"A STUDY OF PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA"

Submitted to

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

In partial fulfilment of the requirements

For the award of degree of

M.D. GENERAL MEDICINE

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

MAY 2019

DECLARATION

I hereby declare that this dissertation entitled **"A STUDY OF PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA"**has been prepared by me during March 2018 – August 2018, under the guidance of Dr. C. SRIDHAR MD, Professor of General medicine,Department of General medicine, Govt. Stanley Medical College,Chennai along with Co-guide Dr. RAJA. MD, assistant professor of general medicine, Govt. Stanley Medical College,Chennai is submitted to the THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITYin partial fulfillment for the award of the degree of M.D. GENERAL MEDICINE. This work has not formed the basis for the award of any degree or diploma to me by any other University before.

Date : Signature

Place: Chennai **Dr. PRAVEEN.R.V**

CERTIFICATE

This is to certify that the study entitled **"A STUDY OF PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA"** is the result of original work carried out by **DR.PRAVEEN. R V**,under my supervision and guidance at **GOVT. STANLEY MEDICAL COLLEGE, CHENNAI.** The thesis is submitted by the candidate in partial fulfilment of the requirements for the award of M.D Degree in General medicine course from 2016 to 2019 at Govt. Stanley Medical College, Chennai.

Prof.Dr.C. SRIDHAR,MD

Professor of General medicine

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Prof.Dr.S. PONNAMBALANAMASIVAYAM, M.D. D.A. DNB.

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ACKNOWLEDGEMENT

I express my immense gratitude to The Dean, **Prof.Dr.S.PONNAMBALAM NAMASIVAYAM M.D. D.A. DNB,** Govt. Stanley Medical College for giving me the opportunity to work on this study.

I express my immense gratitude to The Dean, **Prof.Dr.R.MUTHUSELVAN.MD,**Head of Department,Department of General Medicine**,** Govt. Stanley Medical College for giving me the opportunity to work on this study.

I wish to express my heartfelt and profound indebtness to my teacher and guide **Prof. Dr.SRIDHAR.CMD**, Professor of General Medicine, Department of General Medicine, Govt. Stanley Medical College, Chennai-01, for his invaluable feedback, suggestions and guidance throughout the completion of the study.

My heartfelt thanks to my teachers and Assistant Professors **Dr. RAJA. MD, Dr. NAMITHA NARAYANAN MD, Dr. ELAVAZHAKAN MD** for theirsupervision and assistance during the progression of my study.

My sincere thanks to **Mr.K.BOOPATHI** for his timely help with the statistics.

I take the pleasure to offer my deepest sense of gratitude to my wife and my parents for their moral support and encouragement.

Finally, I express my gratitude to the patients and volunteers who so willingly accepted and cooperated for the study.

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INSTITUTIONAL ETHICS COMMITTEE

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Principal Investigator : Dr.Praveen R V
Designation : Pg in Gen Medicine
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Govt. Stanley Medical College.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 17.02.2018 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

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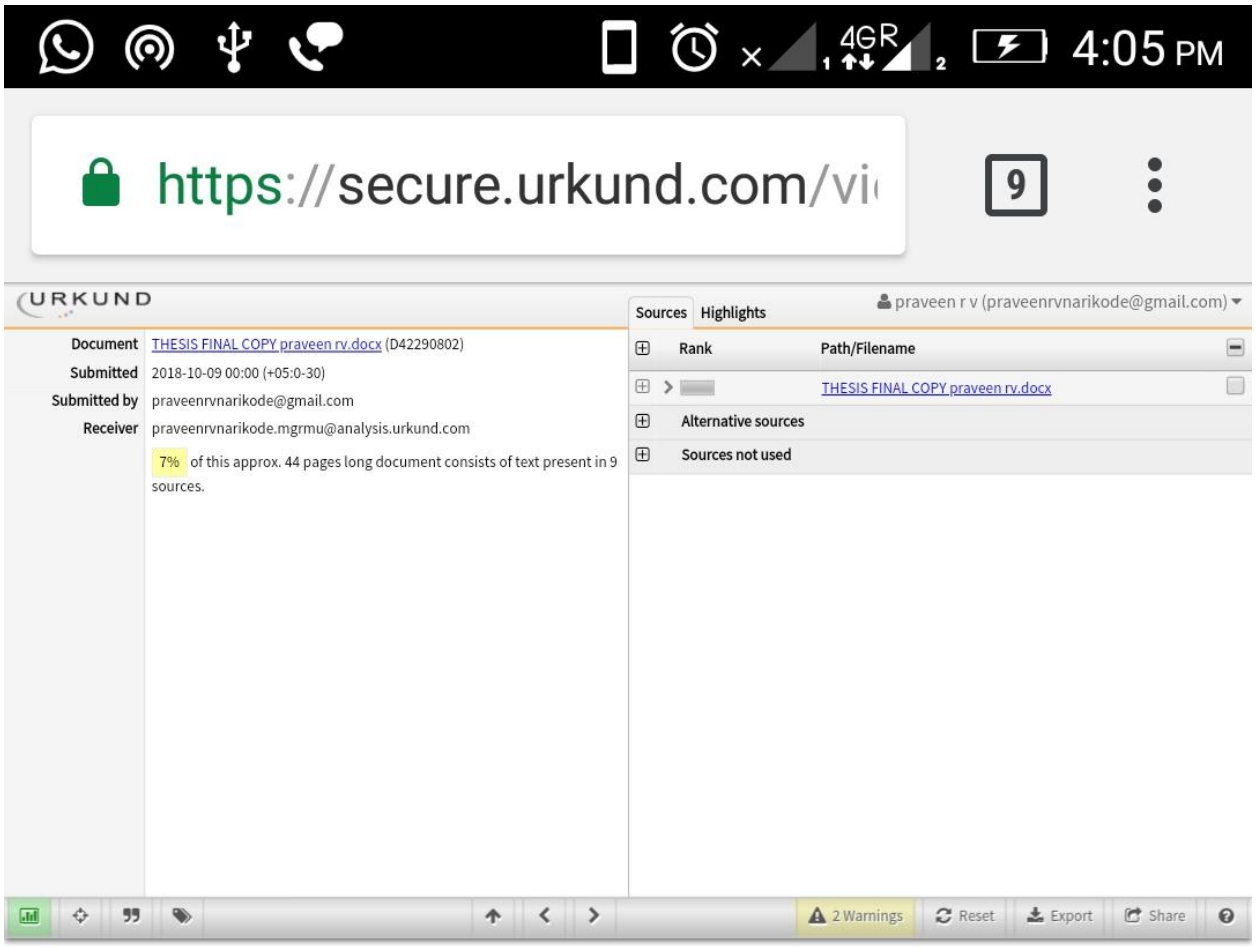

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INTRODUCTION Malaria is a protozoan disease caused by the protozoan ,plasmodium. Five species of the genus plasmodium causes nearly all malarial infections in humans - Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi. Malaria is transmitted by the anopheles mosquitoes. Life cycle When the female mosquito bites a human being,sporozoites are introduced into the circulation. Sporozoites then reaches the liver and undergo pre erythrocytic schizogony. Within the liver cells sporozites get divided and give rise to merozoites. The swollen hepatocytes then burst and release the merozoites. Each merozoite then invades erythrocytes and undergoes erythrocytic schizogony. Merozoites then develop into tropozoites and later into schizonts. The schizonts divided to form merozoites. Then the RBC bursts to release the merozoites which in turn invade new RBCs. Some of the merozoites develop into gametocytes that can transmit the disease. Some of the sporozoites in theb hepatocytes can develop into dormant form called hypnozoites in P.vivax and P.ovale infection. When another mosquito feeds on the malaria patient,the female and male gamatocytes reaches the gut of the mosquito where they combine together to form the zygote. Zygote matures into ookinete and penetrates into the gut wall where it encysts and form oocyst. Later oocyst divides to form sporozoites. These sporozoites are stored in salivary gland of the mosquito and injected into another person during the mosquito bite. Clinical features Malarial fever begins with non specific complaints of headache,fatigue,abdominal discomfort, and myalgia. These non specific symptoms are followed by high grade intermittent fever,associated with chills and rigor. According to the periodicity fever in malaria are classified into tertian fever(p.vivax and p.ovale),quartian fever (p.falciparum) etc. Anemia,jaundice and hepatospleenomegaly are other features seen in malarial fever. If a patients with malaria develops unarousable coma/cerebral malaria,acidosis,severe anemia,renal failure,ARDS,hypoglycemia,shock,DIC, hemoglobinuria,convulsions etc then it is considered as complicated malaria. Further metabolic abnormalities like hypoglycemia,hypocalcemia,hyponatremia etc are also noted in malarial fever. Exact causes of hypocalcemia in malaria is not known. Renal failure,hypomagnesemia and hypoparathyroidism are some of the possible causes of hypocalcemia in malaria. Hypocalcemia Normal serum calcium level is 8.5-10.2 mg% . Of this 50 % remain bound to serum proteins and 50% remain free in the circulation. Serum calcium level > 8.5 mg% is taken as hypocalcemia. Causes of hypocalcemia are classified according to whether serum PTH level are low(hypoparathyroidism) or high(secondary hyperparathyroidism). Patients remain asymptomatic in mild and chronic hypocalccemia or they may present with life threatening complications. Moderate hypocalcemia presents with parasthesia,especiallyover fingers and circum oral areas. Carpopedal spasm. Chevstok's sign and trosseau's signs can be elicited on clinical examination of these patients. Severe hypocalcemia presents

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CERTIFICATE – II

This is to certify that this dissertation work titled entitled dissertation "**A STUDY OF PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA**" of the candidate **Dr.PRAVEEN R V,** with Registration Number **201611059** for the award of **M.D** degree in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7%** of plagiarism in this dissertation.

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Life cycle

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Hypocalcemia

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Carpopedal spasm has been noted in many patients presenting with malarial fever. Most of the patients are ,later found to have hypocalcemia. There are only few studies on the prevalence and clinical implication of hypocalcemia in malaria. Hypocalcemia associated with malaria can cause many clinical manifestations ,including life threatening conditions such as arrhythmias,convulsions etc. Less is known about the prevalence of hypocalcemia in malaria and and its effect on clinical outcome. So, i conducted a cross sectional study among patients presenting with malarial fever in Stanley medical college.

REVIEW OF LITRATURE

Epidemiology

Malaria is a tropical disease. Amongst the different species P. falciparum predominates in Africa,new guinea and Haiti while P.vivax predominates in central America. Both species are equally seen in regions like South America,Indian subcontinent,Eastern asia and Oceania. P .malaria is endemic to sub Saharan region whereas P. ovale is rarely found outside Africa. P.knowlesi is reported in the islands of Borneo and Southeast asia.

Endemic areas have been classified as hypoendemic(<10% of chidren with palpable spllen),mesoendemic(11-50%),hyperendemic(51-75%) and holoendemic(>75%)according to parasites rate or palpable spleen rates in chidren of age 2-9 years. In holo and hyper endemic areas,people get more than one infected mosquito bites per day and are infected repeatedly throughout life. Prevalence and incidence of malarial fever is more in children in endemic areas.

Two types of disease transmission have been noted- stable transmission and unstable transmission. Constant, frequent and year round transmission is called stable transmission whereas low,focal transmission is termed as unstable transmission. Stable transmission is seen in holo endemic and hyper endemic areas whereas unstable transmission is found in hypo endemic areas. Transmission rate of malaria is dependent on density of

vectors,number of human bites per day and life span/longevity of mosquitoes. Malaria is less common in high altitudes and areas with cold climate.

Life cycle of malarial parasite

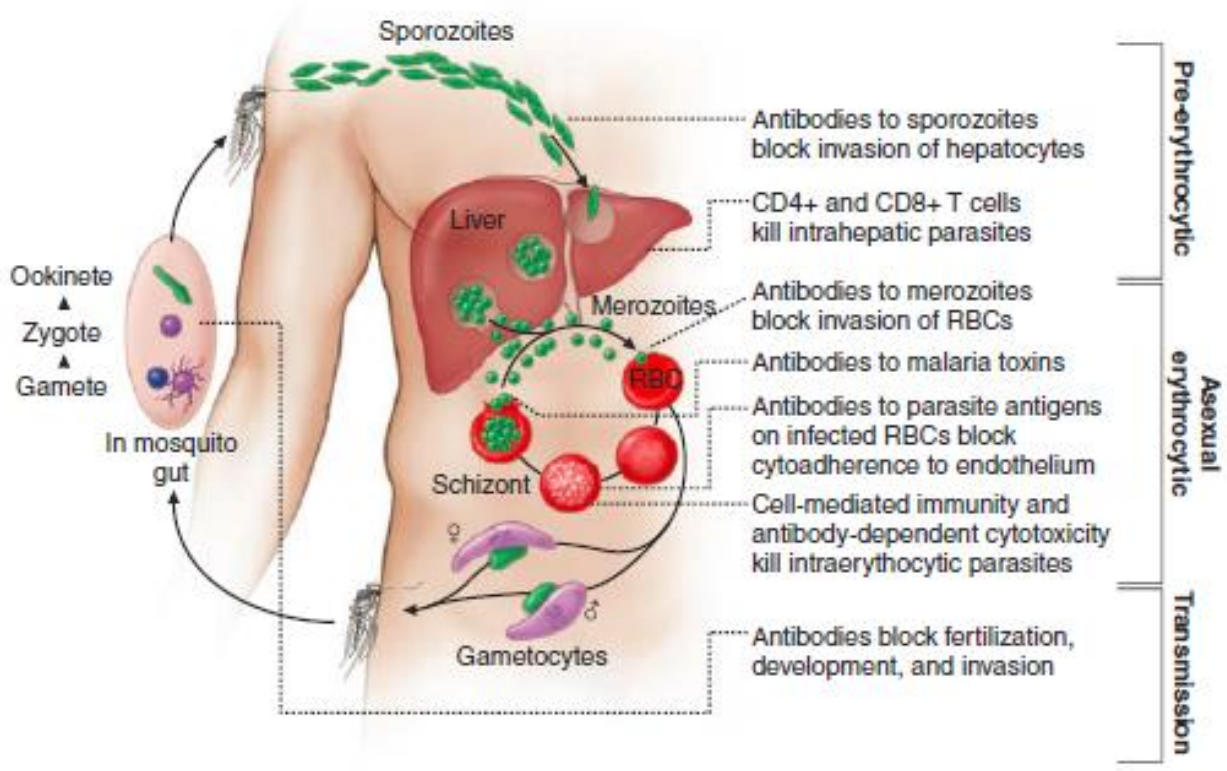


figure 1[1]

Pathophysiology

Severe malaria occurs when there is adhesion and sequestration of parasitized red blood cells(PRBC) in the vasculature,release of bio active molecules by the parasites and host inflammatory responses. The parasitized RBC(PRBC) becomes less deformable so that it can't pass through the microcirculation. This leads to sequestration of PRBC within the microcirculations causing tissue ischemia. Surface of the PRBC become rough and leads

to increased adherence of PRBC to vascular endothelium. Adherence of PRBC with another PRBC (agglutination) and PRBC with non PRBC (rossetting) also take place. Reduction in cell deformability is observed not only in PRBC, but also in NPRBC. All these factorslead to blockade of microcirculation in various tissues, thus causing tissue ischemia.

Host immune responses also contribute to the pathogenesis of complicated malaria. Concentration of various proinflammatory cytokines are found to be elevated. TNF-alpha upregulates endothelial cytoadherence receptors andcan cause hypoglycemia and dyserythropoeisis. Cytoadherence and sequestration of PRBCs in microcirculation is seen in P.falciparum infection.

Clinical features

Malaria is one of the most common causes of acute febrile illness in tropical countries. Initial symptoms of malaria are mostly non specific includingheadache,fatigue,abdominal discomfort, myalgia and arthralgia, which is followed by fever. High grade fever with chills and rigor is seen. The fever spikes occur at regular intervels. The spike of fever corresponds to the release of merozoites from PRBCs. Fever appears every second day in P.vivax and P.ovale malarial infection and is called tertian fever. Quartian fever(fever spikes comes every third day) is seen in P.falciparum and P.malaria infection. In P.knowlesi infection ,fever spike is seen every 24 hours.

Mild jaundice and hepato splenomegaly are seen in malarial infection. Uncomplicated malarial infection resolves over 1-3 weeks.

Manifestations of Severe Falciparum Malaria -

Major

- Unarguable coma/cerebral malaria

Coma persisting for>30 min after generalized convulsion .Failure to localize or respond appropriately to noxious stimuli

- Acidemia/acidosis

Arterial pH of <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; Patients develop labored deep breathing, often termed "respiratory distress"

- Severe normochromic,normocytic anemia

Hemoglobin level of <50 g/L (<5 g/dl) or hematocrit of <15% with parasitemia level of >100,000/μL

- Renal failure

Urine output of<400 ml in 24 hours in adults or <12 ml/kg in children; no improvement with rehydration; serumcreatinine level of >265 μmol/L (>3 mg/dl)

- Pulmonary edema/adult respiratory distress syndrome

Overhydration aggravates noncardiogenic pulmonary edema

- Hypoglycemia

Plasma glucose level of <2.2 mmol/L (<40 mg/dl)

- Hypotension/shock

Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s

- Bleeding/disseminatedintravascular coagulation

Patients will have significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence ofdisseminated intravascular coagulation

- Convulsions

More than two generalized seizures in 24 h. sometimes subtle (e.g., tonicclonicеye movements without limb or face movement) is noted

- Hemoglobinuria

Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzymedefects (such as G6PD deficiency).It is called black water fever.

Other

- Impaired consciousness/arousable

Unable to sit or stand without support

- Extreme weakness

Prostration; inability to sit without help

- Hyperparasitemia

Parasitemia level of >5% in nonimmune patients (>20% in any patient)

- Jaundice

Serum bilirubin level of >50 mmol/L (>3 mg/dl) if combined with other evidence of vital-organ dysfunction

Features Indicating Poor Prognosis in Severe Falciparum Malaria

Clinical

Marked agitation

Hyperventilation (respiratory distress)

Hypothermia (<36.5°C)

Bleeding

Deep coma

Repeated convulsions

Anuria

Shock

Laboratory

Biochemistry

Hypoglycemia (<2.2 mmol/L)

Hyperlactatemia (>5 mmol/L)

Acidosis (arterial pH <7.3, serum HCO3 <15 mmol/L)

Elevated serum creatinine (>265 μmol/L)

Elevated total bilirubin (>50 μmol/L)

Elevated liver enzymes (AST/ALT 3 times upper limit of normal)

Elevated muscle enzymes (CPK ↑, myoglobin ↑)

Elevated urea (>600 μmol/L)

Hematology

Leukocytosis (>12,000/μL)

Severe anemia (PCV <15%)

Coagulopathy

Decreased platelet count (<50,000/μL)

Prolonged prothrombin time (>3 s)

Prolonged partial thromboplastin time

Decreased fibrinogen (<200 mg/dl)

Parasitology

Hyperparasitemia

Increased mortality at >100,000/μL

High mortality at >500,000/μL

>20% of parasites identified as pigment-containing

trophozoites and schizonts

>5% of neutrophils with visible pigment

Hypocalcemia in malaria

Many previous studies revealed the disturbance of calcium homeostasis in malaria. Many possible mechanisms are suggested to explain the relation between malaria and hypocalcaemia. This effect is found most severe in Falciparum malaria .The nature of the mechanisms causing disturbance in Ca++ homeostasis in malarial parasites remained unknown for almost two decades.

