

VENTRICULAR TACHYARRHYTHMIA IN FALCIPARUM MALARIASunil Kumar Sharma¹, Pradeep Kumar Mohanty², Bhabagrahi Rath³, Suresh Chandra Sahoo⁴¹Associate Professor, Department of Cardiology, Veer Surendra Sai Institute of Higher Medical Science and Research, (VSSIMSAR), Burla.²Associate Professor, Department of General Medicine, Veer Surendra Sai Institute of Higher Medical Science and Research, (VSSIMSAR), Burla.³Associate Professor, Department of Pharmacology, Veer Surendra Sai Institute of Higher Medical Science and Research, (VSSIMSAR), Burla.⁴Professor and Head, Department of Cardiology, Veer Surendra Sai Institute of Higher Medical Science and Research, (VSSIMSAR), Burla.**ABSTRACT****BACKGROUND**

Cinchona alkaloids Quinidine, Quinine commonly used as anti-malarial are able to suppress ionic conductance through K⁺ Na⁺ Ca⁺⁺ channels in the membranes of a variety of different cells, blocking of outward membrane repolarising K⁺ current by quinidine can produce EADs and triggered rhythm in presence of low extracellular potassium. Hypokalaemia can occur early in treatment of malaria and is associated with prolonged repolarization. Hence presence of these two substrates can precipitate ventricular tachyarrhythmia in malaria.

The objectives of the study were to evaluate the occurrence of ventricular tachyarrhythmia and whether administration of quinine in dextrose solution is the precipitating factor for development of tachyarrhythmia by precipitating hypokalaemia.

MATERIALS AND METHODS

Present study was conducted in VSS Medical College now VSSIMASR Burla, Sambalpur, Odisha from June 1997 to Dec 2017. Severe falciparum malaria patients in the age group of 5 yrs. to more 70 years patient receiving quinine in dextrose solution and Artesunate IV or IM were observed for development of any sudden cardiac death, survivor cardiac arrest or VT. Serum potassium concentration and Q-Tc interval was measured in all cases.

RESULTS

234 cases of sudden cardiac death, survivor of cardiac arrest and VT were observed in patients receiving IV quinine but no event with Inj. Artesunate. Hypokalaemia and long Q-Tc was observed in all the cases developing ventricular tachyarrhythmia. Arrhythmia improved with rapid correction of potassium.

CONCLUSION

Current practice of administration of quinine in dextrose solution predisposes severe malaria to develop hypokalaemia. Hypokalaemia by prolonging repolarization predispose makes malaria patients susceptible to develop ventricular tachyarrhythmia in presence quinine. Hence quinine should not be used with dextrose solution and if it is essential to use, then early recognition and correction of hypokalaemia is essential to prevent ventricular tachyarrhythmia.

KEYWORDS

Severe malaria, Quinine, Hypokalaemia, Ventricular tachyarrhythmia.

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BACKGROUND

Severe malaria is a medical emergency requiring immediate administration of rapidly effective antimalarial drugs. In the largest randomised trials ever conducted in severe malaria, the artemisinin derivative artesunate proved to be markedly superior to quinine in the parenteral treatment of severe

malaria and is therefore now the treatment of choice for all patients.^{1,2} But Cinchona alkaloid Quinine and Quinidine has been the mainstay of antimalarial treatment of severe malaria for last several years but has now been overtaken by the artemisinin derivatives. Nevertheless, quinine is still widely available and extensively used, and it needs to be kept available in case artemisinin resistance worsens. According National drug policy for malaria 2013 either of Artesunate IV or IM Artemether IM or Quinine IV Infusion should be used irrespective of Chloroquine resistance status of the area.³ Quinine is preferred over more potent quinidine as antimalarial because Quinine rarely cause cardiac complications and QT prolongation is mild unless there is Acute overdose.⁴

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Corresponding Author:

Dr. Pradeep Kumar Mohanty,

Department of General Medicine,

Veer Surendra Sai Institute of Higher

Medical Science and Research, (VSSIMSAR), Burla.

