Int.J.Curr.Microbiol.App.Sci (2024) *13*(11): 82-92

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 13 Number 11 (2024)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2024.1311.010

Efficacy of Twice Daily Quinine Regimen Versus Three Times Regimen in Treating Severe Complicated *Plasmodium falciparum* Malaria among Children

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Keywords

Malaria, Sever Malaria, *Plasmodium falciparum*, Quinine

Article Info

Received:
15 September 2024
Accepted:
20 October 2024
Available Online:
10 November 2024

A B S T R A C T

Malaria is a significant health problem in the tropics, with increasing morbidity and mortality. Children are the population group with the highest malaria case fatality rate. Severe. This will be the first study to investigate the efficacy of a twice-daily regimen versus the three-times daily quinine regimen in treating severe complicated *Plasmodium falciparum* malaria in Sudan. This was a prospective, cross-sectional, comparative hospital-based study. It was conducted in Wad Medani Pediatrics' Teaching Hospital in Gezeira state (Sudan).The study sample was divided into two groups: the first group was children who received quinine at a dose of 10 mg/kg three times a day, and the second group was those who received it at 10mg/kg twice a day. The groups were followed during their hospital stay for the differences in temperature drop, hypoglycemia, coma resolution, parasite clearance, recrudescence, and quinine side effects. 200 patients were included in this study. The mean age of presentation was 4.5 years. Fever was the most common presenting symptom in half of the patients (101 patients), 50.5%, but on examination, all the patients in the study group were febrile 100%. Low blood sugar levels were more common among the three times group in comparison with the twice daily group, 20% compared to 15% respectively on D1, 10% compared to only 2% on D2, Quinine side effects (chinqunism) were reported more frequently in quinine three times group than twice group 33% of patients of three times group developed vomiting and abdominal pain after starting of quinine on day 1,22%on D2,56 % develop tinnitus on D1,48 % on D2,38% on D3, Two patients develop transient visual loss for the 1st 2days. 20% develop tinnitus on D1,5% on D2. 19 % of patients of the times quinine group had parasite recrudescence during follow-up (appearance of symptoms of Malaria with positive blood film) two patients on day 14 and the remaining 17 patients on day 28 and the cause of this parasite recrudescence most probably was due to their poor compliance (missing the dose, stopping quinine prematurely when they felt an improvement of their children among those patients), comparing to only4 patients of twice group. Our study found no statistically significant differences between the two quinine regimens in fever remission time, parasite clearance, and coma resolution time. However, the twice-quinine regimen was associated with less chinqunism (quinine side effect) and a lower risk of hypoglycemia.

Introduction

Malaria in Africa is a significant health problem, with increasing morbidity and mortality. Each year, it is estimated that there are about 1 -billion reported cases of Malaria, which results in more than 1 million deaths (WHO, 2000). About 80% of these deaths occur among children aged below five years in sub-Saharan Africa. The highest malaria case fatality rate was in children (Elmardi *et al.,* 2009). Malaria is one of the most common and severe parasitic diseases worldwide. About 40% of the world's population lives in malaria-endemic areas (Breman, 2001). As per WHO (World Health Organization), Malaria is responsible for up to 500 million episodes of clinical infection and 2.7 million deaths every year.

Plasmodium falciparum is responsible for severe Malaria and deaths since the other malaria species rarely cause death or persistent complications (Guinovart *et al.,* 2006). Since 24 million pregnant women live in malaria-endemic areas, malarial infections are responsible for 3.5 million low birth-weight infants every year (Murphy and Breman, 2001). Children living in Africa bear the brunt of the disease, as they are exposed to Malaria frequently after birth and either die from complications or experience clinical episodes of infection for many years until the slow and erratic development of ant-malarial immunity (Murphy and Breman, 2001). This balance between acquiring immunity and developing severe disease has continued for thousands of years (Bisht *et al.,* 2015).

The typical symptoms of Malaria are fever, fatigue, vomiting, and headaches. In severe cases, it can cause jaundice, seizures, coma or death. Following the biting of mosquitoes, the symptoms usually begin ten to fifteen days later (Ligon, 2006). If Malaria is not appropriately treated, people may have recurrences of the disease months later (recrudescence) (Caraballo and King, 2014). In those who recently had a malaria infection, re-infection typically causes milder symptoms, but this partial immunity against Malaria will disappear over months to years if the person has no exposure to Malaria for a long period (Ligon, 2006).