Some possible mechanisms are:

1. Ca++ based signaling pathway used by plasmodium parasites results in reduced calcium status, especially intracellular calcium, but not Ca++ found in body fluids. Environment of the host cell cytoplasm is disturbed by this. But how the protozoa achieved the calcium homeostasis – was unanswered.

2. Plasmodium Falciparum infected red blood cells show increased permeability for calcium. The magnitude of the increase is greater than that normally require activating the Ca++ dependent K+ channel. Some studies showed that Falciparum infectionincreases the influx of Ca++ to over 1mmol which is much higher than the normal values. The pathway responsible for the enhanced influx was expressed at approximately 30 hrs post invasion.

3. Calcium dependent Transglutaminase activity that reduces the calcium level is found increased, in some studies. This decrease is found simultaneous with maturation of the

parasite. The effect is maximum when the trophozoitesare 48 hrs old and at that time most of the calcium is found in the parasite.

4. Ionized calcium "set point for basal PTH secretion is decreased in malaria. But a normal PTH response to acute hypocalcaemia in malaria skeletal resistance may attenuate the effect of the PTH response but patients with malaria appear relatively resistant to the calcium chelating effects of citrated blood products.

5. Some study showed that serum calcium is utilized by the parasite and this creates drug resistance in parasites. Sometimes, Chloroquine resistance is seen in Plasmodium Falciparum because of intracellular calcium utilization. This causes decreased calcium status in patients as well as drug resistance. The Chloroquine resistance is totally reversed when the channels of calcium were blocked with Verapamil & Fantofarone. Verapamil appeared 2to 3 times more potent than Fantofarone in reversing the drug resistance.

6. Disturbed Parathyroid hormone profile has also contributed to the lowered Calcium Status. 'Sick euparathyroid syndrome' is defined as a state in which the parathyroid response to Hypocalcemia remains depressed during active infection, with recovery of the glandular function as the parasitemia gets cleared.

7. Another possible cause for malaria-induced Hypocalcemia relates to the changes in phosphate metabolism. Hypophosphatemia in malaria occur as a result of lowered renal

threshold for phosphate. Hypercalcuria that occur along with Hypophosphatemia also contributes to hypocalcemia . Hypophosphatemia can cause encephalopathy, depressed leucocyte function, increased susceptibility to Gram-negative infections, platelet dysfunction, coagulation abnormalities, and hemolytic anemia are associated with hypophosphatemia . These abnormalities are also seen in severe and complicated malaria.

8. Mild asymptomatic hypomagnesemia is seen in malaria. Hypomagnesemia impair the release of parathormone by the parathyroid gland and blunt the tissue response to parathormone. This inturn results in Hypocalcemia.

Many studies found out that hypocalcemia has prognostic value in malaria as it may indicate complicated malaria or heavy parasitemia and it's return to normal serum level may indicate clinical recovery and parasite clearance.

Diagnosis of malaria

Demonstration of parasites

Malaria is diagnosed by thedemonstrating asexual forms of the parasite in stained peripheral-blood smears. In case of a negative blood smear, repeat smears should be made if there is high degree of suspicion. Of the Romanowsky stains, Giemsa atpH 7.2 is preferred. Field's, Wright's, or Leishman's stain can alsobe used. Both thin and thick blood smears should be made and examined. The thin blood smear should be fixed in

anhydrous methanol, and stained. The RBCs in the tail of the film should then be examined under oil immersion (×1000magnification). The number ofparasitized erythrocytes per 1000 RBCs expresses the level of parasitemia in the blood. The thick blood film should be of uneven thickness. The smear should be dried thoroughly and stained without fixing. As many layers of erythrocytes overlie one another and are lyses during the staining procedure, the thick film concentrate the parasites (by 40- to 100-foldcompared with a thin blood film) and thus increasing diagnostic sensitivity.Both parasites and white blood cells (WBCs) should be counted, andthe number of parasites per unit volume is calculated from the total leukocyte count. A WBC count of 8000/μL is assumed, as an alternative methode.This figure is converted to the number of parasitized erythrocytespermicro liter. A minimum of 200 WBCs/hpf should be counted.The relationship between parasitemiaand prognosis is complex; in general,risk of dying is increased in patients with >105 parasites/μL .But nonimmunepatients may die with much lower counts, and partially immune persons may tolerateparasitemia levels many times higher withonly minor symptoms. Predominanceof more mature *P. falciparum*parasites (i.e., >20% of parasites with visiblepigment) in the peripheral-blood filmor the presence of phagocytosed malarial pigment in >5% of neutrophils. Indicates poor prognosis in severe malaria.Gametocytemia peaks1 week after the peak of asexual parasites in *P. falciparum* infections. Because the mature gametocytes of *P. falciparum*are not affected by most antimalarialdrugs, their persistence cannot be taken as the evidence of drug resistance. Phagocytosedmalarial pigment is sometimes seen insideperipheral-blood monocytes or polymorphonuclearleukocytes and may provide a clue to recent infection if

malaria parasites are not detectable. After the clearance of the parasites, this intraphagocyte malarial pigment often evident for several days in the peripheral blood or for longer in bone marrow aspirates or smears of fluid expressed after intradermal puncture. More rapid diagnosis of malaria (but not speciation of the infection) in patients with low-level parasitemia can be done by Staining of parasites with the fluorescent dye acridine orange. Interpretation of blood smear films requires someexperience because artifacts are common. 100–200 fields should be examined under oil immersion before a thick smear is judged to be negative. In hightransmission areas, the presence of up to10000 parasites/μL of blood may be toleratedwithout symptoms or signs in partiallyimmune individuals. So detection of malaria parasites is sensitive in these areas buthas low specificity in identifying malaria asthe cause of illness. Low-density parasitemia iscommon in other conditions causing fever.

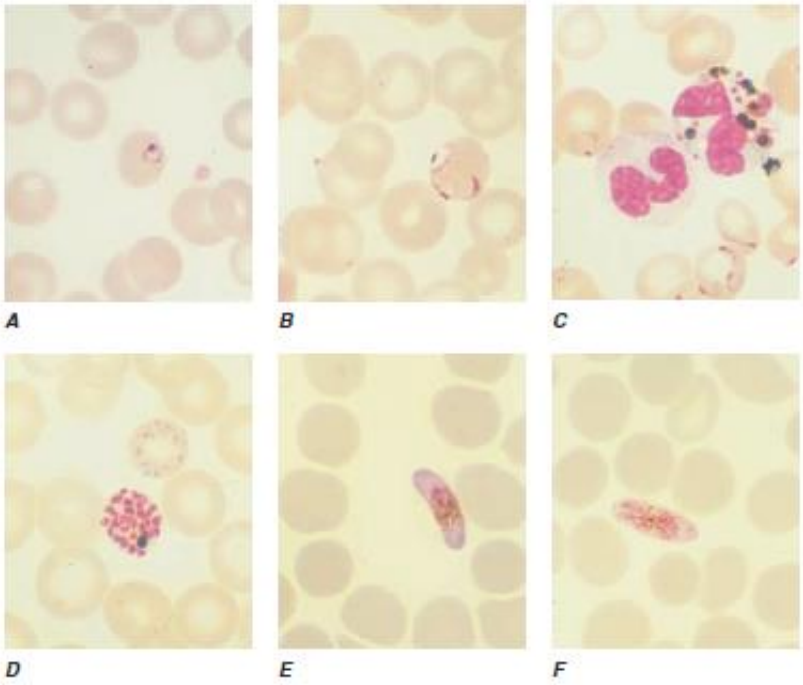


Figure.2 thin blood smear of plasmodium falciparum: A-young trophozoite, B-old trophozoite, C-pigments in polymorphonuclear cells and trophozoite, D-mature schizonts, E-female gametocyte, F-male gametocyte [1]

Rapid, simple, sensitive, and specific antibody-based diagnostic stick or card tests thatdetect *P. falciparum* –specific, histidine-richprotein 2 (PfHRP2) or lactate dehydrogenaseantigens in finger-prick blood samples are now being used widely in control programs. Falciparum malaria can be distinguished from the less dangerous malarias by some of these rapid diagnostic tests (RDTs) carry a second antibody. PfHRP2-based tests are found positive for several weeks after acute infection. This feature is a disadvantage in high-transmission areas where infections are frequent but is of value in the diagnosis of severe malaria in patients who have taken antimalarial drugs and cleared peripheralparasitemia (but in whom the PfHRP2 test remains strongly positive). RDTs are replacingmicroscopy in many areas because of theirsimplicity and speed, but they are relativelyexpensive and do not quantify parasitemia.

Laboratory findings

Normochromic, normocytic anemia is usual. The leukocyte count is generally normal, although it may be raised in very severe infections.Monocytosis, lymphopenia, and eosinopenia,with reactive lymphocytosis and eosinophilia can be seen in the weeks after the acute infection. The erythrocyte sedimentation rate, plasma viscosity,

And levels of C-reactive protein and other acute-phase proteins are high. The platelet count is usually reduced to ~10 5 /μL. Prolonged prothrombin and partial thromboplastin

times and more severe thrombocytopenia are noted in severe infection. Levels of antithrombin III are reduced even in mild infection. Plasma concentrations of electrolytes, blood urea nitrogen (BUN), and creatinine are usually normal in uncomplicated malaria.

Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, calcium, phosphate, and albumin together with elevations in lactate, BUN, creatinine, urea, muscle and liver enzymes, and conjugatedand unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects. Urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean opening pressure at lumbar puncture is ~160 mm of cerebrospinal fluid (CSF).usually the CSF is normal or has a slightly elevated total protein level [<1.0 g/L (<100 mg/dl)] and cell count (<20/μL).

Treatment of malaria

When a patient in or from a malarious areapresents with fever, thick and thin blood smears should be prepared and examined immediatelyto confirm the diagnosis and identify the species of infecting parasite. Repeat blood smears should be performed at least every12–24 h for 2 days if the first smears are negative and malaria is strongly suspected. Alternatively, a rapid antigen detection cardor stick test can be performed. Parenteral antimalarial therapy should be given to patients with severe malaria or those unable to take oral drugs. The organism should be considered resistant if there is any doubt about the resistance status of the infecting organism. Antimalarial drug

susceptibility testing can be performedbut is rarely available and yields results too slowly to influence the choice of treatment. Several drugs are available for oral treatment. The choice of drug depends on the likely sensitivity of the infectingparasites. There is increasing evidence of Chloroquine resistancein *P. vivax* (from parts of Indonesia, Oceania, eastern andsouthern Asia, and Central and South America).Still Chloroquineremains the treatment of choice for the non-falciparum malarias(*P . vivax* , *P . ovale* , *P . malariae* , *P . knowlesi*) except in Indonesiaand Papua New Guinea, where high levels of resistance in*P. vivax* are prevalent.The treatment of falciparum malaria has changed radicallyin recent years. In all endemic areas, the World HealthOrganization (WHO) now recommends artemisinin-basedcombinations as first-line treatment for uncomplicated falciparum malaria.

Uncomplicated malaria

Chloroquine sensitive strains are treated with chloroquine (10mg/Kg stat followed by 10 mg/Kg at 24hrs and 5 mg/kg at 48 hrs). Primaquine at a dose of 0.25mg/Kg body weight od for 14 days, is used for the radical treatment of vivax malaria.

Uncomplicated falciparum malaria is treated with artemether-lumefantrene(1.5/9 mg/Kg body weight at 0 and 8 hrs on day 1 and bd on day 2 and 3). Artesunate(4mg/Kg od for 3days) plus sulphadoxine(25 mg/Kg body weight)/pyramethamine(1.25 mg/Kg body weight) as a single dose can also be used for the treatment of uncomplicated falciparum malarial fever.

Complicated malaria

One of the following regimens are commonly used for the treatment of complicated malarial infection.

1. Artesunate(2.4 mg/Kg bodyweight iv stat followed by 2.5 mg/Kg body weight at 12 and 24 hours and daily)
2. Artemether(3.2 mg/Kg body weight im stat followed by 1.6 mg/Kg body weight)
3. Quinine dihydrochloride(20 mg/Kg body weight infused over 4 hours followed by 10 mg/Kg infused over 2-8 hours.)

Hypocalcemia

Causes of Hypocalcemia

Low Parathyroid Hormone Levels (Hypoparathyroidism)

Parathyroid agenesis

Isolated

DiGeorge syndrome

Parathyroid destruction

Surgical

Radiation

Infiltration by metastases or systemic diseases

Autoimmune

Reduced parathyroid function

Hypomagnesemia

Activating CaSR mutations

High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)

Vitamin D deficiency or impaired 1,25(OH)2D production/action

Nutritional vitamin D deficiency (poor intake or absorption)

Renal insufficiency with impaired 1,25(OH)2D production

Vitamin D resistance, including receptor defects

Parathyroid hormone resistance syndromes

PTH receptor mutations

Pseudohypoparathyroidism (G protein mutations)

Drugs

Calcium chelators

Inhibitors of bone resorption (bisphosphonates, plicamycin)

Altered vitamin D metabolism (phenytoin, ketoconazole)

Miscellaneous causes

Acute pancreatitis

Acute rhabdomyolysis

Hungry bone syndrome after parathyroidectomy

Osteoblastic metastases with marked stimulation of bone formation

(prostate cancer)

Clinical features

Patients with Hypocalcemia remain asymptomatic if the decreases in serum calcium are relatively mild and chronic. Severehypocalcemia may present with life-threatening complications. Moderate to severe hypocalcemia is associated with paresthesias, usually of the fingers, toes, and circumoralregions. It occurs as a result of increasedneuromuscular irritability. Chvostek's sign (twitching of the circum oral muscles in response to gentle tapping of the facial nerve just anterior to the ear) may be elicited in hypocalcemia. Inflation of a blood pressure cuff to 20 mmHg above the patient's systolic blood pressure for 3 min may induce carpopedal spasm (Trousseau's sign). Severe hypocalcemia can induce seizures, carpopedal spasm, bronchospasm, laryngospasm, and prolongation of the QT interval.

Treatment

Acute, symptomatic hypocalcemia is initially managed with calcium gluconate, 10 ml 10% wt/vol (90 mg or 2.2 mmol) intravenously, diluted in 50 ml of 5% dextrose or 0.9% sodium chloride, given intravenously over 5 min. A constant intravenous infusion (typically10 ampoules of calcium gluconate or 900 mg of calcium in 1 L of5% dextrose or 0.9% sodium chloride administered over 24 h) should be given to those with ongoing hypocalcemia.

Accompanying hypomagnesemia, if present, should be corrected with appropriate magnesium supplementation.Calcium supplements (1000–1500 mg/d elemental calcium

in divided doses) and either vitamin D 2 or D 3 (25,000–100,000 Udaily) or calcitriol [1,25(OH) 2 D, 0.25–2 μg/d are used to correct chronic hypocalcemia due to hypoparathyroidism]. Vitamin D deficiency, however, is best treated using vitamin D supplementation. Dose of vit D depends on the severity of the deficit and the underlying cause. Thus, nutritional vitamin D deficiency generally responds to relatively low doses of vitamin D (50,000 U, 2–3 times per week for several months),while vitamin D deficiency due to malabsorption may require much higher doses (100,000 U/d or more). The treatment goal is to bring serum calcium into the low normal range and to avoidhypercalciuria, which may lead to nephrolithiasis.

Studies regarding hypocalcemia in malaria

Prabha M R et al (1998) conducted a study on clinical implication of hypocalcemia in malaria. She took 60 adult cases of malaria and estimated serum calcium in them to find out prevalence and clinical implications of hypocalcemia in different types of malaria.ECG was taken in all patients to look for QTc prolongation, which is found in hypocalcemia.27 out of 60 patients (45%) were found to have hypocalcemia. 88.24% patients with complicated malaria had hypocalcemia whereas hypocalcemia was detectedin only 27.19 patients with uncomplicated malaria.Mean serum calcium level in complicated malaria was (7.4 +/- 0.98mg %) against (8.4 /- 0.4mg %) in uncomplicated malaria. She noted significant correlation between degree of hypocalcemia and QTc prolongation with a significant p value of <0.01. 3 patients with long QTc died of

hypotension,bradycardia and heart block after quinine therapy.She also stated that there is an inverse relationship between serum calcium level and parasite load ($p<0.05$). Serum calcium was found to return to normal with clinical recovery and lowering of parasite load. Though exact cause of hypocalcemia in malaria could not be found out,it was attributed to renal failure, hypomagnesemia and parathyroid dysfunction. She concluded that hypocalcemia in malaria is not uncommon and it can be used as a prognostic indicator in complicated malaria as it can cause cardiac conduction abnormalities and death, and serum calcium level returns to normal with clinical recovery and parasite clearance.

Dr Seema Mishra et al(2013)conducted a study on malaria precipitated hypocalcemia and related complications. 70 case of malaria were studied to find out the clinical and prognostic implication of hypocalcemia and corrected QT interval prolongation in malaria. Parasite species and parasite load were detected by peripheral smear. 30 patients (18 complicated and 12 uncomplicated) out of 70 had P.falciparam malaria. 30 patients were of P.vivax malaria while 10 had mixed infection(both P.falciparum and P.vivax). Hypocalcemia was noted in 44 patients and all of them had prolonged QTc. Out of 14 patients presented with convulsions, 14 patients had prolonged QTc and 10 patients had hypocalcemia. Out of 8 patients presented with muscle spasm, 6 patients had prolonged QTc and 5 patients had hypocalcemia. 54 patients had cerebral malaria; of which 23had hypocalcemia as well as prolonged QTc , 15 developed renal failure

and 14 patients had high parasitemia. 2 patients with hypocalcemia and prolonged QTc died of hepatorenal syndrome. Patients with complicated falciparum malaria were reported to have a mean parasite load, QTc interval and serum calcium ,of (3.07 +/- 1.2), (0411 +/- 0.038) sec and (7.06 +/- 0.77) mg% respectively , whereas it was (1.9 +/- 0.53) , (0.512 +/- 0.033) sec and (7.02 +/- 0.49) mg% respectively in complicated mixed infection. It was (1.04 +/- 0.61),(0.435 +/- 0.035) sec and (8.07 +/- 1.07) mg% in uncomplicated falciparum malaria and (1.43 +/- 0.58),(0.403 +/- 0.019)sec and (8.68 +/- 03)mg% in vivax malaria. She concluded that hypocalcemia is a feature of severe/complicated malaria as it had a good correlation with parasite load and complications. According to her,hypocalcemia also had a prognostic value in malaria as serum calcium level returns to normal with clinical recovery.