E-mail: drpradeepmohanty@rediffmail.com

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There is abundant evidence that quinine and quinidine are able to suppress ionic conductance through K^+ Na^+ Ca^{++} channels in the membranes of a variety of different cell types^{5,6,7,8,9,10} Blocking effect of quinidine on the outward membrane repolarising K^+ current results in prolongation of the action potential which can cause Early after depolarizations (EADs) and triggered activity particularly when the extracellular K^+ concentration is low.¹¹

Even though not widely reported hypokalaemia can develop early during treatment of severe malaria because of GI manifestation, poor oral intake, quinine induced insulin secretion and IV dextrose administration to avoid hypoglycaemia. Hypokalaemia alone can cause prolongation of ventricular repolarisation by inhibition of outward potassium currents and often associated with increased propensity for early after depolarizations. In addition, shortened refractoriness and slowed conduction contribute to reduced excitation wavelength thereby facilitating re-entry. Thus, hypokalaemia by causing prolongation of ventricular depolarization sets the stage for occurrence of arrhythmia in malaria receiving quinine group of drugs which are known to induce EADs and triggered rhythm.

During the resurgence of falciparum malaria in early 90s with severe pernicious manifestation and emergence of chloroquine resistance IV quinine was frequently used and we encountered many cases of sudden death and ventricular. Tachycardia after wide availability of the artemisinin derivative artesunate in the first and second decade of 2000, the incidence of ventricular tachyarrhythmia has diminished raising the possibility that intravenous quinine in dextrose solution was probably responsible for occurrence of ventricular tachyarrhythmia in severe malaria.

Aims and Objectives-

This study was undertaken in our medical college hospital to find the reason for occurrence of tachyarrhythmia in falciparum malaria receiving quinine but not with the artemisinin derivative artesunate and suggest remedial measure to decrease the incidence of ventricular tachyarrhythmia.

MATERIALS AND METHODS

Present study was conducted in VSS Medical College now VSSIMASR Burla, Sambalpur, Odisha from June 1997 to Dec 2017. Data were also collected from nearby private hospital and clinical establishment with special reference to report occurrence of sudden death, ventricular tachyarrhythmia observed by them. As our institute is the only centre having dept. of Cardiology almost all the cases are referred here for further evaluation and treatment or the concerned physician take our opinion regarding such arrhythmia during treatment of severe malaria. Equal number of sick malaria patients receiving artesunate not manifesting with arrhythmia were included for any baseline ECG abnormality and electrolyte concentration as artesunate does not cause any significant cardiovascular abnormality.¹²

All the data are collected and stored for review by the faculties of dept. of cardiology. As this dept. caters to 24 hours emergency we get the opportunity to record all events occurring even in emergency hours so that we do not miss any events. Patients of all age groups from 5 years to more than 70 yrs and sex were analysed. Special care was taken to exclude patient with underlying heart disease, CKD or patient taking diuretic for any other indication which may influence interpretation.

Electrolytes were estimated by ISE (Ion selective electrode) method with fully automatic electrolyte analyser with special reference to sodium and potassium concentration. Calcium Magnesium concentration were also measured. Hyponatraemia was defined when Na concentration is less than 135 meq/L (135 mmol/L) with severe hyponatraemia less than 110 meq/l, hypernatraemia >145 meq/L. Hypokalaemia was defined by serum potassium less than 3.5 meq/L (3.5 mmol/l) hyperkalaemia when serum potassium >5.0 meq/L (5.0 mmol/L). Normal total plasma calcium concentration is 8.5 -10.5 mg/l (2.1-2.6 mmol/l) hypocalcaemia when serum calcium less than 8.5 mg/l (ionized calcium <4.6 mg/l (2.1 mmol/L and 1.15 mmol/L). hypercalcemia >10.5 mg/l (2.6 mmol/L). Normal magnesium concentration is 1.8-3.0 mg/l (0.75-1.25 mmol/l).¹³

12 lead ECG were done in all the cases. 12 lead ECG was analysed by two independent observers with special reference to calculate the PR interval QRS duration ST segment, QT interval and presence of U wave. The following features in ECG was searched for presence of hypokalaemia: flattening or inversion of T wave, Q-T interval prolongation (longer duration of the T wave), visible U wave, mild ST depression (0.5 mm), ventricular extrasystoles. Special reference was given to measure Q-Tc adopting the Bazze's formula¹⁴ $QT_c = QT / \sqrt{RR}$; manually with the help of mathematical calculator and automated ECG machine. The normal value for QT_c is 0.39 sec \pm 0.04 sec (0.35 to 0.43 sec). Patient were monitored continuously if patients were complaining of transient disorientation or acute SOB with suspicion of arrhythmia to detect any VPCS, NSVT, VT during observation period. VT was defined as salvos of more than consecutive bizarre premature complexes at rate more than 100 / min and lasting for 30 secs or more Torsades de pointes was recognised as polymorphic tachycardia characterized by QRS peaks that seem to twist around the baseline.¹⁵

Routine echocardiography was done in all cases who survived Cardiac arrest or VT to exclude underlying structural heart disease.