Malaria is microscopically confirmed by examining blood films or by antigen-based rapid diagnostic tests (RDT) (World Health Organization, 2015). Although cerebral Malaria can be diagnosed by ophthalmoscopy examination (Bazie, 2024), microscopy is still the most commonly used method to detect Malaria. According to WHO, about 165 million blood films were examined for Malaria (Reyburn, 2010).

The anti-malarial mechanism of quinine is unknown. Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites. It is also gametocidal for Plasmodium vivax and malaria not falciparum. Quinine also has analgesic but not antipyretic properties (Frédérich *et al.,* 2002).

Over the years, quinine has been the mainstay in treating severe Malaria and is the first-line Drug in African countries (Cowman *et al.,* 2016).

Tinnitus, slight hearing impairment, headache and nausea. Hearing impairment is usually concentration-dependent and reversible. More severe manifestations include vertigo, vomiting, abdominal pain, diarrhoea, marked auditory loss, and loss of vision (Winstanley *et al.,* 2004; Ibrahim *et al.,* 2004).

General Objective

To determine the efficacy of twice quinine regimen versus eight hourly regimen in the treatment of severe complicated *Plasmodium falciparum* malaria among children in Wad Medani Pediatrics Teaching Hospital.

Specific Objectives

- Identify the degree of hypoglycemia in the first two days in both regimens of quinine use.
-Identify the fever remission time in both regimens.
-Determine the duration of coma resolution in both regimens.
-Identify the parasite clearance time in both regimens.
-Identify the percentage of recrudescence in both regimens.
-To compare quinine side effects (chinqunism) in the two groups.

Materials and Methods

Study Design

The study is a prospective, comparative, cross-sectional, hospital-based study.

Study Area

The study was conducted in Medani city in Wad Medani Pediatrics Teaching Hospital, a general pediatric hospital in Gezira state. It was established in March -1986) with a capacity of 150 beds: 8 in the HDU, 3 in the outpatient ward, and the rest in the inpatient beds.

It receives about 150-300 per day as outpatients from all areas—35078 patients per year (2018). Malaria cases were (12974)36% of patients per year. Total number of admission were (7242) patient. (2972) (41%) of the patients were in a severe malaria case. Medani is the capital of Gezira State.

Study Duration

The study was conducted from (April 2018 to August 2018).

Study Population

Children of all age groups diagnosed as severe *Plasmodium falciparum* malaria based on Clinical features of Malaria according to WHO criteria for diagnosis of severe complicated Malaria, with laboratory confirmation by BFFM or RDT admitted of Wad Medani Pediatrics Teaching Hospital.

Sample size

The Sample size was determined according to the formula below:

$N = z^2Pq\ D^2$

N= Sample size

Z= standard deviation taken as 1.96 at 95% confidence level.

P = Estimate prevalence

Q=1–P.

D= allowable error or level of precision required at 95%, is equal to 0.05.

Sample size = 223

Data Collection

Data was collected by a structured questionnaire which included:

Medical history: age, sex, residence, features of severe Malaria

Clinical examination: splenomegaly and clinical features of severe Malaria.

Investigations Records

Thick and thin blood smears were prepared and stained with Giemsa according to the WHO guidelines and studied by a medical laboratory technician and RDT (ICT for malaria antigen); RBG was done and classified as normal (> 40mg \l) or low (<40mg). Haemoglobin was taken using an auto-analyzer machine (haematological analyzer systemic).

Haemoglobin is classified as low (< 10 gm), normal (> 10 gm), or very low (< 5 gm).

For this phase of the study, patients were classified into two groups; the first group was children who received the standard dose of quinine 10 mg \kg body weight three times for ten days. The 2nd group was those who received 10mg\ kg twice a day for ten days.

Quinine was given under strict supervision, first by intravenous infusion in 5%dextrose solution over 4 hours, and when the patient could tolerate it, therapy was continued orally in the form of tablets.

During their stay in the hospital, all patients were asked daily about the expected side effects of quinine (tinnitus, vomiting and abdominal pain). Axillary temperature was recorded every 8 hours (attempt charts) until it dropped to normal (37.5 °C), and then followed up on days 7, 14 and 28.

Parasite clearance times were followed, and the blood films were repeated every 24 hours until two consecutive films were negative (day 3), then on day 14 (if symptoms and signs of Malaria were present), and then on day 28.