Ankush agarwal et al(2018) carried out a study on effect of malarial parasitemia on serum electrolytes in south east Rajasthan. Serum calcium level was one of the parameters studied. 256 patients with malaria infection (153 females and 103 males) were studied. 215 out of 256 patients were from rural areas whereas 41 were from urban regions. 144 patients had P.falciparum malaria whereas 86 patients were having P.vivax malaria. 26 patients had mixed infection(P.vivax and P.falciparum). Serum sodium,potassium and calcium were measured in each patient. Hypocalcemia(<9 mg%) was detected in 94 patients with falciparum malaria,43 patients with vivax malaria and 18 patients with mixed infection. 45 patients with falciparum malaria,41 patients with vivax malaria and 7 patients with mixed infection had normal serum calcium(9-11mg%). . 5

patients with falciparum malaria,2 patients with vivax malaria and 1 patients with mixed infection had hypocalcemia(>11mg%).

Sony CL et al (2000)did a study on prognostic implication of hypocalcemia and QTc interval in malaria. 100 confirmed malaria cases were included in the study. Out of 100 patients, 50 patients(38 complicated and 12 uncomplicated) were P.falciparum positive cases; 40 patients were of vivax malaria and 10 patients were having mixed infection. 26 patients were reported to have hypocalcemia. All the patients with hypocalcemia had prolonged QTc. 10 patients developed convulsions; all of them were having prolonged QTc and 8 of 10 patients had hypocalcemia. Out of 8 patients who presented with muscle spasms , 6 patients had QTc prolongation and 4 patients had hypocalcemia. Out of 34 cases of cerebral malaria, 18 developed hypocalcemia as well as QTc prolongation,12 of them developed acute renal failure and 14 had high parasitemia. 4 patients with both hypocalcemia and QTc prolongation died of hepatorenal syndrome during the study period. The mean parasite load, QTc interval and serum calcium were 2.69 +/- 1.0 , 0.468 +/- 0.055 sec and 8.16 +/- 0.97 mg% respectively in complicated falciparum infection; 1.6 +/- 0.55 , 0.442 +/- 0.043 sec and 8.72 +/- 0.97 mg% respectively in mixed infection ; 1.33 +/- 0.52 ,0435 +/- 0.035 sec and 9.77 +/- 1.34 mg% respectively in uncomplicated falciparum malaria ; 1.35 +/-0.58, 0.403 +/- 0.019 sec and 9.68 +/- 0.99 mg% respectively in vivax infection. In conclusion, hypocalcemia and QTc prolongation was

found significantly in complicated falciparum and mixed infection as compared to uncomplicated falciparum and vivax malarial infection($p<0.05$)

Asima rani et al (2005) conducted a study on electrolyte disturbance on different types of malarial infection. 173 patients were studied. Out of 173 patients 73 were malarial patients and 100 were non malarial healthy individuals. Study group-malarial patients-were categorized into two groups based on causative species of plasmodium-those with P.falciparum or P.vivax infection. Mean serum level of sodium,potassium,calcium and magnesium are measured in all 173 patients. Serum calcium level in P.falciparum, P.vivax infection and normal healthy individual were 6.52 +/- 1.09 mg% ,6.07 +/- 1.32 mg% and 9.08 +/- 4.48 mg% respectively. They had also looked for any gender wise difference in serum calcium level in different malarial infection. Mean serum calcium in P.falciparum infection, P.vivax infection and healthy individuals in male population were 6.54 +/- 1.05 mg% , 5.93 +/- 1.29 mg% and 8.96 +/- 4.61 mg% respectively whereas it was 6.43 +/- 1.33 mg%,6.58 +/- 1.48 mg% and 9.09 +/-4.34 mg% respectively in female population. She concluded that there is no significant difference in the prevalence of hypocalcemia in falciparum and vivax malaria. No variation in level of serum calcium was noted due to gender difference.

Davis TM et al (1993) conducted a study on serum calcium, serum and intracellular phosphate and serum parathormone concentration in acute malaria. He had measured serum ionized calcium and intracellular phosphate in 18 malarial patients(10 with P.falciparum and 8 with P.vivax malaria) and 10 healthy individuals. 6 out of 18 malarial patients(4 falciparum,2vivax) were having low serum ionized calcium at the time of admission and a further 6 patients(3 falciparum,3 vivax) developed hypocalcemia during treatment. Development of hypocalcemia was prominent in those with P.falciparum infection. Serum parathormone level was found to be depressed in malarial fever , especially in falciparum malaria.

T M E Davis et al (1991) studied about calcium and phosphate metabolism in acute falciparum malaria. He measured serum calcium and phosphate in 172 Thai adults ,at the time of presentation. They were of mean age 35 and 87 were males and 85 were females. A subgroup of 10 severely ill patients was studied prospectively for any changes in serum calcium and phosphate during treatment. 61 patients in cross sectional study developed hypocalcemia and he could not find out difference in degree of hypocalcemia between those with uncomplicated and complicated malaria. 6 out of 10 patients ,studied prospectively developed hypocalcemia during treatment. Serum parathormone level was also found low in these patients. Serum phosphate concentration was low in 74 patients. He concluded that mild hypocalcemia in malaria is common regardless of disease

severity. According to him, low serum parathormone level contributes to hypocalcemia in acute malaria.

J C Petithory et al (1985) did a study on hypocalcemia in malaria-study of correlation with other parameters. He measured serum calcium and albumin 26 non Africans with malaria. They had meanserum calcium of 8.5 mg% and average hypoalbuminemia of 3.7 mg%. he also measured serum calcium level in 30 each Africans with and without malaria. Those with malaria had average calcium of 8.75 mg% whereas those without malaria had average serum calcium of 9.15mg%.

Ayoola et al (2005) carried out a study on serum calcium and phosphatelevel in Nigerian children with malaria. He detected serum calcium and phosphate level in 39 children with malaria(6 complicated and 33 uncomplicated) and 39 healthy children. Hypocalcemia was detected in 23.1 % of malarial cases and 5.1% of controls. 38.5% of cases and 15.4% of controls had Hypophosphatemia. With these findings he concluded that hypocalcemia and Hypophosphatemia are associated with malaria in Nigerian children.

Sudhindra Rao Mananje et al (2017) conducted a study on QTc prolongation as an indicator of complications in malaria. 92 patients were included in the study. 12 patients had prolonged QTc. 10 out of 12 patients had associated complications. Of 80 patients

with normal QTc ,only 17 patients developed complications. Hypokalemia and hypocalcemia are the two dyselectrolemia that cause QTc prolongation. Mean serum potassium level was found to be low in those with QTc prolongation. Serum calcium level was not considered in this study. He concluded that, QTc prolongation is significantly associated with P.vivax malaria and AKI in malaria. So, malaria patients with QTc prolongation should be carefully monitored for complications.

Mohapathra M K et al (2009) studied about parathyroid dysfunction in complicated falciparum malaria. 42 patients with complicated falciparum malaria ,10 patients with uncomplicated falciparum malaria and 10 healthy individuals were included in the study. Serum calcium,magnesium,phosphate and parathormone level were measured. The study revealed the occurrence of hypocalcemia,hypomagnesemia and hypophosphatemia in malaria, regardless of disease severity. Patients had low parathormone level, in spite of hypocalcemia. It can be explained by low ionized calcium set point for parathormone secretion which occurs as a result of malaria induced parathyroid gland dysfunction.

B A Iwalokun et al (2017) did a study of calcium dynamics in infected erythrocytes of Nigerian children with plasmodium falciparum malaria. He carried out this study to find out the ghost membrane Ca 2+ ATPase activity in infected erythrocytes and its relationship with intracellular calcium concentration, parasite maturation and age. 32

children of mean age 5.8 years, with plasmodium falciparum parasitemia were selected for the study. Ghost membrane was prepared from the blood sample collected from these children by isotonic hemolysis and resealing. Ghost membrane Ca 2+ATPase activity(micromole of inorganic phosphate liberated from ATP substrate per hour) and intracellular calcium content in RBC were detected by spectrophotometric method. The infected erythrocytes were harboringring form(56.3%), schizonts/trophozoites(34.4%), and gametocytes(9.3%). A significant 1.9 – 3.9 fold increase in intracellular calcium concentration and 14. – 2.0 decrease in ghost membrane Ca 2+ ATPase activity were noted in infected erythrocytes ,as compared to control. This inverse relationship was found to be prominent ,with maturation of parasites. He concluded that decreased Ca 2+ATPase activity is responsible for increased concentration of intracellular calcium that is essential for maturation of parasites within the RBCs. So , this intracellular shift of calcium may contribute to development of hypocalcemia in malaria.

Zyed ahammed zaki et alin his article on atypical manifestations of malaria stated that mild asymptomatic cases of hypocalcemia are commonly seen in one – third of cases of malaria. According to him sick euparathyroid syndrome is the main cause of hypocalcemia in acute malaria. He said that, hypophosphatemia and mild asymptomatic hypomagnesemia occurring in acute malarial infection also contribute to hypocalcemia. Lowered renal threshold for phosphate was considered as the cause of hypophosphatemia in malaria. Hypophosphatemia in turn cause hypercalcuria and hypocalcemia.

Mohsin Ali Baloch et al (2018) did a study on determination of serum calcium in patients with malaria by flame photometer. 50 each patients and controls were studied. He detected hypercalcemia in malarial patients.

Maitland K et al (2005) conducted a study on perturbations in electrolytes levels in Kenyan children with severe malaria complicated by acidosis. 52 kenyan children with complicated malaria (impaired consciousness or deep breathing) ,complicated by acidosis(base deficit >8 mmol/l) were included in the study. Serum potassium,calcium,magnesium and phosphate levels were measured in these children. Mild to moderate hypercalcemia was common, particularly in those presented with severe malaria. Hypocalcemia was infrequent (<5%) at point of time. Hyperkalemia complicated malaria in 9 patients; 7 of them died. Hypokalemia , hypomagnesemia and hypophosphatemia were also uncommon(<7%) at the time admission, but 30 % of patients developed the same in 24 hours. They have noted an increased Intraerythrocytic calcium levels in PRBCs. So, authors have suggested that increase in calcium levels resulted from the release of intracellular calcium secondary to the erythrocyte lysis in malaria. Association of hypercalcemia and severe malarial anemia, supported the inverse linear relationship between plasma calcium and hemoglobin levels. ie;hypercalcemia is noted in those with severe hemolytic anemia. In addition, the

acidosis in severe malaria can displace the ionized calcium bound to albumin and cause hypercalcemia.

Zayed ahammed zaki et al (2010)had reported an unusual presentation of malaria as tetany. 12 years old boy was admitted with complaints of high grade fever with chills and rigor and painful , intermittent muscle spasm of left foot for one day. His dietary history was normal with adequate calcium intake. Physical examination reveled tachycardia,tachypnoea and a normal blood pressure. Liver was tender and palpable 4 cm below the RCM. Spleen was palpable 3 cm below the LCM. Peripheral smear showed plasmodium falciparum. There was anemia and thrombocytopenia. Serum calcium at the time of admission was 7.1 mg% . Serum albumin was low(3mg%). Serum phosphate and magnesium was within normal limits. ECG was normal. The patient was treated with iv artesunate, calcium phosphate and magnesium infusion. Patient became asymptomatic on day 4 of the treatment.

Akinyele akinlade et al reported a case of symptomatic hypocalcemia associated with acute severe malaria. 25 years old female presented with 5 day history of high grade fever with chills and rigor. She also had post prandial vomiting,epigastric pain, generalized tiredness, malena and cramps in hands and feet. No past history of cramps. She was diagnosed to have plasmodium falciparum malaria. Carpopedal spasm was noted on physical examination. Total calcium at the time of admission was low(1.37 mmol/l).

Total calcium raised to 1.8 mmol/l on next day, but still below normal. Serum albumin was 3.05gm%. ECG showed APCs and prolonged QTc. She was treated with iv artesunate and calcium gluconate. Serum calcium came to normal(2.16 mmol/l) on fifth day of admission and she became asymptomatic.

Lacunae in knowledge

- There are very few studies in the literatures regarding prevalence and clinical implication of hypocalcemia in malaria.
- There is paucity of studies conducted on this topic in this part of the country that makes this study very pertinent.

AIMS AND OBJECTIVES

Aim of the study

The aim of present study is to determine the prevalence and clinical profile of hypocalcemia in different types of malarial fever.

Objectives

Primary objects:

To evaluate the prevalence of hypocalcemia in malarial fever.

Secondary objects:

To study association between

1. Serum calcium level and types of malaria.
2. QTc prolongation and types of malaria.
3. Clinical manifestation of hypocalcemia and types of malaria.

MATERIALS AND METHODS

Type of Study: cross sectional study.

Study center: Stanley Government Medical College, Chennai.

Sample size: 110

$n= 4pq/d^2$

p---45 %,

q=100-p = 55%

d --- error, taken as 10% for this study

so, n= 45*55/10*10 = 99

non responsive rate is 10 %

so, sample size =99 +9= 108

so, final sample size is **110**

(**Ref**: 1 .clinical implication of hypocalcaemia in malaria; journal of medical research, 8/1/98: Prabha,M R Adhikari)

Study duration: March 2018 to August 2018 (6 Months)

Inclusion criteria:

Patients with acute febrile illness (less than 7 day's duration) and peripheralsmear positivity for malarial parasite

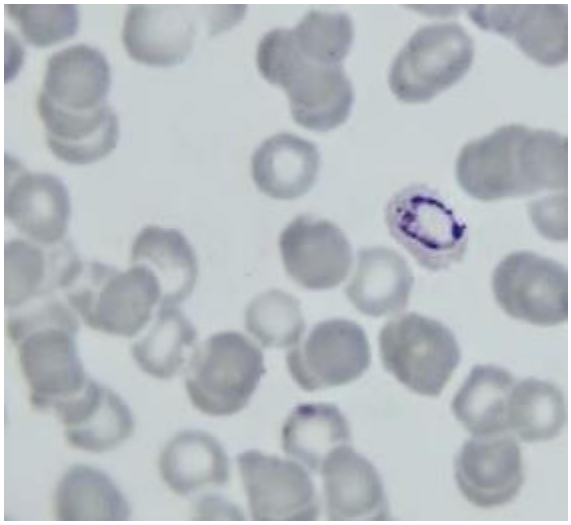
Exclusion criteria:

1. Patients with fever more than 7days duration
2. Patients who have undergone thyroid surgery
3. Patients with chronic kidney disease
4. Patients with chronic liver disease
5. Patients with hypoalbuminemia

METHODOLOGY

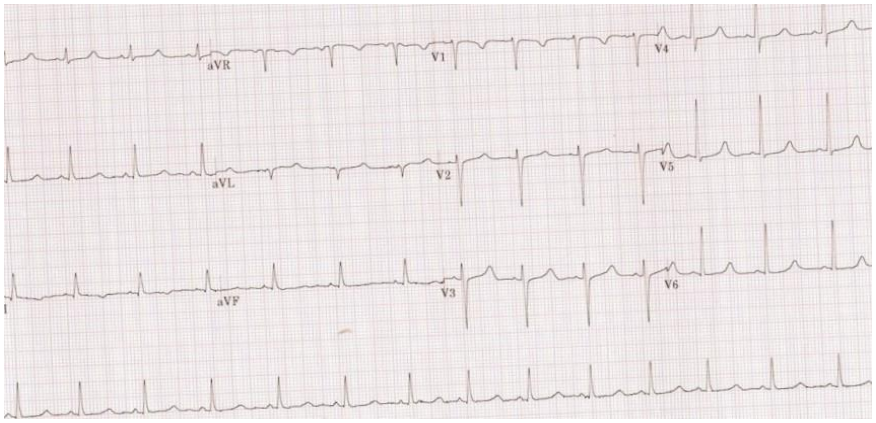
All the patients admitted in the medicine wards in Stanley medical college hospital from March 2018, who are found positive for peripheral smear for malaria, were included in the study until the sample size of 110 is achieved. Both thick and thin smear were done for diagnosing malaria. Thick smear gives a diagnosis of malaria whereas thin smear was done to identify the species of malaria. Serum calcium was measured in all the patients at the time of admission. No patient was included more than once. A detailed profoma/case report form was used for each patient, that included the following details.

- History and detailed clinical examination was done with special emphasis on signs and symptoms of complicated malaria and hypocalcaemia. Cerebral malaria, acute renal failure, ARDS, shock, severe anemia, hypoglycemia, DIC, jaundice and pulmonary edema were considered as complicated malaria for this study. Convulsions , carpopedal spasms,numbness, Trausseu's sign and Chevstok's sign were considered as the clinical manifestation of hypocalcemia in this study. Malarial patients were stratified into 2 groups according to the severity of the disease – complicated and uncomplicated malaria.
- Those with peripheral smear positivity for malaria was taken as the cases of malarial fever and enrolled for the studies. Patients were stratified into 3 groups according to the species of plasmodium parasite causing the disease. Patients with P.falciparum infection, P.vivax infection and mixed infection(P.falciparum +P.vivax) constituted the 3 groups.



(Malarial parasite (plasmodium vivax) ,detected in peripheral smear in a patient)

- Blood was collected from the patient for serum calcium at the time of admission and within 7 days of onset of fever. Serum calcium was measured in central lab by Arsenazo method (reference range-8.8-10.5mg/dl). Total serum calcium level was analyzed in each patients. Total calcium level of < 8.8 mg% was taken as hypocalcemia for this study.
- ECG was taken for all patients at the time of admission. QT segment was analyzed in each patients. Normal QTc in an ECG is equal to less than 0.44 sec. QTc of duration > 0.44 sec was considered as prolonged QTc for this study.



(ECG changes of hypocalcemia(QTc prolongation) detected in a patient)

- Patients were also stratified into different groups according to sex and age ; age and sex wise distribution of hypocalcemia in malarial patients was also analyzed.

Human subject protection

Full protocol along with proforma and informed consents was kept in institutional ethical committee and approval was obtained.

Informed consent

Consent form was available in both English and Tamil. The consent was obtained from all the participants and confidentiality was maintained.