Pt having underlying LV dysfunction or valvular lesion were excluded from study as it may influence analysis. Case records of all the patient who died suddenly and could not be survived were analysed retrospectively for baseline ECG abnormality particularly Q-T-c and serum electrolyte concentration specially serum potassium concentration.

Observation

Total number of 234 documented sudden cardiac death (138 cases), survivor of cardiac arrest (30 cases) and ventricular tachycardia (66 cases) was observed during the study period which covered period when quinine was frequently used as drug of choice in severe malaria in 90s and 1st decade of

2000 and subsequently replaced by artemisinin derivative (artesunate IV or IM, artemether IM) group of drugs in the late half of first and second decade of 2000. All the cases were observed during the period from 1995 to 2009 with rapid decline after 2009 coinciding with period when artemisinin derivative replaced quinine as drug of choice.

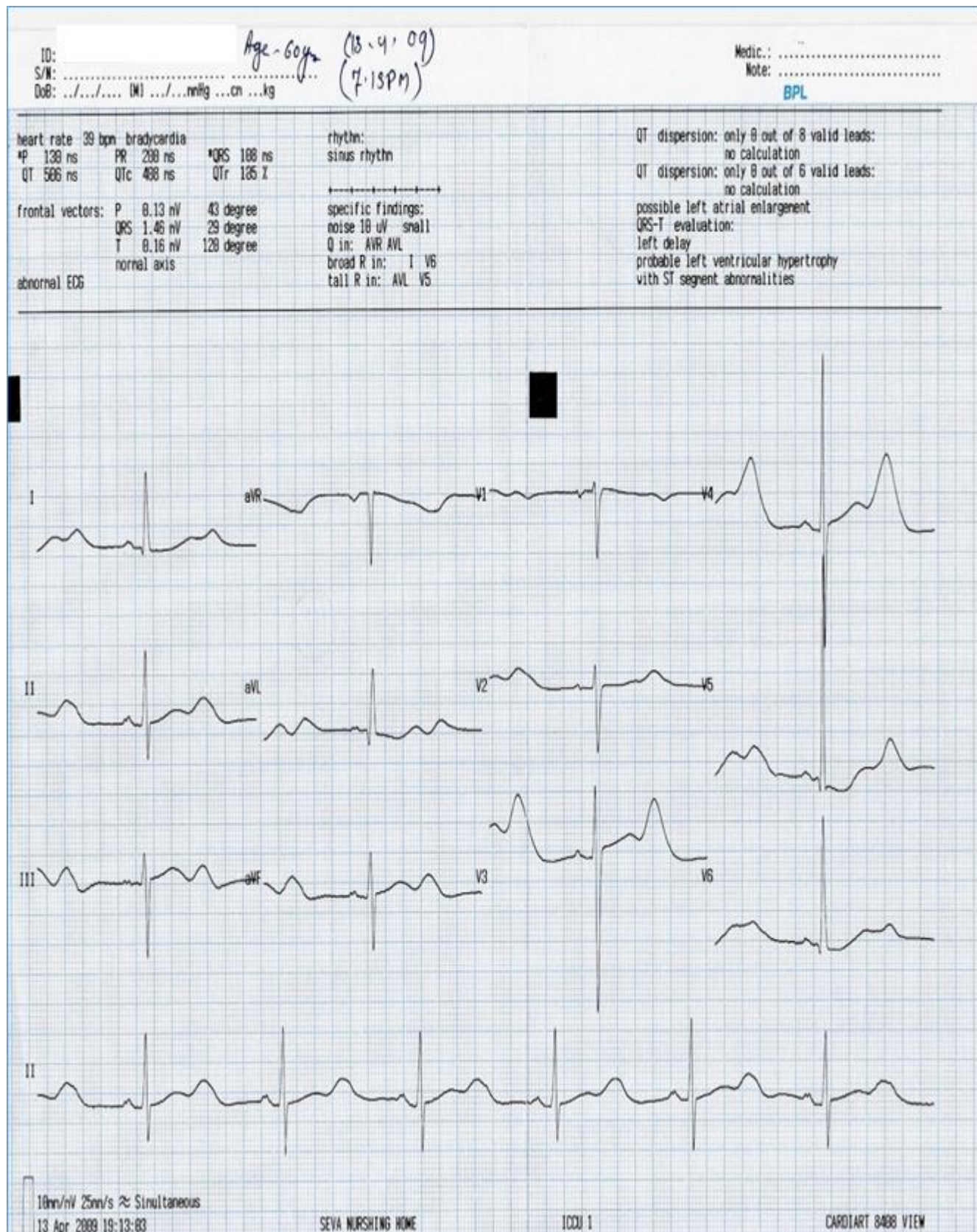


Figure 1. Baseline ECG 60/ F Presenting with Recurrent VT

Age group in yrs.	Percentage
5-20	20(8.5)
20-30	28(11.9)
30-40	48(20.5)
40-50	26(11.1)
50-70	112(47.8)
Table 1. Age Distribution	

Maximum no of cases (112) were in the age group of 50 -70 years, 28 cases in the age group of 20-30 years, 48 cases in the age group of 30-40 years, 26 cases in the age group of 40 - 50 years and only 16 cases of sudden death and 4 cases of documented VT was observed in children in the age group of 5 -20 yrs. even though they were more sick. Female sex dominated over male and there 34 cases were observed in pregnant lady out of whom sudden death was reported in 24 cases. Out of 138 cases of SCD Polymorphic VT Torsades de pointes and VF was observed in 32 cases who could not be saved inspite of early intervention with repeated defibrillation.

Hypokalaemia was observed in all the cases with documented ventricular tachyarrhythmia with severe hypokalaemia was invariable in all the cases of sudden death survivor of cardiac arrest. Mild Hypokalaemia was detected only in 12% cases of patient receiving artesunate. Hypocalcaemia, Hypomagnesemia was observed along with hypokalaemia in 16% of cases and all needed correction. There was dramatic improvement of baseline ECG changes and VPCS with rapid correction of potassium and quinine was continued as treatment option without any further occurrence of arrhythmia.

Maximum deaths were reported in initial few days and unfortunately when patients were improving, and attention was reduced as they were improving, and max deaths were reported in late night or early morning hrs.

ECG Changes	Percentage
Long Q-Tc	100%
U Wave	80%
VPCS	34%
NSVT	11%
Table 2. Baseline ECG Changes	