Random blood glucose was measured on admission and then on day 3.

Coma resolution time was monitored using the Glasgow coma scale. After discharge, children of both groups were followed by asking them about symptoms and signs of Malaria on days 7, 14 and 28. If present, a blood film was done, or RDT was searched for recrudescence.

Statistical Analysis

The computer analyzed the collected data using Statistical Package for Social Science (SPSS) version (Freedman *et al.,* 2008), Anova style. The results obtained were presented in tables. The level of significance was considered if P- value < 0.05.

Ethical Consideration

The study was presented to the ethics review committee of the Sudan Medical Specialization Board, Council of Pediatrics and Child Health for approval.

Verbal consent was obtained from the hospital administrator and the mothers/caregivers accompanying the infant.

Results and Discussion

During five months, 223 patients were diagnosed with severe *Plasmodium falciparum* malaria according to WHO criteria of diagnosis (Burrows and Wells, 2016), who were included in this study. Twenty-three patients were excluded from the study because they lost follow-up, so the exact number of study children was 200 (100 patients received quinine three times (three-time group), and 100 patients received quinine twice (twice group)). The mean age of presentation was 4.5 years, with under five groups being the most common age group, 86(43%) patients, with a male: female ratio was 1.1:1. Regarding residence, 109 (54%) patients from urban areas and 91(45.5%) patient from a rural area (Table 1 P.value=0.49).

Regarding presenting symptoms and signs in table 2,101 patients (50.5%) had fever, followed by fever and convulsions in 46 patients (23%), only central nervous system symptoms (coma) in 29(14.5%)patients, Gastrointestinal tract (GIT)symptoms alone in 16 (8%)patient and GIT symptoms with fever in 7 (3.5%) patients. Pallor was found in 110(55%) patients, 17 (8.5%) patients had low blood pressure, and palpable spleen was seen in 170(85%) patients.

In Table 3, as per the WHO level of the parasite, parasitemia (+++) was found in 93(46.5%)patients, followed by 45 (22.5%) patients had (++++), and 62(31%) patients had (++).

In Tables 3 and 4, 35(17.5%) of the studied patients had low random blood glucose on admission (RBG less than 2.2 mmol, 40 mg|dl), 20 (20%) of them belonged to the three-time quinine group, and 15 (15%) patients belonged to the twice-time quinine group. Regarding haemoglobin level, 110 (55%) patients had low haemoglobin.

In Table 5, fever remission within 24 hours occurs in 38(38%) patients in the time quinine group and 60(60%) patients in the time quinine group. Fever remission within 36 hours from starting quinine was found in 31(31%) patients of both studied groups, while fever remission within 48 hours after starting treatment with quinine was found in 21 (21%)patients of three times quinine group and 7(7%)patients of twice quinine group, and fever remission in more than 48hours from starting quinine was found in 10(10%) patients of three times quinine group, and in two (2%) patients of twice quinine group, p-Value = .05. Table 9.

Concerning parasite clearance time in Table 6, those patients twice quinine per day, group had parasite clearance within 36 hours in 54(54%) patients, 26 (26%) patients had parasite clearance within 24 hrs, and 20 (20%) patients had parasite clearance in 48hrs. patients on three times quinine group showed 19(19%) patients had parasite clearance in 24 hrs, 40(40%) patients in 36 hrs and 41(41%) patients in 48 hrs, (p-Value = 0.43).

Regarding follow-up of fever in patients of both study groups, in Table 7, fever was present in all patients on day 1 of treatment and in 38(38%) patients in both groups on day 2. No fever was documented in all patients in both study groups on days 3 and 7. Two (2%) patients in both study groups became febrile by day 14, and on day 28 of hospital admission and completed malaria treatment, 17(17%) patients from 3 times quinine and 2 (2%) patients from twice quinine developed fever. Regarding quinine side effects (Table 8): 33 (33%) of patients of the three-times quinine group developed vomiting and abdominal pain on day 1,22(22%) patients on Day 2, 56 (56 %) patients developed tinnitus on Day 1, 48 (48%) patients on Day 2, 38 (38%)patients on Day 3, and two (2%)patients developed transient visual loss (pvalue = 0.53).