RESULTS

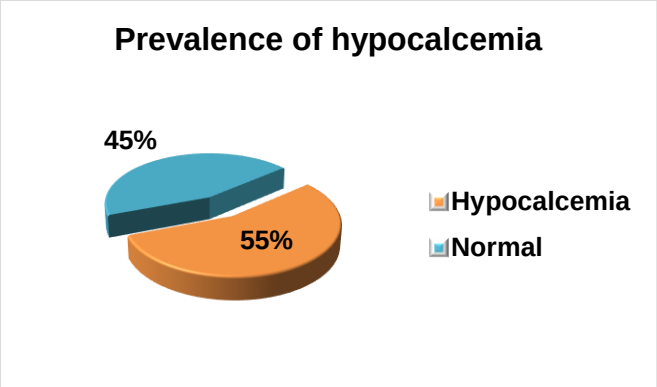
Demography

A total of 110 malarial fever patients were included in the study. 68patients were males and 42 patients were females. Out of 110 malarial cases 49 patients were infected with plasmodium falciparum. Of 49 falciparum malaria 15 patients presented with complicated malaria while 34 patients had uncomplicated malaria. Fifty out of 110 patients were having vivax malaria. Ten out of 50 had complicated vivax malaria whereas 40 patients had uncomplicated vivax malaria. Eleven out of 110 patients presented with mixed infection. Six patients with mixed infection had complicated malaria while 5 patients had uncomplicated malaria.

Prevalence of hypocalcemia in our study population

Out of 110 malarial cases 61 patients(55.5%) were found to have hypocalcemia. 49 patients (44.5 %) presented with normal serum calcium level.

Serum Calcium level	N	%
Hypocalcemia	61	55.5%
Normal	49	44.5%
Total	110	100.0%



Comparison of prevalence of hypocalcemia in malaria in males and females

Out of 68 males with malaria 41 patients(60.3%) have hypocalcemia while 27 patients(39.7%) didn't have hypocalcemia. 20 out of 42 female patients(47.6%) developed hypocalcemia while 22 patients(52.4%) had normocalcemia. There was no statistically significant difference of prevalence of hypocalcemia in malaria between males and females.

Gender	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Male	41	60.3%	27	39.7%	68	100.0%
Female	20	47.6%	22	52.4%	42	100.0%
Total	61	55.5%	49	44.5%	110	100.0%

Chi-Square Test	Value	p-value
Pearson Chi-Square	1.689	0.194

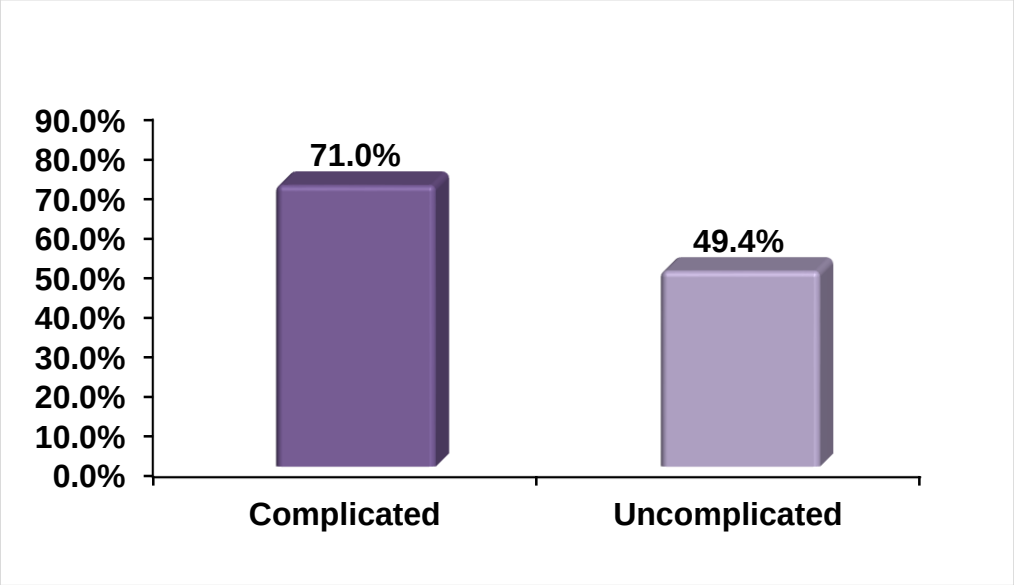
Comparison of prevalence of hypocalcemia in complicated and uncomplicated malaria

Out of 110 malarial cases 31 patients(28.18%) were having complicated malaria. 22 patients(71%) out of 31 complicated malaria had hypocalcemia while 39 patients(49.4%) out of 79 uncomplicated malaria presented with hypocalcemia. 9 patients with complicated malaria (29%) had normal serum calcium.40 patients with uncomplicated malaria(50.6%) had normal serum calcium. Hypocalcemia was found to be more prevalent in complicated malaria than uncomplicated malaria. The results were analyzed with Pearson chi square test and p- value was found to be significant(p value-0.040).

Malaria complication	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Complicated	22	71.0%	9	29.0%	31	100.0%
Uncomplicated	39	49.4%	40	50.6%	79	100.0%
Total	61	55.5%	49	44.5%	110	100.0%

Chi-Square Test	Value	p-value
Pearson Chi-Square	4.205	0.040*

* p value <0.05 is significant



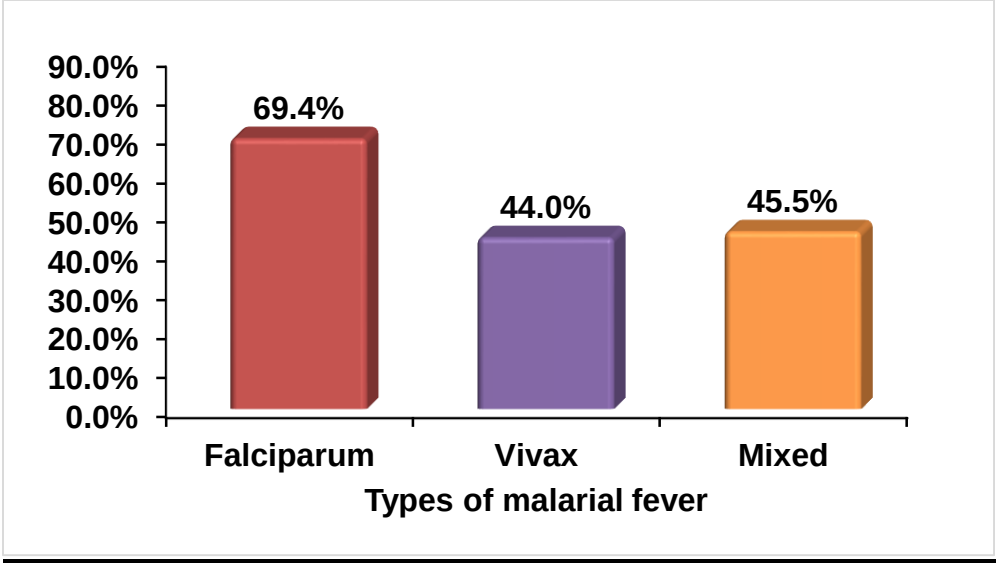
Comparison of hypocalcemia in different species of malaria

Out of 49 cases of falciparum malaria 34 patients(69.4%) had hypocalcemia whereas 30.6 % patients had normocalcemia. 22 patients with vivax malaria cases(44%) developed hypocalcemia whereas 56% vivax malarial patients were having normocalcemia. 5 (55.5%) out of 11 patients with mixed infection had hypocalcemia. Normocalcemia was noted in 6 patients(54.5%) with mixed infection. Hypocalcemia was found to be prevalent in falciparum malaria. Dates were analyzed with fisher's exact test and found to be significant with p- value of <0.05(0.028)

Malaria species	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Falciparum	34	69.4%	15	30.6%	49	100.0 %
Vivax	22	44.0%	28	56.0%	50	100.0 %
Mixed	5	45.5%	6	54.5%	11	100.0 %
Total	61	55.5%	49	44.5%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	6.979	0.028*

* p value <0.05 is significant



Prevalence of hypocalcemia in different species of complicated and uncomplicated malaria

80% (12 patients) of complicated falciparum malaria cases had hypocalcemia. Only 20%(3 patients) of complicated falciparum malaria patients had normocalcemia. 64.7% of patients with uncomplicated falciparum malaria presented with hypocalcemia whereas 35.3% patients had normocalcemia. 60% of those with complicated vivax malaria had hypocalcemia. Normocalcemia was noted in 40% of patients with complicated hypocalcemia. 40% of patients with uncomplicated vivax malaria were having hypocalcemia whereas normocalcemia was reported in 60% patients with uncomplicated vivax malaria. Hypocalcemia was detected in 66.7% of those with complicated mixed infection while 33.3% of them had normocalcemia. Only 20% patients with uncomplicated mixed infection developed hypocalcemia. 80% of those with

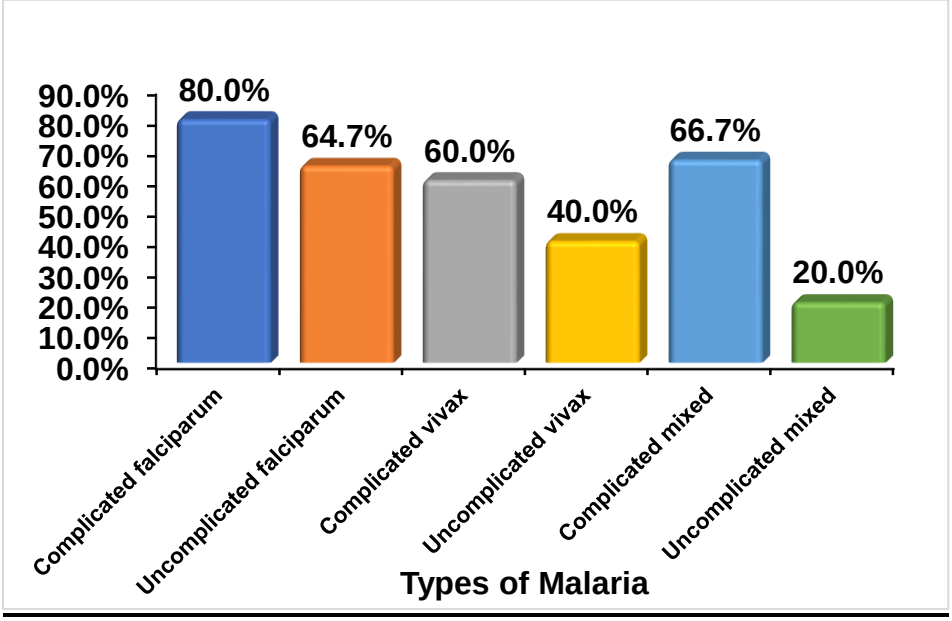
uncomplicated mixed infection had normocalcemia. Prevalence of hypocalcemia was found to be highest in those with complicated falciparum malaria. There was a statistically significant difference in the prevalence of hypocalcemia between the different types of malaria.(p value – 0.004)

Types of Malaria	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Complicated falciparum	12	80.0%	3	20.0%	15	100.0 %
Uncomplicated falciparum	22	64.7%	12	35.3%	34	100.0 %
Complicated vivax	6	60.0%	4	40.0%	10	100.0 %
Uncomplicated vivax	16	40.0%	24	60.0%	40	100.0 %
Complicated mixed	4	66.7%	2	33.3%	6	100.0 %

Uncomplicated mixed	1	20.0%	4	80.0%	5	100.0 %
Total	61	55.5%	49	44.5%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	11.369	0.004*

* p value <0.05 is significant



Types of Malaria	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Complicated falciparum	12	80.0%	3	20.0%	15	100.0 %
Uncomplicated falciparum	22	64.7%	12	35.3%	34	100.0 %
Total	34	69.4%	15	30.6%	49	100.0 %

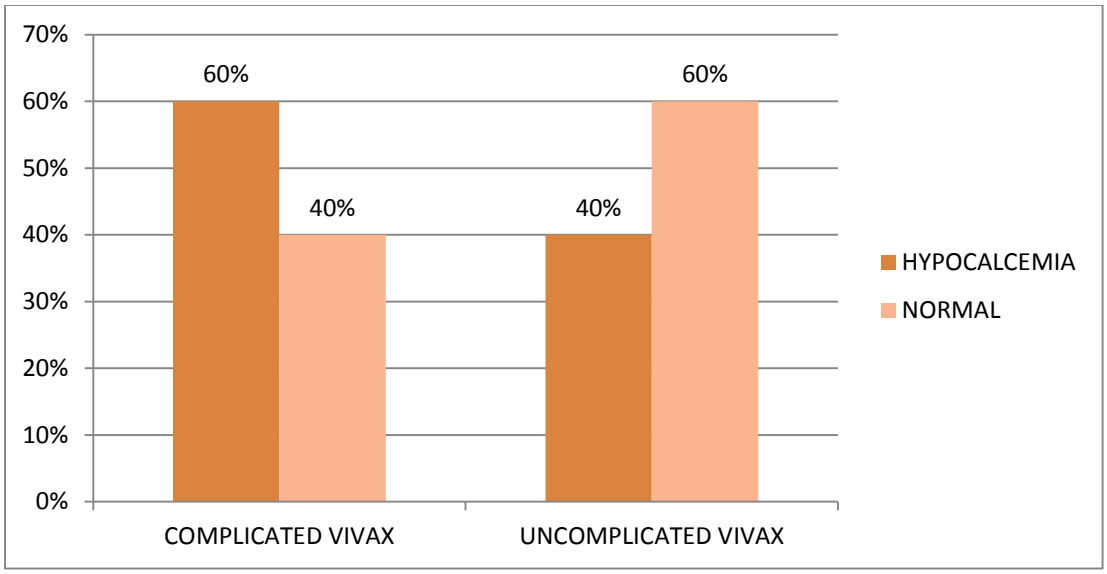
Chi-Square Test	Value	p-value
Fisher's Exact Test	-	0.336

Prevalence of hypocalcemia in complicated falciparum malaria was found to be 80% while it was 64.7% in uncomplicated malaria. 20% of those with uncomplicated falciparum malaria and 35.3% of those with uncomplicated malaria had normocalcemia. The data were analyzed with fisher's exact test. The difference in prevalence of hypocalcemia between complicated and uncomplicated falciparum malaria was found to

be statistically insignificant. So, complexity of falciparum malaria doesn't seem to have any influence on serum calcium level. This statistical insignificance may be because of the less number of falciparum malarial cases studied.

Types of Malaria	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Complicated vivax	6	60.0%	4	40.0%	10	100.0 %
Uncomplicated vivax	16	40.0%	24	60.0%	40	100.0 %
Total	22	44.0%	28	56.0%	50	100.0 %

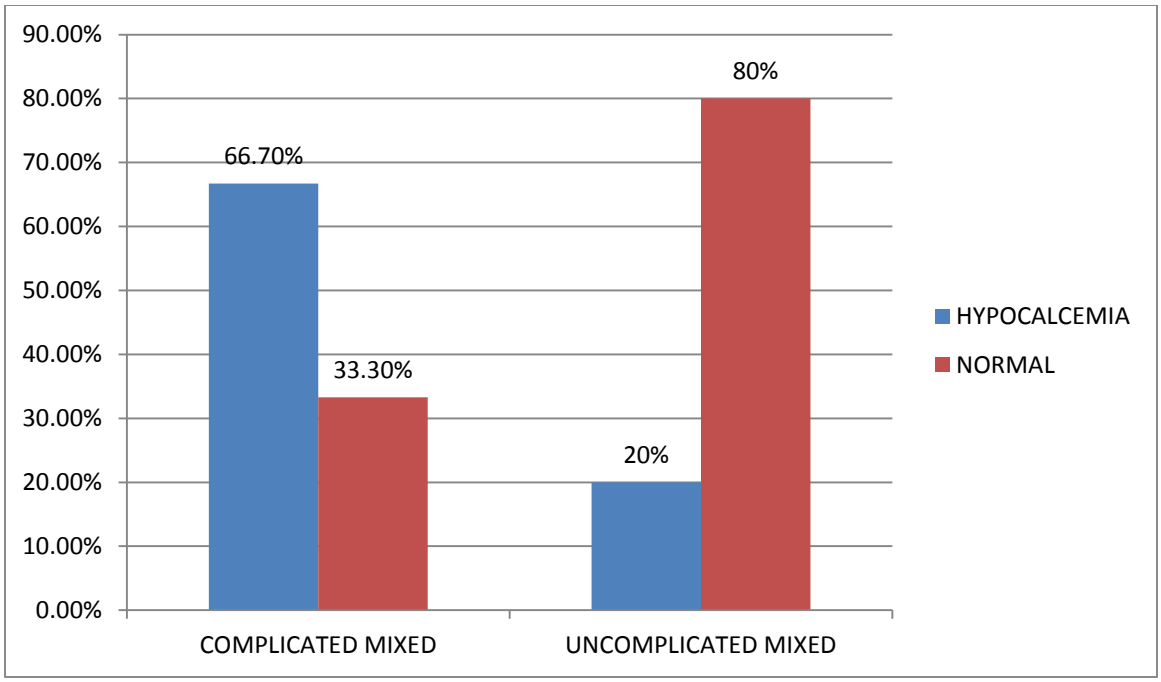
Chi-Square Test	Value	p-value
Fisher's Exact Test	-	0.302



Prevalence of hypocalcemia in complicated vivax malaria was found to be 60% while it was 40% in uncomplicated vivax malaria. 40% of those with uncomplicated vivax malaria and 60% of those with uncomplicated vivax malaria had normocalcemia. The data were analyzed with fisher's exact test. The difference in prevalence of hypocalcemia between complicated and uncomplicated vivax malaria was found to be statistically insignificant(p-value-0.302). So, complexity of vivax malaria doesn't seem to have any influence on serum calcium level. This statistical insignificance may be because of the less number of vivax malarial cases studied.

