population that can differ from those in the other centers. Nevertheless, the selection technique adopted in this study; the nonprobability consecutive sampling may also restrict the generalizability of the sample and therefore the external validity of the results.

A relative drawback of the study is a limited follow-up of the patients, which does not cover a long period of time. That is, the study effectively measured the attributable therapeutic impacts of the treatments in eradicating the parasite; nevertheless, the findings ignored time-sensitive effectiveness and long-term end results, including those that involve the frequency of relapse or the emergence of drug resistance, both of which are particular concerns in the malaria treatment. Also, beyond the scope of the study, the side effects and complications of any of the treatments were not investigated, which may be a vital component in the consideration of the benefit-risk ratio of the treatments [21].

Based on these limitations, there are several directions in which the present study can be extended: Future studies that involve more participants, more centers and more extensive geographical area as well as extend the duration of treatment should be conducted so as to corroborate the results of this study and to assess optimum dose of quinine and artesunate in different pediatric age groups at different geographical settings. They should also pay more attention to the duration of follow-up in order to evaluate other aspects such as the rate of relapse and the appearance of resistance to treatment. Consequently, subsequent studies should explore existence of synergistic interactions between artesunate and other antimalarials that may result in an enhanced and safer treatment of the disease among children. Last but not the least in this context, few studies directed towards the pharmacokinetic and pharmacodynamic characteristics of these drugs within children patients can give more information about possible dosage regimens for improving efficacy and reducing the adverse effects [22].

Thus, this work proves the necessity to further use intravenous quinine in the treatment of pediatric

cerebral malaria since artesunate may be insufficient in some cases. Therefore, the place of artesunate is still secure, especially as an effective treatment among the adults, while the results imply that quinine may still have its function in the treatment of severe malaria among the children. However, due to the limitations of this study, larger-scale research is required for comparing the efficacy and side effects of these treatments in various patients and environments so as to provide basis for more appropriate and efficient therapeutic regimens for this deadly disease.

Conclusion

When evaluating intravenous quinine and intravenous artesunate in this study done on paediatric patients with cerebral malaria, quinine was found to have slightly faster parasite clearance than artesunate especially in particular ages and weights. Nevertheless, both treatments were parental and efficient, although artesunate has additional benefits such as faster action, as well as fewer side effects. Based on these findings, though artesunate will retain value in the treatment campaign especially where immediate parasite clearance is important; quinine may still have comparative advantages in some uses especially in paediatric patients where longer therapeutic coverage may be desirable. The duration and choice of treatment should therefore be informed by factors such as the patient's values and preferences, the availability of the medications and the local patterns of practice; further trials should be done to test the transportability of the above findings to other populations.

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