Table.1 Demographic data of patients

Variable		Number	%
Age	<1 year old	28	14
	1-5 year old	86	43
	5-10years old	54	27
	>10 years old	32	16
Sex	Male	98	49
	Female	102	51
Residences	Rural area	91	45.5
	Urban area	109	54.5

Table.2 Symptoms and Signs of Malaria at presentation

Variables		Number	%
Symptoms at presentation	Fever only	101	50.5
	GIT symptoms only	16	8
	CNS symptoms only-Coma	29	14.5
	GIT symptoms and fever	7	3.5
	CNS symptoms and fever	46	23
	Bleeding	1	0.5
Consciousness level	Comatose	29	14.4
	conscious	171	85.5
Pallor	Pale	110	55
	Not pale	90	45
Blood Pressure	Normal Blood Pressure	183	91.5
	Low Blood Pressure	17	8.5
Splenomegaly	Yes	170	85
	No	30	15

Table.3 Investigations during admission to the hospital

Variable		Number	%
Parasitemia level as per WHO	++	62	31
	+++	93	46.5
	++++	45	22.5
Hemoglobin level	Normal	110	55
	Low	90	45
Blood glucose level	Normal	35	17.5
	Low	165	82.5

Table.4 Distribution of random blood glucose on admission between two studied groups in the study period

	Three times group		Twice group	
	Frequency	Percent	Frequency	Percent
Normal	80	80%	85	85%
Low	20	20%	15	15%
Total	100	100%	100	100%

Table.5 Fever remission time between two study groups during the study period

	Quinine 3times		Quinine twice	
	Frequency	Percent	Frequency	Percent
24 hrs.	38	38	60	60
36 hrs.	31	31	31	31
48 hrs.	21	21	7	7
> 48 hrs.	10	10	2	2
Total	100	100	100	100

P.value=0.05Fever remission time (S.D)=2.1day in G.A,1.6 day in G.B

Table.6 shows Parasite clearance time between two study groups during the study period

	Quinine 3times		Quinine twice	
	Frequency	Percent	Frequency	Percent
24 hrs.	19	19	26	26
36 hrs.	40	40	54	54
48 hrs.	41	41	20	20
Total	100	100	100	100

Table.7 Distribution of higher Temperatures in malaria patients in the two groups during 1st 3 days of admission within the study period

High Temperature in :	Group A: Quinine three times	Group B: Quinine twice
Day 1	100	100
Day 2	38	38
Day3	0	0
Day7	0	0
Day14	2	2
Day28	17	2

Table.8 Symptoms of quinine side effect (chinqunism) after starting quinine between the two groups

	Quinine three times group				Quinine twice group			
	Day1	Day 2	Day 3	Day 28	Day1	Day 2	Day 3	Day 28
Vomiting and Abdominal pain	33	22	0	0	29	16	3	0
Tinnitus	56	48	38	0	20	5	0	0
Visual loss	2	2	1	0	0	0	0	0

For Vomiting and abdominal pain P.value =0.001,for tinnitus P.value=.0.004, for visual loss =0.53

Table.9 Distribution of Positive Blood film in the two groups during follow-up (within the study period)

	Positive B.F in Group A: Quinine 3times	Positive B.F in Group B:Quinine twice
Day 1	100	100
Day 2	78	73
Day 3	0	0
Day 7	0	0
Day 14	2	2
Day 28	17	2

Table.10 Glasgow Coma Scale Follow-up Chart between two groups in the study period

	Glasgow Coma Scale (< 10)		Glasgow Coma Scale (11 - 15)		Glasgow Coma Scale (15)	
	Three times group	Twice group	Three times group	Twice group	Three times group	Twice group
Day 1	19	10	0	0	0	0
Day 2	2	1	9	3	8	7
Day 3	0	0	1	0	18	10
Day 28	0	0	0	0	19	10

In Twice quinine group, 29 (29%) developed vomiting and abdominal pain on Day1, 16(16 %) patients on Day 2, and three (3%) patients on Day3 (p. value.001),

Tinnitus was occurred in 20(20%) patients on Day1, and in 5(5%) patients on Day2, (P.value = .004)

In Table 9: All patients in both study group had positive blood film for Malaria on Day1 of starting treatment,78(78%) patients of those on three times quinine group and 73(73%) patients of twice quinine group still had positive blood film for Malaria on Day 2 and 7 of treatment, on day 3 of treatment in both study group no malaria in the blood film, two (2%) patients of both study groups on D14 had positive blood film for Malaria,17 (17%) patients of three times quinine group, and 2 (2%) patients from twice quinine group had positive blood film for Malaria.