ECG was done routinely in all sick patients with special emphasis on presence of long Q-Tc. Sick patients with transient sudden disorientation or SOB were monitored continuously with bedside monitor revealed multiple VPCS. Baseline ECG was abnormal in all of cases with documented SCD or VT in the form of long Q-Tc. ECG was normal in all patients receiving artesunate Marked QT prolongation more than 0.5 sec were observed frequently in patient having very low potassium and VPCS. Prominent U wave was observed in 80% of cases of long Q-Tc Multiple ectopic was observed in 34% of cases.

Echocardiography revealed normal LV function an all cases who survived VT events or who presented with VT. No valvular lesion was observed except mild MR or mild TR which many times are physiological.

Hypotension was observed in 24% of cases with severe malaria with arrhythmia requiring fluid replacement and vasopressor support for hemodynamic stability. Hypoglycaemia was observed in 12 % of severe malaria and evidence of raised serum bilirubin level with normal enzymes and mildly raised creatinine was observed in 8% of cases which were probably part of pernicious manifestation of severe falciparum malaria.

DISCUSSION

Resurgence of falciparum malaria in 90s and 1st decade of 2000 was associated with high morbidity and mortality among all the age groups due to its different pernicious manifestation like impaired consciousness, acidosis, hypoglycaemia, severe anaemia renal impairment, jaundice, pulmonary oedema significant bleeding, shock, hyperparasitaemia. Before widespread use of artesunate, Cinchona alkaloids quinine and quinidine orally or parentally were the cornerstone treatment due to high prevalence of chloroquine resistance falciparum malaria. Present study was conducted for long period from 1997 to 2017 and covered the period when quinine was used routinely and was replaced gradually by artemisinin derivative. We observed around 234 cases of sudden death and ventricular tachyarrhythmia most cases during use of intravenous quinine as treatment for severe malaria but no case during the period of when artesunate has replaced quinine. High doses of artemether and artemotil have been associated with QT prolongation in dogs, raising the possibility of a class effect with the artemisinin derivatives.¹⁶ But in a study on intravenous administration of artesunate, patients with severe P.falciparum malaria did not show significant cardiovascular effects¹² Our present study also did not observe any arrhythmia in patients receiving artesunate. In severe falciparum malaria hypokalaemia can occur due to various causes which will be described later. Hence presence of both substrate (Quinine and hypokalaemia) for development of arrhythmia are present and interaction both factors can result in development of lethal ventricular tachyarrhythmia, the torsades de pointes. But only limited studies are available regarding electrophysiological properties of quinine and prevalence of ventricular tachyarrhythmia in falciparum malaria.^{6,7,17}