Types of Malaria	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Complicated mixed	4	66.7%	2	33.3%	6	100.0 %
Uncomplicated mixed	1	20.0%	4	80.0%	5	100.0 %
Total	5	45.5%	6	54.5%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	-	0.242



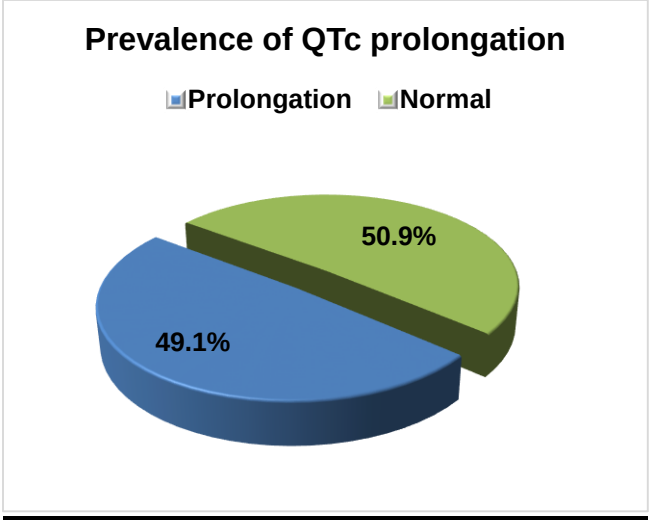
Prevalence of hypocalcemia in complicated mixed malaria was found to be 80% while it was 66.7% in uncomplicated mixed malaria. 20% of those with uncomplicated mixed malaria and 33.3% of those with uncomplicated mixed malaria had normocalcemia. The data were analyzed with fisher's exact test. The difference in prevalence of hypocalcemia between complicated and uncomplicated mixed malaria was found to be statistically insignificant(p value- 0.242). So, complexity of mixed malarial infection doesn't seem to have any influence on serum calcium level. This statistical insignificance may be because of the less number of falciparum malarial cases studied.

Although a statistically significant difference was observed in the prevalence of hypocalcemia in complicated vs uncomplicated malaria,when cases were considered overall,such difference couldnot be established when individual species were considered.

Prevalence of QTc prolongation in our study population

54 (49.1%) out of 110 malarial cases were found to have prolonged QTc. QTc was normal in 56 patients(50.9%).

QTC status	N	%
Prolongation	54	49.1%
Normal	56	50.9%
Total	110	100.0%



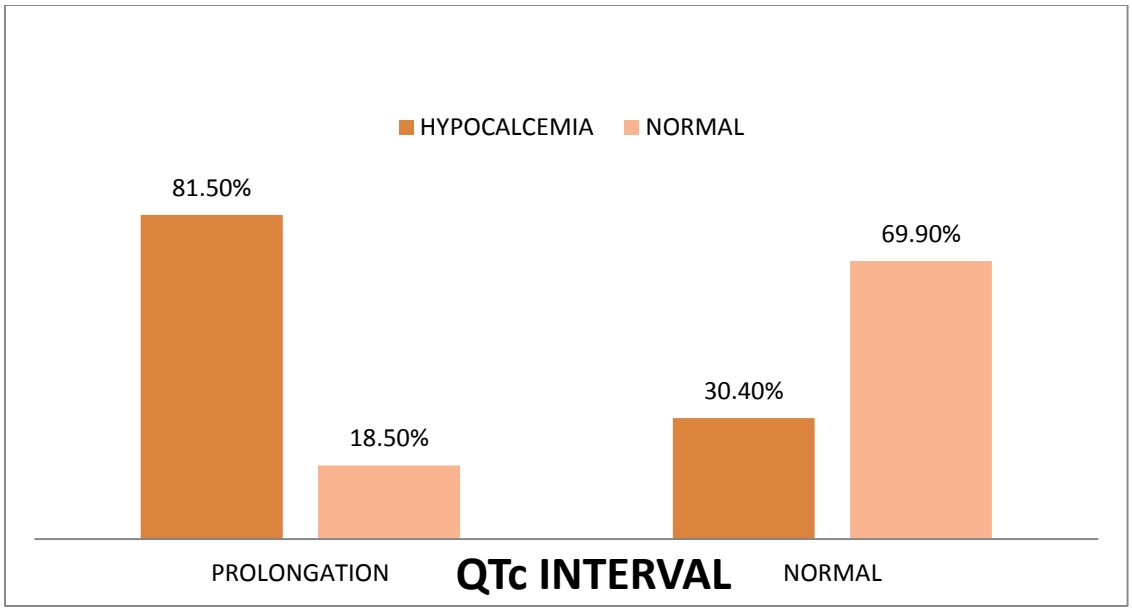
44 (81.5%) out of 54 patients with prolonged QTc had hypocalcemia while 10 (18.5%) patients had normocalcemia. 17 patients(30.4%) with hypocalcemia had normal QTc

interval. Both serum calcium and QTc were normal in 39 patients. QTc prolongation is found to be related to low serum calcium level. Data were analyzed with Pearson chi square test and found to be statisticallysignificant(p-value 0.001).

QTC status	Serum Calcium level					
	Hypocalcemia		Normal		Total	
	N	%	N	%	N	%
Prolongation	44	81.5%	10	18.5%	54	100.0 %
Normal	17	30.4%	39	69.6%	56	100.0 %
Total	61	55.5%	49	44.5%	110	100.0 %

Chi-Square Test	Value	p-value
Pearson Chi-Square	29.087	<0.001*

* p value <0.05 is significant



72.1% of patients with hypocalcemia were found to have QTc prolongation while 27.9% patients had normal QTc interval. 20.4% patients with normocalcemia also developed QTc prolongation.

Serum Calcium level	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Hypocalcemia	44	72.1%	17	27.9%	61	100.0 %
Normal	10	20.4%	39	79.6%	49	100.0 %

Total	54	49.1%	56	50.9%	110	100.0 %

Chi-Square Test	Value	p-value
Pearson Chi-Square	29.087	<0.001*

* p value <0.05 is significant

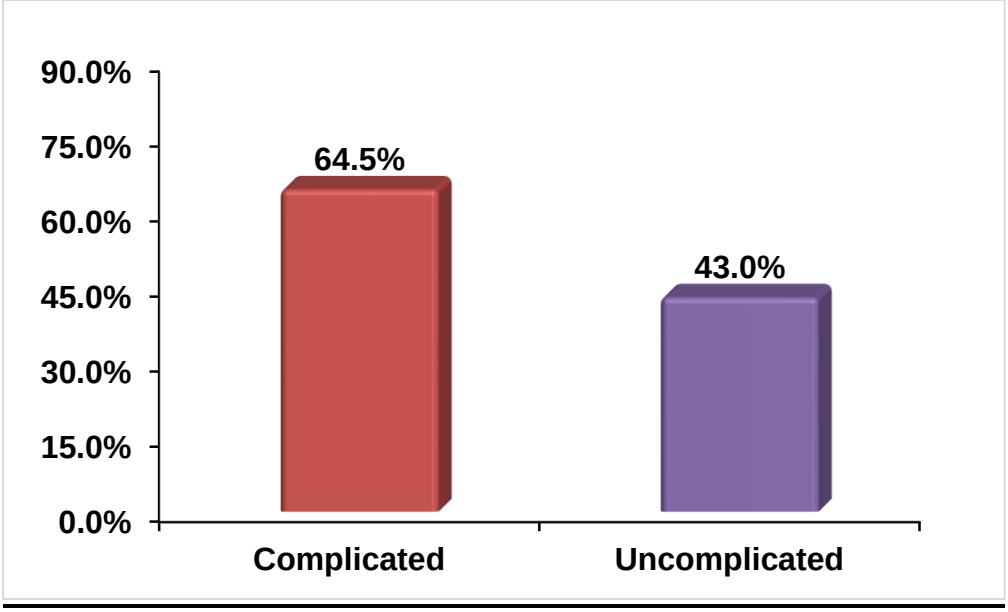
Comparison of prevalence of QTc prolongation in complicated and uncomplicated malaria

64.5% patients with complicated malaria were found to have QTc prolongation while 35.5% patients didn't have QTc prolongation. 43% patients with uncomplicated malaria developed QTc prolongation. QTc interval was normal in 57% of patients with uncomplicated malaria. Prevalence of QTc prolongation was higher in complicated malaria than that in uncomplicated malaria. The data were analyzed with Pearson chi square test and found to be statisticallysignificant ,with a p value of 0.043.

Malaria complication	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Complicated	20	64.5%	11	35.5%	31	100.0 %
Uncomplicated	34	43.0%	45	57.0%	79	100.0 %
Total	54	49.1%	56	50.9%	110	100.0 %

Chi-Square Test	Value	p-value
Pearson Chi-Square	4.110	0.043*

* p value <0.05 is significant



Malaria complication	Serum Calcium level	QTC status					
		Prolongation		Normal		Total	
		N	%	N	%	N	%
Complicated	Hypocalcemia	18	90.0%	4	36.4%	22	71.0%
	Normal	2	10.0%	7	63.6%	9	29.0%
	Total	20	100.0%	11	100.0%	31	100.0%
Uncomplicated	Hypocalcemia	26	76.5%	13	28.9%	39	49.4%
	Normal	8	23.5%	32	71.1%	40	50.6%
	Total	34	100.0%	45	100.0%	79	100.0%

Malaria complication	Chi-Square Test	Value	p-value
Complicated	Fisher's Exact Test	-	0.003*
Uncomplicated	Pearson Chi-Square	17.542	<0.001*

* p value <0.05 is significant

90% of patients with QTc prolongation in complicated malaria were found to have hypocalcemia while 10% of patients didn't have hypocalcemia. Hypocalcemia was noted in 76.5% of patients with QTc prolongation in uncomplicated malaria. 23.5% of patients with QTc prolongation in uncomplicated malaria didn't have hypocalcemia. It was found to be statistically significant.

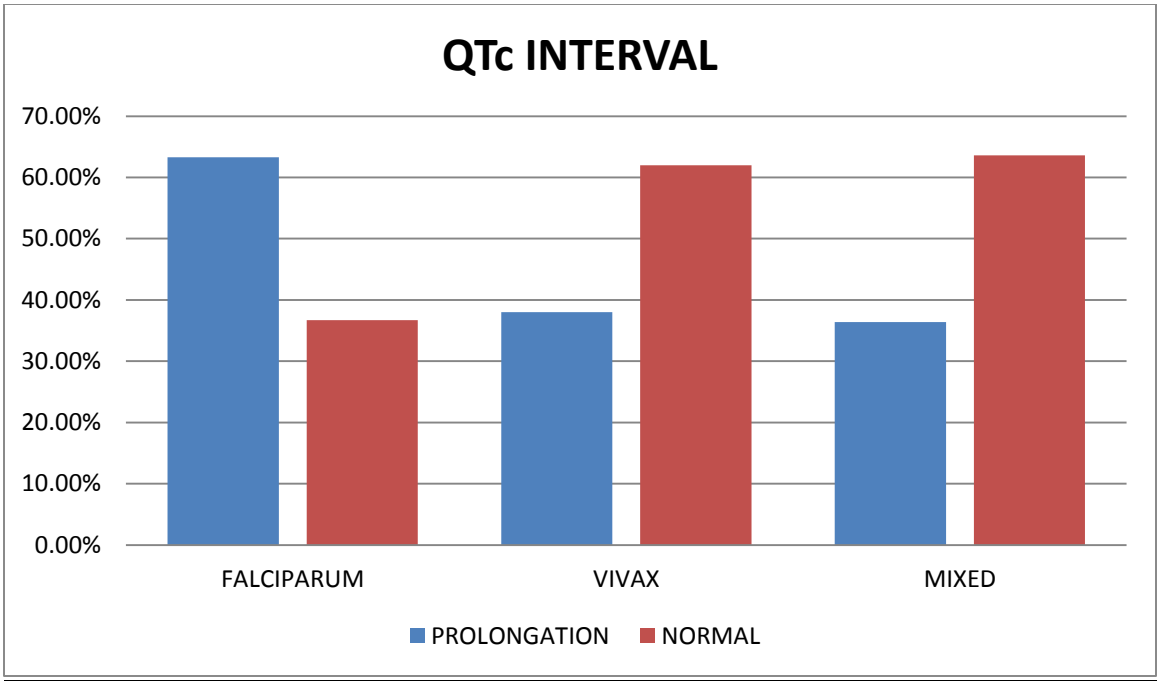
Comparison of prevalence of QTc prolongation in different species of malaria

63.3% of patients with falciparum malaria were having prolonged QTc while it was normal in 36.7% cases of falciparum malaria. 38% of vivax malaria cases showed QTc prolongation while 62% patients had a normal QTc. QTc was prolonged in 36.4% patients with mixed malarial infection. QTc was normal in 63.6% cases of mixed infection. Prevalence of QTc prolongation was highest in falciparum malarial fever. Pearson chi square test gave a p value of 0.029 which was statistically significant.

Malaria species	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Falciparum	31	63.3%	18	36.7%	49	100.0 %
Vivax	19	38.0%	31	62.0%	50	100.0 %
Mixed	4	36.4%	7	63.6%	11	100.0 %
Total	54	49.1%	56	50.9%	110	100.0 %

Chi-Square Test	Value	p-value
Pearson Chi-Square	7.113	0.029*

* p value <0.05 is significant



Malaria species	Serum Calcium level	QTC status					
		Prolongation		Normal		Total	
		N	%	N	%	N	%
Falciparum	Hypocalcemia	25	80.6%	9	50.0%	34	69.4%
	Normal	6	19.4%	9	50.0%	15	30.6%
	Total	31	100.0%	18	100.0%	49	100.0%

Vivax	Hypocalcemia	16	84.2%	6	19.4%	22	44.0%
	Normal	3	15.8%	25	80.6%	28	56.0%
	Total	19	100.0%	31	100.0%	50	100.0%
Mixed	Hypocalcemia	3	75.0%	2	28.6%	5	45.5%
	Normal	1	25.0%	5	71.4%	6	54.5%
	Total	4	100.0%	7	100.0%	11	100.0%

Malaria species	Chi-Square Test	Value	p-value
Falciparum	Pearson Chi-Square	5.035	0.025*
Vivax	Pearson Chi-Square	20.109	<0.001*
Mixed	Fisher's Exact Test	-	0.242

* p value <0.05 is significant

80.6% of patients with falciparum malaria and prolonged QTc were found to have hypocalcemia. Hypocalcemia was not detected in 19.4% of patients with falciparum malaria and QTc prolongation. 84.2% of vivax malarial cases were having QTc prolongation and hypocalcemia while 15.6% patients with QTc prolongation didn't have hypocalcemia. 75% of patients with mixed infection had both QTc prolongation and hypocalcemia while 25% patient had QTc prolongation without hypocalcemia. Association between QTc prolongation and hypocalcemia was statistically significant in

falciparum and vivax malaria; but not in mixed infection. This statistical insignificance in mixed infection may be because of less number of mixed infection studied.

Comparison of prevalence of QTc prolongation in different species of complicated and uncomplicated malaria

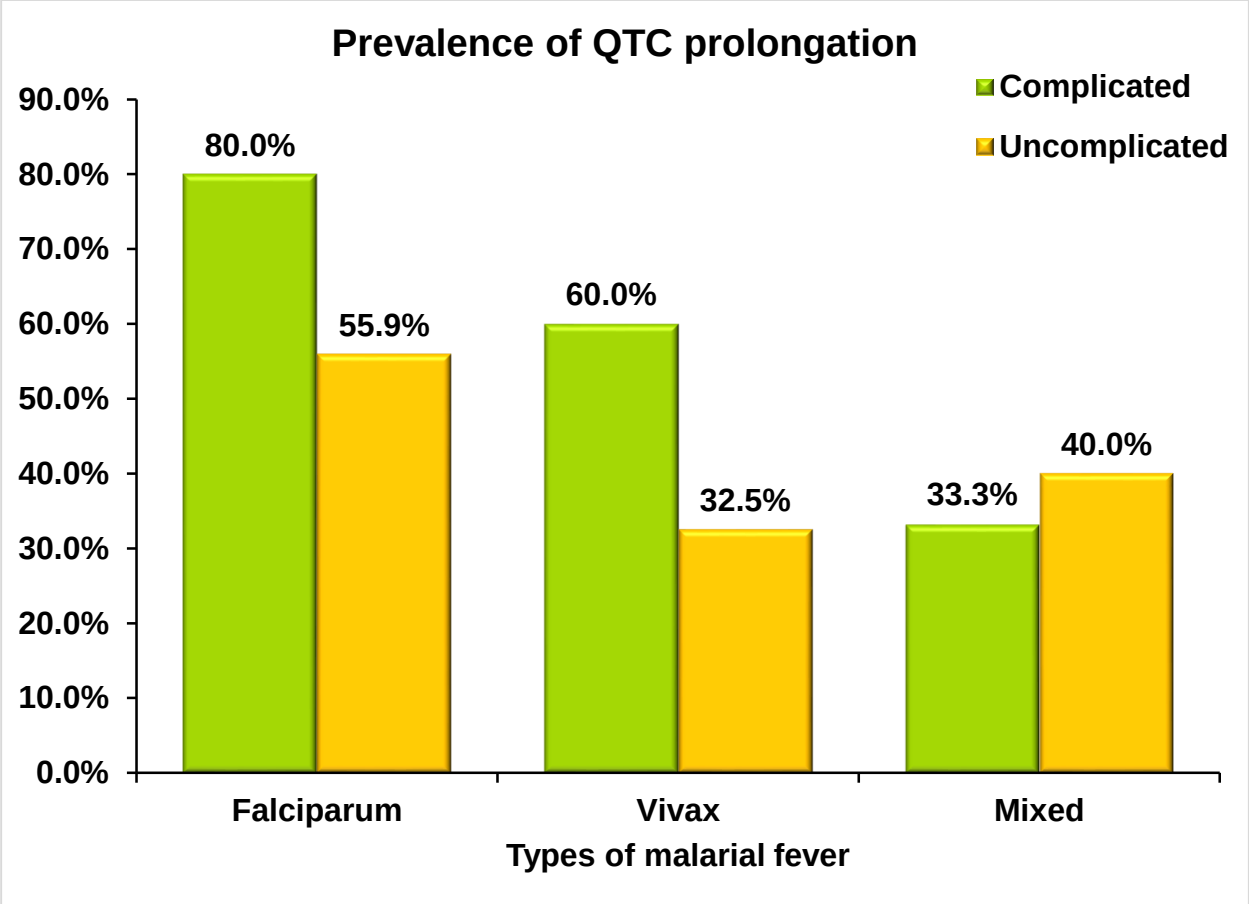
80% of patients with complicated falciparum malaria patients had prolonged QTc. Prevalence of QTc prolongation in complicated vivax malaria and complicated mixed malarial infection were 60% and 33.3% respectively. QTc was normal in 20%,67.5% and 60% patients with uncomplicated falciparum malaria, uncomplicated vivax malaria and uncomplicated mixed malarial infection respectively. Complicated falciparum malarial patients were found to have the highest prevalence of QTc prolongation. It was found to be statistically significant.