In Table 10: Patients on twice quinine per day group showed that 10(10%) patients had G C S <10 on day 1, 1% on the day, 3(3%) patients had GCS (11-15) on day 2 of treatment, 7(7%) patients had GCS 15 on day 2 of treatment, 10(10%) patients had GCS 15 on day three and day 28 of treatment (p-Value 0.6). While three-time quinine group showed 19(19%) patients had GCS<10 on day 1, two(2%) patients had GCS < 10 on day 2, 9(9%) patients had GCS(11-15)on day 2, and one (1%) patient had GCS (11-15) on day 3. GCS 15 in 3 times quinine was found in 8(8%) patients on day 2, 18(18%) patients

on day 3 and 19(19%) patients on day 28.

Severe Malaria is a medical emergency and may rapidly progress to death.

Without prompt and appropriate treatment, the mortality of untreated severe Malaria can be 100%, but with anti-malarial treatment, the overall mortality falls to 15– 20% (WHO, 2016). This is the first study to investigate the efficacy of a twice-daily regimen versus the three-times daily quinine regimen in treating severe complicated *Plasmodium falciparum* malaria among children in Sudan.

The study groups were divided into two groups, with 100 patients in each group. The first group consisted of children who received quinine three times per day, labelled as the three-times group, and the second group consisted of those who received it twice per day, labelled as the twice group. In our study, the mean age of presentation was 4.5 years, with children under five being the most common age group, this is comparable to the study done in South Africa, which shows that children <5 years were the most affected age group Elmardi *et al.,* (2009). There was no significant difference in sex affection (p value= 0.49). The male-to-female ratio was 1.1:1. Usually, Malaria affects both sexes equally. This agrees with WHO malaria studies (Elmardi *et al.,* 2009; Gething *et al.,* 2010; Murphy and Breman, 2001). Adult females are more affected by Malaria than males (Elsharif Ahmed Bazie *et al.,* 2016).

Regarding residence, more than half of our patients in the study groups were from urban areas, 109 patients (54%); this is not statistically significant (P.value=.05); the geographic distribution of Malaria within large regions is complex (Network TMGE, 2008), which consistent to high temperatures and high humidity, along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding (Cui *et al.,* 2012). The presence of Malaria in an area requires a combination of high human population density, high anopheles mosquito population density and high transmission rates from humans to mosquitoes and from mosquitoes to humans (Freedman, 2008). All these factors are common in cities; this is not comparable to a study done on Southeast Asia, which shows that Malaria is more common in rural areas than in cities (Harper and Armelagos, 2010). It is comparable to the study done on Africa shows that, Malaria is present in both rural and urban areas (Akande and Musa, 2005).

The present study showed that fever was the most common presenting symptom. Half of the patients in the study groups 101 patients (50.5%) presented with fever, followed by fever and convulsion in 46 patients (23%), central nervous system symptoms (comma), 29 patients (14.5%), gastrointestinal tract symptoms (8%). After clinical examinations, all the patients in our study were febrile (100%). However, there was no significant difference between the two groups in fever remission time, but it seems to be slightly longer in the time's quinine group where (10 %) had fever remission time 72 hrs with mean fever remission time S.D(2.1) day compared to only two patients of twice group, fever remission time S.D (1.6 days)(P.value.05), also the parasite clearance time shorter in twice group, (P.value 0.43). Also, the two groups had no significant difference in coma resolution time (P.value =0.6). This is comparable with studies done by many authors Achan *et al.,* (2011); Adam *et al.,* (2004); (Kofoed *et al.,* 1999) revealed no significant differences between the two quinine regimens in fever remission time, parasite clearance, and coma resolution times. Low haemoglobin level was found in most of our study population, which is similar to El khalifa *et al.,* (2021) as they mentioned low haemoglobin is associated with Malaria infection in Sudan, although anaemia is not a marker for malaria diagnosis (El khalifa *et al.,* 2021).