Prevalence of hypokalaemia in setting of malaria has not been not been evaluated. The main focus has been on sodium concentration disturbances in severe malaria.¹⁸ But hypokalaemia can occur frequently in severe malaria.^{19,20} Gastrointestinal symptoms like Nausea, vomiting and diarrhoea which maybe watery occur in adults with severe malaria. Patient with severe malaria are sick and disoriented during acute phase there is very poor oral intake predisposing them to develop electrolyte disturbances like hyponatremia, hypokalaemia in acute setting. As hypoglycaemia is an important complication of falciparum malaria and its treatment²¹ it is a routine practice is to give quinine along with dextrose solution in treatment of severe malaria to prevent hypoglycaemia .The concurrent use of dextrose and quinine can further aggravate or as such can

cause hypokalaemia Quinine is potent beta cell stimulator and induces insulin secretion and Insulin shifts potassium into cells by stimulating the activity of $\text{Na}^+\text{-H}^+$ antiporter on cell membrane, causing decline in serum potassium levels²¹ and dextrose infusion to prevent hypoglycaemia can further aggravate hypokalaemia as exogenous glucose stimulates insulin secretion which shifts potassium into the cell.²² Thus severe malaria patient can have hypokalaemia during acute severe stage though it has not been properly in setting of severe malaria. Hypokalaemia as such can induce arrhythmia and animal studies demonstrate that hypokalaemia-induced arrhythmogenicity is attributed to prolonged ventricular repolarization, slowed conduction, and abnormal pacemaker activity. The prolongation of ventricular repolarization in hypokalaemic setting is caused by inhibition of outward potassium currents and often associated with increased propensity for early after depolarizations. In hypokalaemic heart preparations, the prolongation of action potential may be associated with shortening of effective refractory period, thus increasing the propensity for ventricular re-excitation over late phase of repolarization. Shortened refractoriness and slowed conduction contribute to reduced excitation wavelength thereby facilitating re-entry. The interplay of triggering factors (early and delayed afterdepolarizations, oscillatory prepotentials in Purkinje fibers) and a favourable electrophysiological substrate (unidirectional conduction block, reduced excitation wavelength, increased critical interval for ventricular re-excitation) may account for the mechanism of life-threatening tachyarrhythmias in hypokalaemic patients.²³

Interestingly this arrhythmias may occur at low plasma concentration that do not cause widening of the QRS complex in the ECG and within the first days of quinidine treatment.^{24,25} Hypokalaemia predisposes to occurrence of quinidine induced torsades de pointes and both have shown to potentiate induction of EADs^{26,27} Our Present study also observed ventricular tachyarrhythmia very early in course of treatment of severe malaria Biochemical as well as ECG evidence of hypokalaemia was present in all documented cases of ventricular tachyarrhythmia Thus hypokalaemia induced by various factors mentioned above predisposes patient with severe malaria to develop tachyarrhythmia. Hence it is the underlying hypokalaemia precipitated by various factors during treatment of malaria particularly the mode of administration of quinine in dextrose solution seems to be the main factor precipitating ventricular tachyarrhythmia. When potassium was corrected rapidly ECG abnormality normalized and PVCs suppressed and the patient completed treatment with quinine even in parental route. It is very essential to detect hypokalaemia early and corrected rapidly to avoid development of arrhythmia.

CONCLUSION

Hence it is mode of administration of quinine in dextrose solution in sick patient with very poor oral intake and various GI manifestation that sets the stage for development of hypokalaemia by interplay of various factors discussed

above. Hypokalaemia by prolonging repolarisation and promoting unidirectional conduction block predispose malaria patients receiving potent outward membrane repolarising K^+ current blocker quinine to develop ventricular tachyarrhythmia. Hence the practice of quinine infusion in dextrose solution to prevent hypoglycaemia should be avoided and Inj. quinine infusion should be infused in other fluid. Early detection and correction of hypokalaemia is very essential to prevent ventricular tachyarrhythmia in falciparum malaria.

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