Types of Malaria	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Complicated falciparum	12	80.0%	3	20.0%	15	100.0 %

Uncomplicated falciparum	19	55.9%	15	44.1%	34	100.0 %
Complicated vivax	6	60.0%	4	40.0%	10	100.0 %
Uncomplicated vivax	13	32.5%	27	67.5%	40	100.0 %
Complicated mixed	2	33.3%	4	66.7%	6	100.0 %
Uncomplicated mixed	2	40.0%	3	60.0%	5	100.0 %
Total	54	49.1%	56	50.9%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	12.056	0.027*

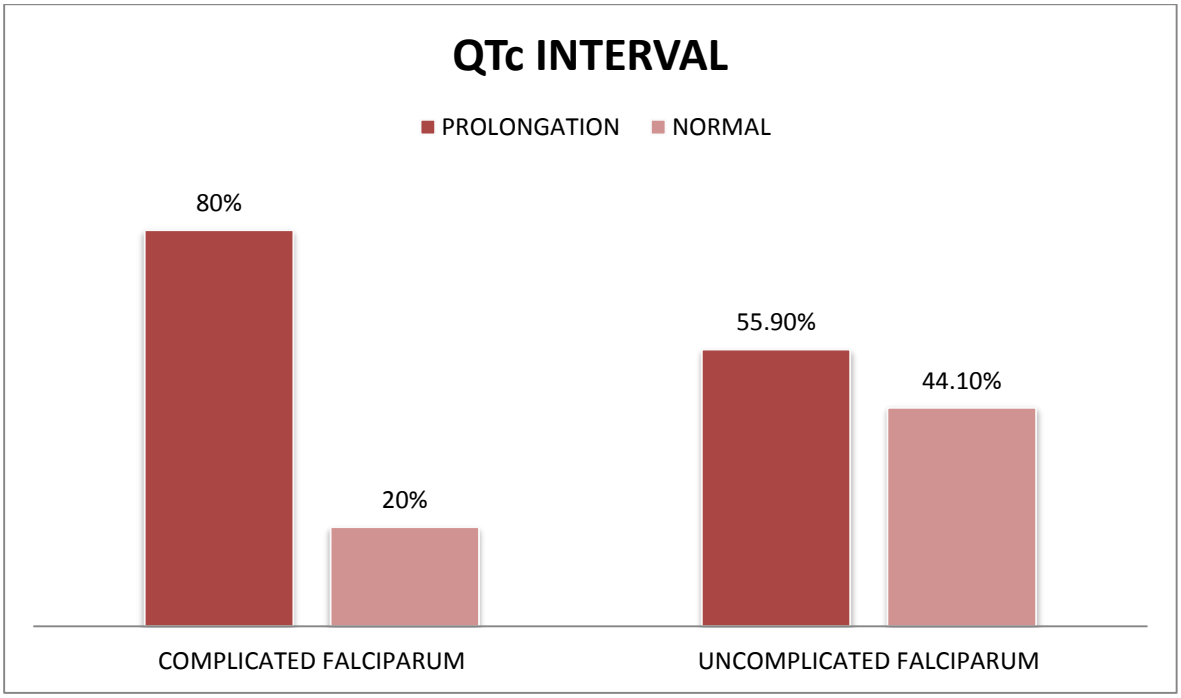
* p value <0.05 is significant



Types of Malaria	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Complicated falciparum	12	80.0%	3	20.0%	15	100.0 %
Uncomplicated falciparum	19	55.9%	15	44.1%	34	100.0 %

Total	31	63.3%	18	36.7%	49	100.0 %

Chi-Square Test	Value	p-value
Pearson Chi-Square	2.605	0.107

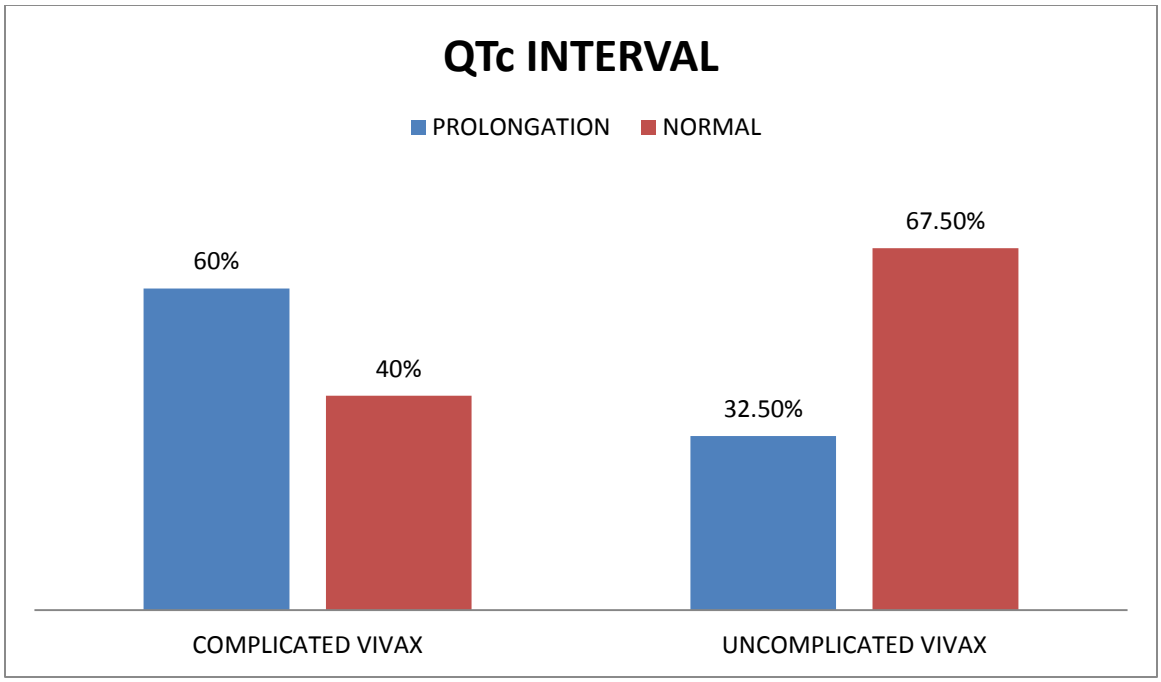


80% of patients with complicated falciparum malaria had prolonged QTc while 55.9% of those with uncomplicated falciparum malaria developed QTc prolongation. Prevalence of normal QTc in complicated and uncomplicated falciparum malaria was 20% and 44.1% respectively. . The data were analyzed with fisher's exact test. The

difference in prevalence of QTc prolongation between complicated and uncomplicated falciparum malaria was found to be statistically insignificant(p value- 0.107). So, complexity of falciparum malarial infection doesn't seem to have any influence on QTc. This statistical insignificance may be because of the less number of falciparum malarial cases studied.

Types of Malaria	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Complicated vivax	6	60.0%	4	40.0%	10	100.0 %
Uncomplicated vivax	13	32.5%	27	67.5%	40	100.0 %
Total	19	38.0%	31	62.0%	50	100.0 %

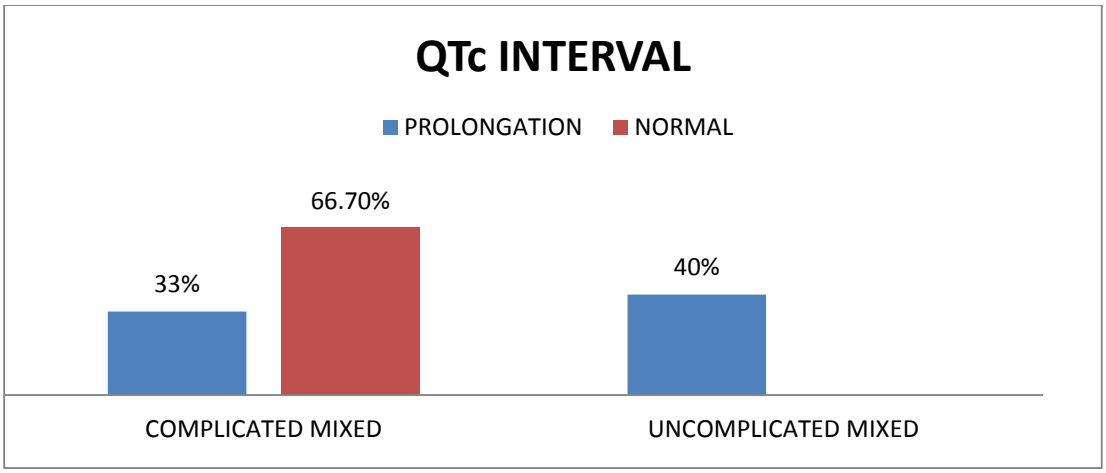
Chi-Square Test	Value	p-value
Fisher's Exact Test	-	0.150



60% of patients with complicated vivax malaria had prolonged QTc while 32.5% of those with uncomplicated vivax malaria developed QTc prolongation. Prevalence of normal QTc in complicated and uncomplicated vivax malaria was 40% and 67.5% respectively. . The data were analyzed with fisher's exact test. The difference in prevalence of QTc prolongation between complicated and uncomplicated vivax malaria was found to be statistically insignificant(p value- 0.150). So, complexity of vivax malarial infection doesn't seem to have any influence on QTc. This statistical insignificance may be because of the less number of falciparum malarial cases studied.

Types of Malaria	QTC status					
	Prolongation		Normal		Total	
	N	%	N	%	N	%
Complicated mixed	2	33.3%	4	66.7%	6	100.0 %
Uncomplicated mixed	2	40.0%	3	60.0%	5	100.0 %
Total	4	36.4%	7	63.6%	11	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	-	0.999



80% of patients with complicated mixed malaria infection had prolonged QTc while 55.9% of those with uncomplicated mixed malaria infection developed QTc prolongation. Prevalence of normal QTc in complicated and uncomplicated mixed malaria infection was 20% and 44.1% respectively. . The data were analyzed with fisher's exact test. The difference in prevalence of QTc prolongation between complicated and uncomplicated mixed malaria infection was found to be statistically insignificant(p value- 0.999). So, complexity of mixed malarial infection doesn't seem to have any influence on QTc. This statistical insignificance may be because of the less number of falciparum malarial cases studied.

Although a statistically significant difference was observed in the prevalence of QTc prolongation in complicated vs uncomplicated malaria,when cases were considered overall,such difference couldnot be established when individual species were considered.

Types of Malaria	Serum Calcium level	QTC status					
		Prolongation		Normal		Total	
		N	%	N	%	N	%
Complicated falciparum	Hypocalcemia	10	83.3%	2	66.7%	12	80.0%
	Normal	2	16.7%	1	33.3%	3	20.0%
	Total	12	100.0%	3	100.0%	15	100.0%
Uncomplicated falciparum	Hypocalcemia	15	78.9%	7	46.7%	22	64.7%
	Normal	4	21.1%	8	53.3%	12	35.3%
	Total	19	100.0%	15	100.0%	34	100.0%
Complicated vivax	Hypocalcemia	6	100.0%	0	0.0%	6	60.0%
	Normal	0	0.0%	4	100.0%	4	40.0%
	Total	6	100.0%	4	100.0%	10	100.0%
Uncomplicated vivax	Hypocalcemia	10	76.9%	6	22.2%	16	40.0%
	Normal	3	23.1%	21	77.8%	24	60.0%
	Total	13	100.0%	27	100.0%	40	100.0%
Complicated mixed	Hypocalcemia	2	100.0%	2	50.0%	4	66.7%
	Normal	0	0.0%	2	50.0%	2	33.3%
	Total	2	100.0%	4	100.0%	6	100.0%

Uncomplicated mixed	Hypocalcemia	1	50.0%	0	0.0%	1	20.0%
	Normal	1	50.0%	3	100.0%	4	80.0%
	Total	2	100.0%	3	100.0%	5	100.0%

Types of Malaria	Chi-Square Test	Value	p-value
Complicated falciparum	Fisher's Exact Test	-	0.516
Uncomplicated falciparum	Pearson Chi-Square	3.825	0.051
Complicated vivax	Fisher's Exact Test	-	0.005
Uncomplicated vivax	Pearson Chi-Square	10.940	0.001*
Complicated mixed	Fisher's Exact Test	-	0.467
Uncomplicated mixed	Fisher's Exact Test	-	0.400

* p value <0.05 is significant

Both QTc prolongation and hypocalcemia were noted in 83.3% ,78.9%, 100%, 76.9%, 100% and 50% of patients with complicated falciparum malaria,uncomplicated falciparum malaria, complicated vivax malaria, uncomplicated vivax malaria, complicated mixed infection and uncomplicated mixed infection. The association between QTc prolongation and hypocalcemia was found to be statistically significant only in complicated and uncomplicated vivax malaria.

One-way ANOVA test to compare mean values of serum calcium and QTc between different species of malaria

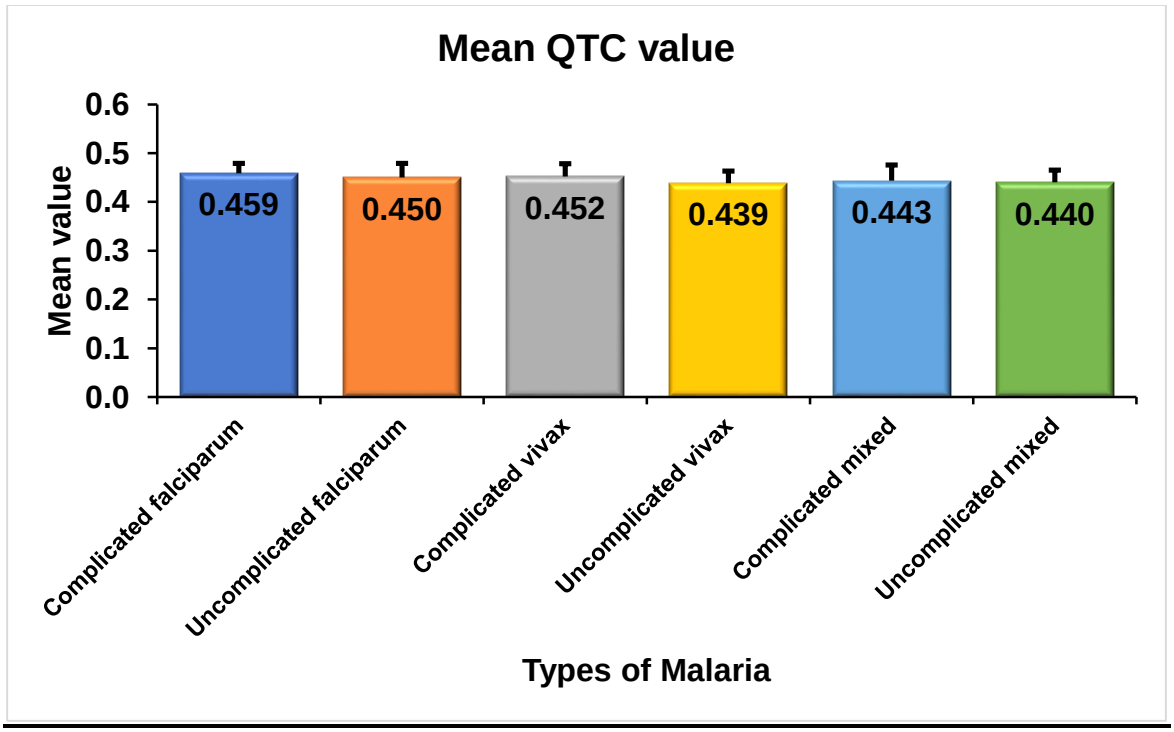
One way anova test was done to compare the mean value of serum calcium and QTc between different types of malaria. Lowest mean serum calcium was observed in complicated falciparum malaria while highest mean serum calcium was observed in uncomplicated mixed malarial infection. Difference in mean serum calcium level in different types of malaria was found to have statistical significance with a pvalue of 0.001.

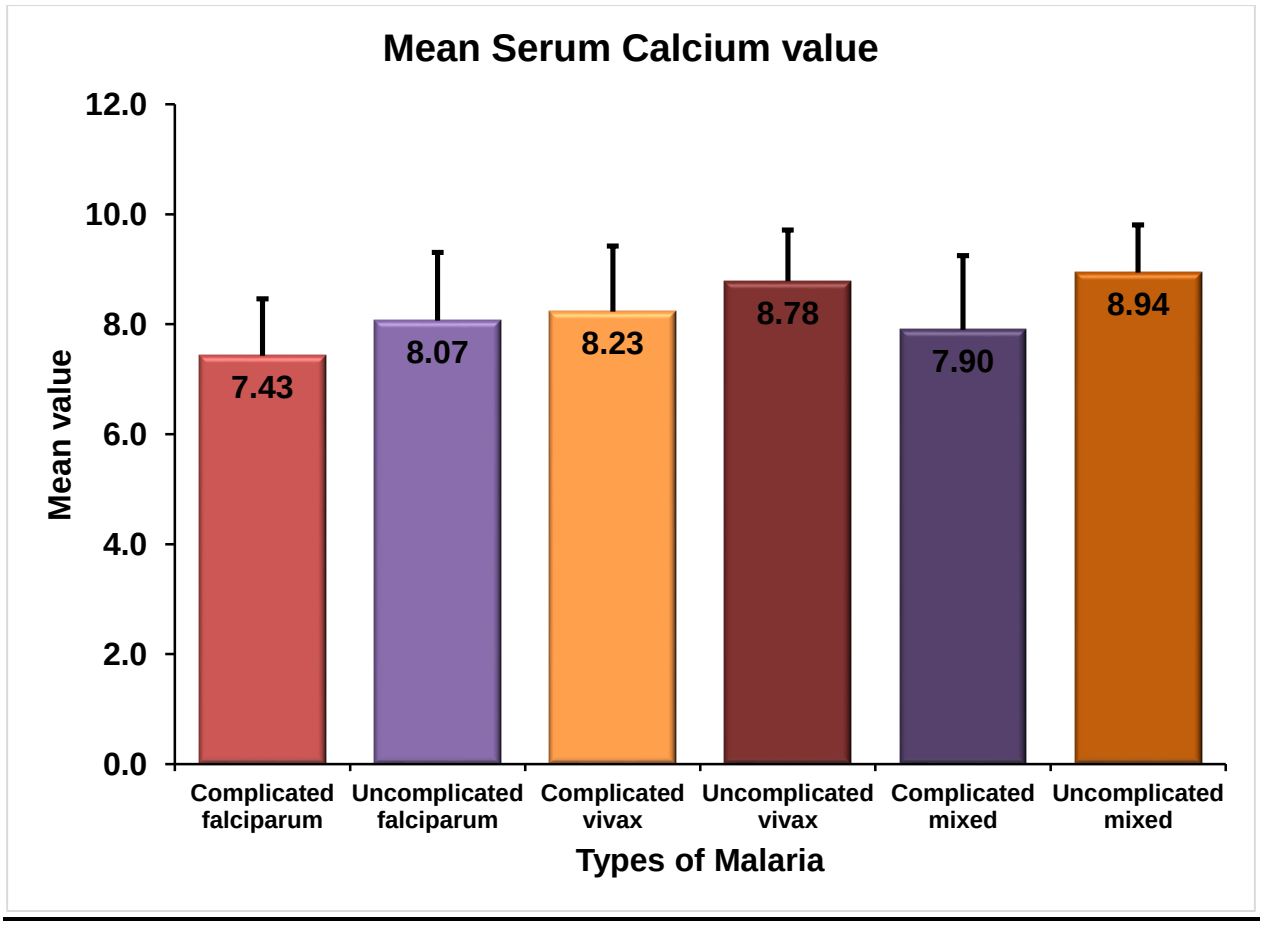
Longest mean QTc was observed in complicated falciparum malarial fever. Uncomplicated vivax malarial cases had shortest QTc. But, there was no statistical significance for the difference in mean QTc between different types of malaria. P value was 0.143.