The present study showed that chinqunism (quinine side effects) was reported more frequently in the three-times group than in the twice group, with more patients suffering from vomiting and abdominal pain after administration of quinine in three times(33%), (22%) on D1,2 respectively compared to (29%), (16%) in D1,2 respectively in twice quinine group (P-value 0.001). This percentage was statistically significant. This is in agreement with a study by a Yekaon in Uganda, which showed that quinine had significant tolerability problems, which may lead to poor compliance and, hence, poor therapeutic outcomes (Yeka, 2013). Although these side effects were more frequent in this group, it might be considered a subjective assessment of these two doses of quinine regimen. Nevertheless, even objective side effects were more frequent in the three times quinine group than twice time quinine group; for example, hypoglycaemia was seen more in the patients of the three times group (20%) of patients in D1 (10%) in D2 and this exacerbated by quinine therapy comparing to (15%) on D1, and only(2%) on D2 for twice group. (P.value=0.003), this percentage was statistically insignificant. This is comparable with a study done by

Elased and Playfair (1994), which showed that quinine stimulates insulin secretion, and in therapeutic doses, it can cause hypoglycemia. This can be more severe in patients with severe infection and pregnancy (Elased and Playfair, 1994). 2 patients in the times group developed transient visual loss for the first 2 days, resulting in a decrease in the frequency of quinine for them, although this is not statistically significant (P-value 0.530). Our results were similar to two studies by Winstanley *et al.,* (2004) and Ibrahim *et al.,* (2004) showing that quinine three times a day expresses high chinqunism compared to twice a day regimen.

The study showed that (19%) of patients in the time's quinine group had parasite recrudescence during follow-up, two patients on day 14 and 17 patients on day 28, and this was explained by their poor compliance (missing the dose, stopping quinine prematurely when they felt an improvement of their children clinical symptoms). In comparison, only four patients were in twice group, (P.value.05). This result is comparable to two studies done by two authors: Adam, and Achan, which show that both regimens of quinine were similar in effect (Adam *et al.,* 2004; Achan *et al.,* 2011) and parasite recrudescence (Bardají *et al.,* 2012). It differs from the Guinea Basso study, which showed that a three-quinine regimen was associated with a lower rate of recurrent infections on day 28 (6.3%) compared to the 10 mg/kg twice-daily regimen (16.1%) (Achan *et al.,* 2011; Kofoed *et al.,* 1999).

The twice-quinine regimen was used in Wad Medani Pediatrics Teaching Hospital for 20 years by one of the largest hospital units where many patients are employed in this unit. This study was done to determine the efficacy of this quinine regimen, and the result showed that there were no significant differences between the two quinine regimens in fever remission time, parasite clearance, and coma resolution times. Also, the twice quinine regimen had less Hinduism. In addition to the simplicity of twice the regimen, which is three times in nursing, this was the impression of hospital nursing staff and the patients, as well as ensuring good compliance.

There was no mortality in our studied groups, but after referencing the hospital's records, it was shown that there was no significant difference in mortality rate between the two quinine regimens.

In conclusion, quinine at dose 10 mg /kg twice a day for 7-10 days causes fewer subjective side effects and more simple than the standard three times regimen and therefore is likely to improve patient compliance. Also it has a lower risk of hypoglycemia (which is very important specially in the outpatient setting), and objective side effects such as tinnitus. There was no recorded mortality among the two groups during the study period.

Recommendations

This study showed that there is no difference in efficacy between the twice daily dose of quinine and the three times daily dose, more studies using larger sample size needed.

Acknowledgement

We would like to express our sincere gratitude and thankfulness to our supervisor Prof: ALI BABIKER HABOUR for his guidance, meticulous supervision, revising and discussing all aspects of this study. His valuable advices and comments are highly appreciated. Our great thanks also extend to all who contributed in a way or another for the success of this study.

Fund: No Fund

Author Contributions

Noura Abdelhalim Mohamed Ahmed: Investigation, formal analysis, writing—original draft. Ali Babiker Habour: Validation, methodology, writing—reviewing. Mohanad Yousif Nagmeldeen Mohamed:—Formal analysis, writing—review and editing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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How to cite this article:

Noura Abdelhalim Mohamed Ahmed, Ali Babiker Habour and Mohanad Yousif Nagmeldeen Mohamed. 2024. Efficacy of Twice Daily Quinine Regimen Versus Three Times Regimen in Treating Severe Complicated *Plasmodium falciparum* Malaria Among Children. *Int.J.Curr.Microbiol.App.Sci.* 13(11): 82-92.
doi: https://doi.org/10.20546/ijcmas.2024.1311.010