Variables	Types of malaria	N	Mean	Std. Dev	F-value	p-value
Serum Calcium	Complicated falciparum	15	7.427	1.0368	4.270	0.001*
	Uncomplicated falciparum	34	8.065	1.2417		
	Complicated vivax	10	8.230	1.1898		
	Uncomplicated vivax	40	8.780	.9313		

	Complicated mixed	6	7.900	1.3461		
	Uncomplicated mixed	5	8.940	.8649		
	Total	110	8.284	1.1735		
QTC	Complicated falciparum	15	.4587	.02031		
	Uncomplicated falciparum	34	.4500	.02902		
	Complicated vivax	10	.4520	.02616	1.691	0.143
	Uncomplicated vivax	40	.4385	.02445		
	Complicated mixed	6	.4433	.03266		
	Uncomplicated mixed	5	.4400	.02550		
	Total	110	.4464	.02653		

* p value <0.05 is significant


Mean QTC value
Mean value
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.459
0.450
0.452
0.439
0.443
0.440
Complicated falciparum
Uncomplicated falciparum
Complicated vivax
Uncomplicated vivax
Complicated mixed
Uncomplicated mixed
Types of Malaria


Mean Serum Calcium value
Mean value
12.0
10.0
8.0
6.0
4.0
2.0
0.0
7.43
8.07
8.23
8.78
7.90
8.94
Complicated falciparum
Uncomplicated falciparum
Complicated vivax
Uncomplicated vivax
Complicated mixed
Uncomplicated mixed
Types of Malaria

Tukey HSD Post Hoc Tests for Multiple Comparisons for Serum Calcium level

Since one way anova test found out the statistical significance of difference in mean serum calcium level between different types of malaria, tukey HSD post hoc test was done to find out most significant difference in mean serum calcium level between different types of malaria. It was found that, statistically significant difference in mean serum calcium was only observed between complicated falciparum malarial and uncomplicated vivax malarial cases.

Types of Malaria		Mean Difference	p-value
Complicated falciparum	Uncomplicated falciparum	-.6380	0.420
	Complicated vivax	-.8033	0.471
	Uncomplicated vivax	-1.3533	0.001*
	Complicated mixed	-.4733	0.947
	Uncomplicated mixed	-1.5133	0.088

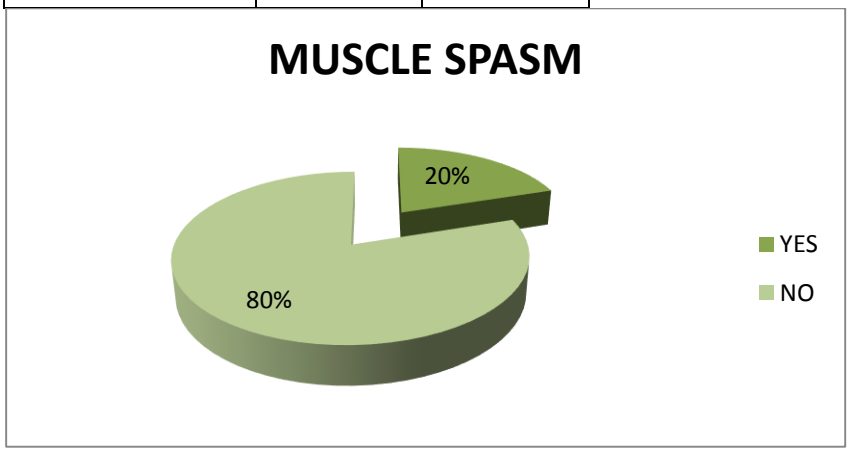
Uncomplicated falciparum	Complicated vivax	-.1653	0.998
	Uncomplicated vivax	-.7153	0.065
	Complicated mixed	.1647	0.999
	Uncomplicated mixed	-.8753	0.555
Complicated vivax	Uncomplicated vivax	-.5500	0.714
	Complicated mixed	.3300	0.992
	Uncomplicated mixed	-.7100	0.843
Uncomplicated vivax	Complicated mixed	.8800	0.447
	Uncomplicated mixed	-.1600	0.999
Complicated mixed	Uncomplicated mixed	-1.0400	0.620

* p value <0.05 is significant

Prevalence of symptomatic hypocalcemia(muscle spasm,convulsions and numbness) in study population

22 (20%) out of 110 patients with malaria had muscle spasm. 80% malarial cases didn't have muscle spasm.

Muscle spasm	N	%
Yes	22	20.0%
No	88	80.0%
Total	110	100.0%

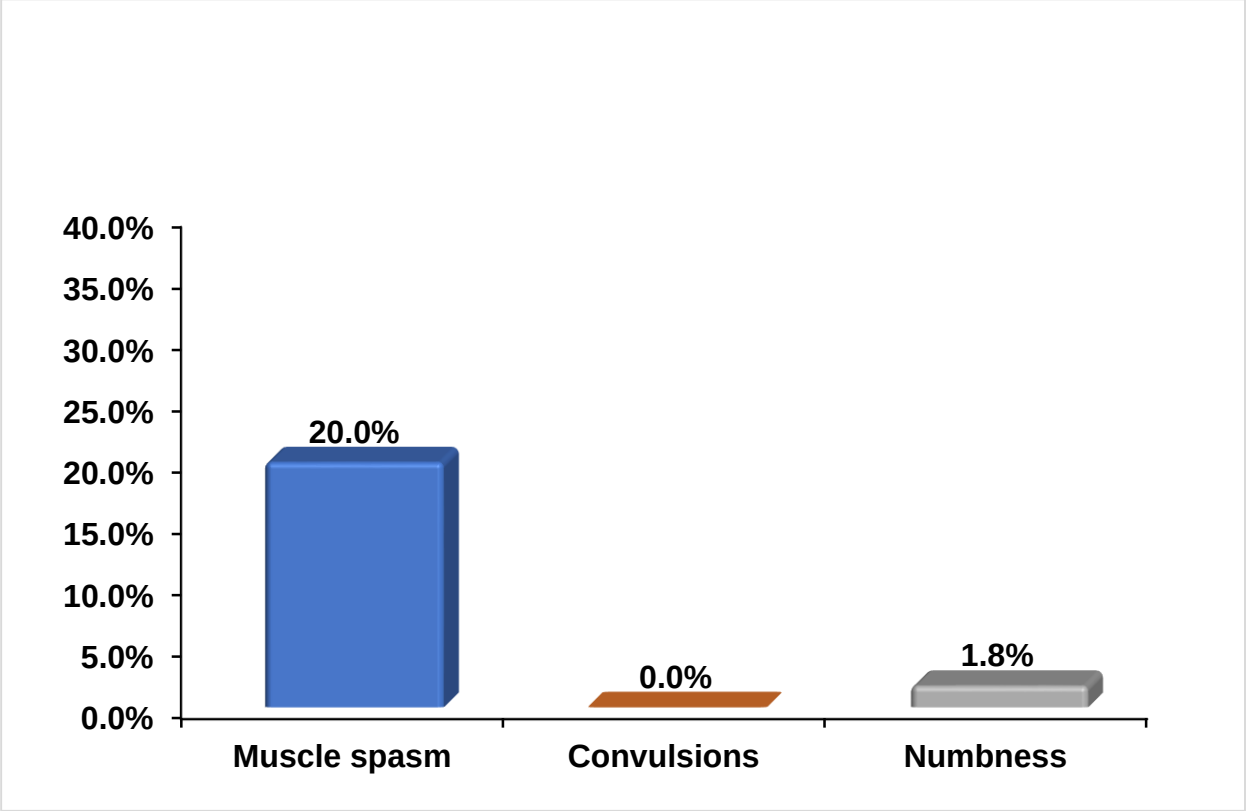


No patients in the study population presented with convulsion.

Convulsions	N	%
Yes	0	0.0%
No	110	100.0%
Total	110	100.0%

Only 2 (1.8%) out of 110 patients with malarial fever presented with numbness.108(98.2%) patients didn't have numbness.

Numbness	N	%
Yes	2	1.8%
No	108	98.2%
Total	110	100.0%



Comparison of symptomatic hypocalcemia in different species of complicated and uncomplicated malaria

60%(9 patients) of patients with complicated falciparum malaria presented with muscle spasm while 40%(6 patients) didn't have muscle spasm. 5 (14.7%) out of 34 cases of uncomplicated falciparum malaria had muscle spasm while 29 (85.3%)patients didn't

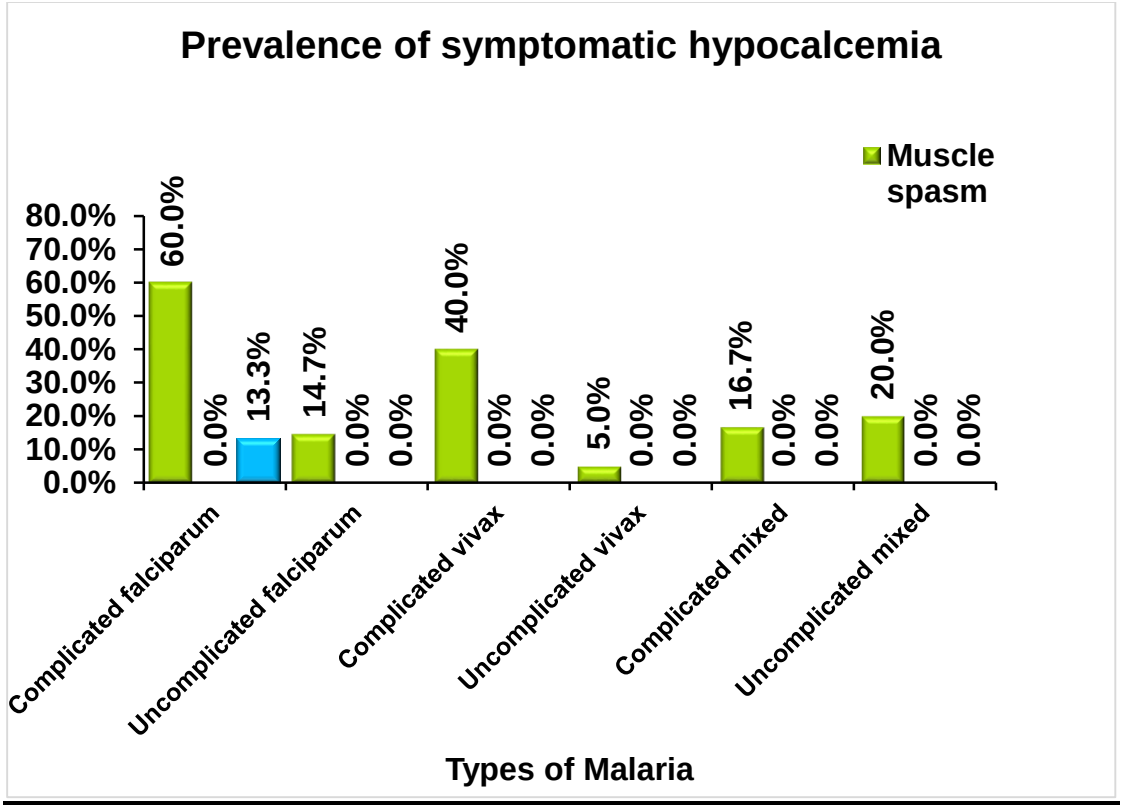
have. 4(40%)out of 10 cases of complicated vivax malaria had muscle spasm while 6 (60%)patients didn't have it. Muscle spasm was observed in only 2 (5%) out of 40 cases of uncomplicated vivax malaria. 1(16.7%)out of 6 cases of complicated mixed malarial infection were having muscle spasm while 5(83.3%) patients didn't have it. 1 (20%) out of 5 cases of uncomplicated mixed infection had muscle spasm while 4 (80%) out of 5 patients didn't have muscle spasm. Prevalence of muscle spasm was found to be highest in complicated falciparum malaria. When the data were analyzed with fisher's exact test ,it was found to be statistically significant(p-value <0.01)

Types of Malaria	Muscle spasm					
	Yes		No		Total	
	N	%	N	%	N	%
Complicated falciparum	9	60.0%	6	40.0%	15	100.0 %
Uncomplicated falciparum	5	14.7%	29	85.3%	34	100.0 %
Complicated vivax	4	40.0%	6	60.0%	10	100.0 %

Uncomplicated vivax	2	5.0%	38	95.0%	40	100.0 %
Complicated mixed	1	16.7%	5	83.3%	6	100.0 %
Uncomplicated mixed	1	20.0%	4	80.0%	5	100.0 %
Total	22	20.0%	88	80.0%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	21.498	<0.001*

* p value <0.05 is significant



No patients in the study population presented with convulsions

Only 2 patients in the study population presented with numbness. Both of them were having complicated falciparum malaria. It was found to be statistically insignificant.

Types of Malaria	Numbness					
	Yes		No		Total	
	N	%	N	%	N	%
Complicated falciparum	2	13.3%	13	86.7%	15	100.0 %

Uncomplicated falciparum	0	0.0%	34	100.0 %	34	100.0 %
Complicated vivax	0	0.0%	10	100.0 %	10	100.0 %
Uncomplicated vivax	0	0.0%	40	100.0 %	40	100.0 %
Complicated mixed	0	0.0%	6	100.0 %	6	100.0 %
Uncomplicated mixed	0	0.0%	5	100.0 %	5	100.0 %
Total	2	1.8%	108	98.2%	110	100.0 %

Chi-Square Test	Value	p-value
Fisher's Exact Test	8.102	0.080

DISCUSSIONS

(If P-Value is <0.05 then statistically significant)

The Normality tests Kolmogorov-Smirnov and Shapiro-Wilks tests results reveal that the variables follow Normal distribution. Therefore, to analyze the data Parametric methods are applied. To compare the mean values between different types of Malaria one-way ANOVA is applied followed by Tukey's HSD post hoc tests for multiple pair wise comparisons. To compare two mean values independent samples t-test is applied. To compare proportions Chi-Square test is applied, if any expected cell frequency is less than five then Fisher's exact test is used. To analyze the data SPSS (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp. Released 2015) is used. Significance level is fixed as 5.

The data were analyzed statistically and results were compared with literature reviewed, as given below.

Prevalence of hypocalcemia in malaria

In our study, hypocalcemia was found to be more prevalent in complicated malaria than uncomplicated malaria. This result concurs with most of the literature we reviewed.

Prabha et al in her study observed that 27 (45%) out of 60 malarial cases were having hypocalcemia. 88.24% of complicated malarial patients developed hypocalcemia while only 27.19% patients with uncomplicated malaria had hypocalcemia. So she concluded

that hypocalcemia is not uncommon in malaria and found to be more prevalent in complicated malarial cases.

Dr Seema Mishra et all detected hypocalcemia in 44 (62.86%) out of 70 cases of malaria.She concluded that hypocalcemia is a feature of severe/complicated malaria as it had a good correlation with parasite load and complications.

Ankush agarwall et all in their study found that 155 (63%) out of 246 malarial patients studied developed hypocalcemia.

Sony C L et all conducted a study on prognostic implication of hypocalcemia and QTc interval in malaria. Out of 100 malarial cases studied 26(26%) were found to have hypocalcemia.

David TM et all in their study observed that 12(66.66%) out of 18 patients with malaria had hypocalcemia.

T M E Davis et all studied about calcium and phosphate metabolism in acute falciparum malaria. 61(35.47%) out of 172 adults with malaria developed hypocalcemia. He could not find out difference in degree of hypocalcemia between those with uncomplicated and complicated malaria.He concluded that mild hypocalcemia in malaria is common regardless of disease severity.

Ayoola oo et all in their study detected hypocalcemia in 23% of malarial cases.

Mohapathra M K et all studied about parathyroid dysfunction in complicated falciparum malaria.The study revealed the occurrence of hypocalcemia,hypomagnesemia and hypophosphatemia in malaria, regardless of disease severity.

Mohsin Ali Baloch et all conducted a study on determination of serum calcium in patients with malaria by flame photometer. They observed hypercalcemia in malarial cases. This finding deviates from our study results.

Zyed ahammed zaki et all in their review article stated that asymptomatic hypocalcemia is seen in 1/3rd cases of malaria.

Maitland et all in their study observed that hypocalcemia was infrequent at any point of time in 52 kenyan children with severe malaria. It is against our findings.

Prevalence of hypocalcemia in different types of malaria

In our study, prevalence of hypocalcemia was found to be highest in those with complicated falciparum malaria (69.4%). It is also observed that complexity/severity of any type of malaria doesn't seem to have any influence on serum calcium level.

Ankush agarwall et all in their study found that 94(65.28%) out of 144 falciparum malarial cases were having hypocalcemia. 50% cases of vivax malaria (43 out of 86 cases) had hypocalcemia. 18 out 28 patients with mixed malarial infection developed hypocalcemia. Hypocalcemia was found to be prevalent in falciparum and mixed malarial infection.

Sony C L et all in their study found out that hypocalcemia was found significantly in complicated falciparum and mixed infection as compared to uncomplicated falciparum and vivax malarial infection.

Asima rani et all in their study noted that there is no significant difference in the prevalence of hypocalcemia in falciparum and vivax malaria. This finding is not consistent with our results.

David T M et all in their study observed that 7 out of 10 cases of falciparum malaria had hypocalcemia while 5 out of 8 vivax malarial case developed hypocalcemia.

T M E Davis et all did a study on calcium and phosphate metabolism in acute falciparum malaria. 61(35.47%) out of 172 adults with malaria developed hypocalcemia. He could not find out difference in degree of hypocalcemia between those with uncomplicated and complicated malaria.He concluded that mild hypocalcemia in malaria is common regardless of disease severity. It is consistent with our findings.

Mohapathra M K et all studied about parathyroid dysfunction in complicated falciparum malaria.The study revealed the occurrence of hypocalcemia, hypomagnesemia and hypophosphatemia in malaria, regardless of severity of falciparum malaria. This finding is consistent with our study results.

Mean serum calcium level in different types of malaria

Lowest mean serum calcium was observed in complicated falciparum malaria while highest mean serum calcium was observed in uncomplicated mixed malarial infection. That was7.429 mg% and 8.940 mg% respectively.

Prabha M R et all in their study found out that mean serum calcium level in complicated malaria was (7.4 +/- 0.98mg%) against (8.4 /- 0.4mg%) in uncomplicated malaria.

Dr Seema Mishra et all in their study observed that mean serum calcium level in complicated falciparum, complicated mixed ,uncomplicated falciparum and vivax malarial infection were (7.06 +/- 0.77) mg%, (7.02 +/- 0.49), (8.07 +/- 1.07) mg% and (8.68 +/- 03)mg% respectively. Complicated malarial cases were found to have significant hypocalcemia.

Sony C L et all observed a mean serum calcium of 8.16 +/- 0.97 mg% , 8.72 +/- 0.97 mg% , 9.77 +/- 1.34 mg% and 9.68 +/- 0.99 mg% in complicated falciparum malaria, mixed infection, uncomplicated falciparum and vivax malaria respectively. He concluded that hypocalcemia was found significantly in complicated falciparum and mixed infection as compared to uncomplicated falciparum and vivax malarial infection.

Asima rani et all in their study reported mean serum calcium level in P.falciparum, P.vivax infection and normal healthy individual were 6.52 +/- 1.09 mg% ,6.07 +/- 1.32 mg% and 9.08 +/- 4.48 mg% respectively.

J C Petithory et all in their study found out that those with malaria had an average calcium of 8.75 mg% whereas those without malaria had an average serum calcium of 9.15mg%.

Prevalence of QTc prolongation in malaria

In our study, it is found thatprevalence of QTc prolongation was higher in complicated malaria than that in uncomplicated malaria. Prevalence of QTc prolongation was highest in falciparum malarial fever.80% of patients with complicated falciparum malaria patients had prolonged QTc. Prevalence of QTc prolongation in complicated vivax malaria and complicated mixed malarial infection were 60% and 33.3% respectively. Complicated falciparum malaria was found to have highest prevalence of QTc prolongation.The association between QTc prolongation and hypocalcemia was found to be statistically significant only in complicated and uncomplicated vivax malaria.

Prabha et all noted significant correlation between degree of hypocalcemia and QTc prolongation.

Dr Seema Mishra et all noted that all 44 malarial patients with hypocalcemia had QTc prolongation.

Sony C L et all in their study found that all 26 cases of malaria with hypocalcemia had QTc prolongation. She concluded that QTc prolongation was significant in complicated falciparum and mixed malarial infection as compared to uncomplicated falciparum and vivax malaria.

Sudhindra Rao Mananje et all carried out a study on QTc prolongation as an indicator of complications in malaria. 92 patients were included in the study. 12 patients had prolonged QTc. 10 out of 12 patients had associated complications. Of 80 patients with normal QTc ,only 17 patients developed complications.He concluded that, QTc prolongation is significantly associated with P.vivax malaria and AKI in malaria.

Mean QTc in different types of malaria

Longest mean QTc was observed in complicated falciparum malarial fever while uncomplicated vivax malarial cases had shortest QTc. That was 0.4587 sec and 0.4385 sec respectively. There was no significant difference in QTc interval between different types of malaria.

Dr Seema Mishra et all found out that mean QTc interval in complicated falciparum, complicated mixed infection, uncomplicated falciparum and vivax malaria were (0411 +/- 0.038) sec , (0.512 +/- 0.033) sec ,),(0.435 +/- 0.035) sec and),(0.403 +/- 0.019) sec respectively. Vivax malaria was found to have shortest mean QTc and complicated mixed infection had longest mean QTc.

Sony C L et all in their observed that mean QTc interval in complicated falciparum, complicated mixed infection, uncomplicated falciparum and vivax malaria were 0.468 +/- 0.055 sec ,, 0.442 +/- 0.043 sec ,0435 +/- 0.035 sec and 0.403 +/- 0.019 sec respectively. Complicated falciparum malaria had longest QTc while vivax malaria had shortest QTc.

Prevalence of symptomatic hypocalcemia in malaria

In our study, 22 (20%) out of 110 patients with malaria had muscle spasm. 80% malarial cases didn't have muscle spasm. No patients had convulsions. Only 2 (1.8%) out of 110 patients with malarial fever presented with numbness. Prevalence of muscle spasm was found to be highest in complicated falciparum malaria.

There was not much studies conducted regarding prevalence of symptomatic hypocalcemia in malaria.

Dr Seema Mishra et all in their study observed that 5 out of 8 malarial case presented with muscle spasm had hypocalcemia. She also noted that 10 out of 14 malarial cases presented with convulsion had hypocalcemia.

Sony C L et all noted that 8 out of 10 patients presented with convulsion had hypocalcemia. Hypocalcemia was noted in 4 out of 8 patients with muscle spasm.

Zayed ahammed zaki et all had reported a case of falciparum malaria ,presented as tetany. 12 years old boy was admitted with complaints of fever, chills and rigor and painful intermittent muscle spasm of left foot. Serum calcium was 7.1 mg%. Symptoms got relieved after hypocalcemia correction and artesunate therapy.

Akinyele akinlade et all had reported a case of falciparum malaria presented with high grade fever, chills, vomiting, epigastric pain and cramps in hands and feet. She also had carpopedal spasm. Serum calcium was 1.37 mmol/l and QTc was prolonged. She was treated with iv calcium and artesunate.

CONCLUSIONS

1. Prevalence of hypocalcemia in malaria was found to be 55.5% in our study.
2. Hypocalcemia was more prevalent in complicated malaria than uncomplicated malaria
3. Among different types of malaria, prevalence of hypocalcemia was highest in falciparum malaria.
4. Complicated falciparum malaria showed highest prevalence of hypocalcemia. Status of complexity of malaria was not found to be related to occurrence of hypocalcemia in any types of malaria.
5. Lowest mean serum calcium was observed in complicated falciparum malaria while highest mean serum calcium was seen in uncomplicated mixed malarial infection
6. Prevalence of QTc prolongation in malaria was found to be 49.1%. 72.1% of patients with hypocalcemia had prolonged QTc.
7. Prevalence of QTc prolongation was found to be more in complicated malaria than uncomplicated malaria. 90% of complicated malarial patients with QTc prolongation were found to have hypocalcemia.
8. QTc prolongation was most prevalent in complicated falciparum malaria. 83.3% of those with QTc prolongation had hypocalcemia.

9. Longest QTc was observed in complicated falciparum malaria while shortest was in uncomplicated vivax malaria. There was no significant difference in QTc between different types of malaria.
10. Prevalence of muscle spasm in malaria was found to be 20%. Muscle spasm was most prevalent in complicated falciparum malaria
11. Prevalence of numbness in malaria was 1.8%
12. There was no statistically significant difference of prevalence of hypocalcemia in malaria between males and females.

LIMITATIONS

1. Limited number patients were evaluated
2. It was a cross sectional study. Serum calcium and QTc at the time of admission was evaluated. Development of hypocalcemia or QTc prolongation during treatment was not considered.
3. Other electrolyte abnormalities (eg : hypokalemia) that can cause QTc prolongation were not considered.

RECOMMENDATIONS

1. Studies may be undertaken with more number of patients in all age groups
2. A prospective studies may be undertaken to find out the exact incidence of hypocalcemia in malaria
3. It will be interesting to analyze occurrence of hypokalemia in malaria. Its association with QTc prolongation may be found out.
4. Studies may be undertaken to find out association between serum calcium level and serum PTH.

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STUDY PROFOMA

NAME : AGE: SEX:

ADDRESS: CONTACT NO:

COMPLAINTS:

HISTORY:

ALCOHOLISM YES NO DURATION:

HEAD INJURY YES NO

HYPOTHYROIDISM YES NO

KIDNEY DISEASE YES NO

SMOKER YES NO

LIVER DISEASE YES NO

THYROID SURGERIES YES NO

H/O MEDICATION

RELEVANT CLINICAL EXAMINATION:

GENERAL EXAMINATION

SYSTEMIC EXAMINATION:

CARDIOVASCULAR:

RESPIRATORY:

ABDOMEN :

CNS:

MUSCULO SKELETAL SYSTEM:

LABORATORY INVESTIGATIONS

HB: TC: PLATELET:

RBS RFT:

LFT

SERUM CALCIUM:

PERIPHERAL SMEAR:

QBC:

ECG FINDINGS:

COMMENT:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI –600001

INFORMED CONSENT

"**PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA"**

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:

Name and address

Signature/thumb impression:

Date:

Witness:

Name and address

Signature/thumb impression

Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

“PREVALENCE AND CLINICAL IMPLICATION OF HYPOCALCEMIA IN MALARIA’’

AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

நான்இந்தஆராய்ச்சியில்விவரங்களைமுற்றிலும்புரிந்துகொண்டேன்.

ஆய்வில்பங்குஎடுத்துபோது,

சாத்தியமானஅபாயங்கள்மற்றும்பயன்களைபற்றிநான்அறிந்துள்ளேன்.

நான்எந்தவொருவேளையிலும்ஆய்வில்இருந்துதிரும்பமுடியும், அதன்பின்னர்,

நான்வழக்கம்போல்மருத்துவசிகிச்சைபெறமுடியும்என்றுபுரிந்துகொள்கிறேன்

நான்ஆய்வில்பங்குஎடுத்துபணம்எதையும்பெறமுடியாதுஎன்றுஅறிந்துள்ளேன்.

இந்தஆய்வின்முடிவுகள்எந்தமெடிக்கல்ஜர்னலில்வெளியிடப்படஇருந்தால்நான்எதி

ர்க்கவில்லை, என்தனிப்பட்டஅடையாளத்தைவெளிப்படுத்தப்பட்டுஇருக்ககூடாது.

நான்இந்தஆய்வில்பங்கெடுப்பதன்மூலம்நான்என்னசெய்யபோகிறேன்என்றுதெரி

யும்

நான்இந்தஆய்வில்என்முழுஒத்துழைப்பையும்கொடுப்பேன்என்றுஉறுதியளிக்கிறே

ன்.

தன்னார்வளர் சாட்சி

பெயர்மற்றும்முகவரி பெயர்மற்றும்முகவரி

கையொப்பம் / விரல்ரேகை: கையொப்பம் /

விரல்ரேகை:

ஆராய்ச்சியாளராக கையொப்பம்மற்றும்தேதி

FINANCIAL DISCLOSURE

There was no financial interest while conducting the study.

							CLINICAL FEATURES		
Sl.No	NAME	AGE	SEX	DIFFERENT TYPES OF MALARIA	SERUM CALCIUM	QTC	MUSCLE SPASM	CONVULSIONS	NUMBNESS
1	SELVI	58	F	2	8.9	0.49	N	N	N
2	ANUSHIYA	15	F	5	6.9	0.49	N	N	N
3	DESAYAN	15	M	4	8.9	0.41	N	N	N
4	SELVI	13	F	2	9.1	0.42	N	N	N
5	SELLADURAI	68	M	1	7.2	0.45	Y	N	N
6	MANNARU	68	M	3	7.7	0.46	Y	N	N
7	DATCHANA MOORTHY	55	M	4	7.7	0.46	N	N	N
8	GEETHA	32	F	1	8.2	0.46	N	N	N
9	RAJESH KUMAR	24	M	2	7.8	0.49	N	N	N
10	ROSELIN JOSEPH	23	F	4	7.8	0.42	N	N	N
11	MEENA	67	F	2	8.1	0.43	N	N	N
12	DASS	18	M	1	7.6	0.43	N	N	N
13	THANVIR	18	M	2	8	0.47	N	N	N
14	RAMKUMAR	20	M	4	7.7	0.47	N	N	N
15	JOTHI	57	F	2	6.9	0.47	Y	N	N
16	NARESH	21	M	2	10	0.42	N	N	N
17	ARUNACHALAM	51	M	4	9.1	0.45	N	N	N
18	MALATHI	32	F	3	9	0.42	N	N	N
19	MUTHULAKSHMI	62	F	2	9.3	0.48	N	N	N
20	INDRANI	56	F	2	7.3	0.47	N	N	N
21	SABITH	18	M	2	6.6	0.41	Y	N	N
22	HASEEN	36	M	4	6.9	0.42	Y	N	N
23	THANGARAJ	55	M	1	6.9	0.48	Y	N	N
24	KALLIYAPERUMAL	70	M	4	10	0.42	N	N	N
25	ANBAZHAGAN	67	M	3	6.3	0.47	Y	N	N
26	BOOMINATHAN	60	M	2	7.9	0.42	N	N	N
27	SHANMUGAN	60	M	1	7.1	0.45	Y	N	N
28	RAJESWARI	33	F	2	10.1	0.41	N	N	N
29	SUSEELA	50	F	2	6.5	0.47	Y	N	N
30	CHANDRA	48	F	5	6.6	0.48	Y	N	N
31	NABISA	51	F	4	9.9	0.43	N	N	N
32	CHIMMAYAIN	66	M	2	7	0.43	N	N	N
33	KARTHIKEYAN	71	M	1	6.2	0.49	Y	N	N
34	ARUN	23	M	4	7.8	0.49	N	N	N
35	ASLAM	18	M	4	9.6	0.43	N	N	N
36	NATESAN	61	M	2	6.8	0.47	N	N	N
37	SURESH	21	M	2	6.5	0.45	N	N	N
38	MOHAN	28	M	6	9.1	0.43	N	N	N

39	NAGARAJ	23	M	1	6.6	0.47	Y	N	N
40	RAVI	39	M	1	8.9	0.46	N	N	N
41	LOGESWARI	13	F	6	9.5	0.42	N	N	N
42	SARAVANAN	25	M	4	7.3	0.49	N	N	N
43	ANJALI	55	F	2	7.1	0.47	N	N	N
44	RANGASAMY	56	M	2	9.6	0.43	N	N	N
45	BABU	42	M	4	9.7	0.42	N	N	N
46	SWETHA	16	F	1	7	0.46	N	N	Y
47	SUDHA	28	F	4	10	0.42	N	N	N
48	NAVEEN	19	M	4	7.9	0.49	N	N	N
49	ARUMUGASAMY	52	M	4	8.3	0.43	N	N	N
50	AMBUSELVAM	45	M	2	9.2	0.41	N	N	N
51	LAKSHMI	16	F	1	6.3	0.49	Y	N	N
52	SRINIVASAN	30	M	4	8.9	0.42	N	N	N
53	KAMMARUNNISA	55	F	6	9.7	0.45	N	N	N
54	DILEEP KUMAR	33	M	4	9.1	0.44	N	N	N
55	SUJITH VARMA	16	M	2	6.8	0.42	N	N	N
56	DINESH KUMAR	17	M	2	9.6	0.42	N	N	N
57	JACOB	29	M	4	9.1	0.41	N	N	N
58	JOSEPH	35	M	6	8.9	0.42	N	N	N
59	PERIYASAMY	42	M	4	8	0.42	N	N	N
60	GANGA	25	F	5	10	0.42	N	N	N
61	SAKTHIVEL	24	M	2	7.2	0.48	N	N	N
62	REVATHY	24	F	2	9.2	0.41	N	N	N
63	PRASADH	21	M	4	7.7	0.47	N	N	N
64	HARI LAL	51	M	4	9	0.42	N	N	N
65	PRIYA	35	F	5	7.5	0.42	N	N	N
66	ANJALI	18	F	4	7.5	0.43	N	N	N
67	KASTHURI	39	F	4	9.3	0.43	N	N	N
68	RAMESH	52	M	2	10	0.46	N	N	N
69	NAVAMANI	42	M	1	6.6	0.48	Y	N	N
70	RAMU	40	M	2	6.9	0.49	N	N	N
71	SUNDARI	32	F	4	9.3	0.43	N	N	N
72	MUHAMMED HAJI	64	M	4	8.2	0.48	N	N	N
73	CHANDRASEKHAR	54	M	5	7.3	0.43	N	N	N
74	HANIFA	54	M	2	6.6	0.45	Y	N	N
75	KALA	20	F	2	9.6	0.47	N	N	N
76	PETER	41	M	6	7.5	0.48	Y	N	N
77	RADHA	54	F	3	8.2	0.47	N	N	N
78	EZHUMALAI	54	M	4	9.3	0.45	N	N	N
79	RAMA DEVI	45	F	4	9	0.42	N	N	N
80	RADHAKRISHNAN	49	M	4	9	0.41	N	N	N
81	SURESH	33	M	1	9.1	0.45	N	N	N

82	RADHA	22	F	4	7.6	0.46	N	N	N
83	SANDHYA	15	F	4	10.1	0.42	N	N	N
84	SAMBATH	15	M	3	9.3	0.42	N	N	N
85	SASIKUMAR	38	M	4	9.9	0.42	N	N	N
86	GOKUL	26	M	2	7.7	0.48	N	N	N
87	RAMKUMAR	31	M	2	8.2	0.41	N	N	N
88	VIJAYALAKSHMI	35	F	4	9.7	0.42	N	N	N
89	ARUL SANTHA	68	F	3	6.9	0.48	Y	N	N
90	RAMESH	24	M	4	7.1	0.46	Y	N	N
91	SANTHA	38	F	4	10	0.43	N	N	N
92	MUTHUKUMAR	58	M	4	9.9	0.44	N	N	N
93	RAMESH	26	M	1	7.4	0.45	Y	N	N
94	MEENATCHI	55	F	4	8.4	0.48	N	N	N
95	GANESAN	50	M	3	9.2	0.42	N	N	N
96	MEENATCHI	35	F	4	9.2	0.42	N	N	N
97	KANDAN	69	M	3	8.7	0.47	N	N	N
98	GOWRI	69	F	4	9.7	0.43	N	N	N
99	RAMAN	70	M	5	9.1	0.42	N	N	N
100	SIVAGAMY	35	F	4	9	0.46	N	N	N
101	SRUTHI	28	F	2	7.8	0.45	N	N	N
102	SUNDARI	45	F	1	9.5	0.43	N	N	N
103	DURAISAMI	70	M	2	7.2	0.44	N	N	N
104	SHUHAIB	19	M	3	9.9	0.43	N	N	N
105	MALARMATHI	30	F	4	8.6	0.42	N	N	N
106	THULASI RAM	22	M	3	7.1	0.48	Y	N	N
107	VAISHNAVI	22	F	2	7.9	0.49	N	N	N
108	BALAMURUGAN	59	M	2	6.6	0.49	Y	N	N
109	PETER	47	M	1	6.8	0.43	Y	N	Y
110	MOHD.HANEEFA	66	M	2	10.2	0.43	N	N	N

complicated falciparum malaria	1
uncomplicated falciparum malaria	2
complicated vivax malaria	3
uncomplicated vivax malaria	4
complicated mixed infection	5
uncomplicated mixed infection	6

normal serum calcium	8.8-10.5mg%
hypocalcemia	<8.8mg%
hypercalcemia	>10.5mg%
QTc prolongation	>0.44seconds