Prognostic Efficacy Assessment of ACT Therapy and Quinine in Severe Falciparum Malaria

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ABSTRACT

In this study, the changes in prognostic indicators such as haemoglobin levels, serum lactate levels, liver function tests, blood sugar levels and glassgow coma scale in patients of severe falciparum malaria treated with Artesunate combination therapy and Quinine have been observed. One hundred patients of severe falciparum malaria were selected from medicine indoor wards. The patients were randomly assigned to artesunate based combination therapy or quinine based therapy. Prognostic parameters like haemoglobin, glasgow coma scale, serum lactates, liver function test and blood sugar levels were monitored. The present study suggests that artesunate is an effective alternative to quinine in the treatment of severe malaria.The mortality, incidence of posttreatment hypoglycemia, coma recovery time, time to normalization of plasma lactate levels and liver function tests, variability in Haemoglobin were not found to be statistically significant. Occurrence of hypoglycemia and hearing disturbances in quinine treatment group was found to be statistically significant.

KEY WORDS: artesunate combination therapy, infectious disease, malaria, pharmacotherapy, quinine

INTRODUCTION:

Malaria results from the multiplication of plasmodium parasites within red blood cells, causing symptoms that typically include fever and headache. It may lead to death in severe cases. It is common in tropical and subtropical regions. Severe disease is largely caused by Plasmodium falciparum while the disease caused by Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae is generally a milder disease that is rarely fatal[1,2] . Plasmodium knowlesi is a zoonosis that causes malaria in macaques but can also infect humans. Malaria is transmitted through the bites of infected mosquitoes. Features indicating poor prognosis in severe falciparum malaria- clinically are marked agitation, hyperventilation (respiratory distress), hypothermia(36.5c), bleeding, deep coma, repeated convulsions, anuria and shock. Hypoglycemia (<2.2mmol/l), hyperlactatemia (>5mmol/l), acidosis, elevated serum creatnine, total bilirubin, liver enzymes,muscle enzymes, urate; leucocytosis, severe anaemia, coagulopathy and Hyperparasitemia are observed[2,7] . A variety of antimalarial medications are available. Severe malaria is treated with intravenous or intramuscular quinine or, since the mid-2000s, the artemisinin derivative artesunate, which is superior to quinine in both children and adults. In patients with severe malaria, artesunate combination therapy is recommended. Certain parameters like hypoglycemia, acidosis, glassgow coma scale, liver function tests and serial changes in hematocrit guide towards the severity of underlying disease and response to treatment and hence should be monitored throughout the course of disease[1,2,3]. This study planned to compare these parameters in two treatment groups i.e. artesunte in combination with clindamycin and quinine[4,5].

Hypoglycemia, an important and common complication of severe malaria, is associated with poor prognosis[6] . It results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both host and, to a much lesser extent, the malarial parasites. The situation is further compounded by the use of quinine (and quinidine), which is a powerful stimulant of pancreatic insulin secretion. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycemia is difficult: the usual

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physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria. Hypoglycemia may also be associated with low plasma insulin concentrations and with elevated plasma concentrations of lactate, alanine, and 5-nucleotidase - a finding that suggests that impaired hepatic gluconeogenesis but not hyperinsulinemia contributes to the pathogenesis of pretreatment hypoglycemia[11]. These observations indicate that in falciparum malaria quinine-induced insulin secretion may precipitate hypoglycemia, but other factors may also contribute. This important complication, associated with pregnancy and severe disease, must be excluded in all patients with falciparum malaria who have impaired or deteriorating consciousness and who are receiving treatment with Quinine.

Acidosis, an important cause of death from severe malaria, results from accumulation of organic acids. Hyperlactatemia commonly coexists with hypoglycemia. The prognosis of severe acidosis is poor. In adult patients, acidosis results from metabolic, circulatory, and renal dysfunction, whereas in children, metabolic factors appear to predominate. It is often followed by circulatory failure refractory to volume expansion or inotropic drug treatment and ultimately by respiratory arrest. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory perfusion leads also to cellular dysfunction consequent on release of host and parasite – derived toxic mediators, hypovolemia, lactate production by the parasites, and a failure of hepatic and renal lactate clearance[12] . Hyperlactatemia (plasma lactate, >4mmol/L), metabolic acidosis (Standard Base Deficit [SBD],>3.3 or arterial Pco2, >45 torr [6kPa]), and academia (Ph<7.3range, 1.8-4.1), respectively, are the poor prognostic indicators[3,6]. After treatment, lactate concentrations falls rapidly in survivors but only slightly, or even rise, in fatal cases. Sustained hyperlactataemia (raised lactate concentrations, 4 h after admission) prove to be the best overall prognostic indicator.

Coma is a characteristic and ominous feature of falciparum malaria and, despite treatment, is associated with death rates of 20% among adults and 15% among children[8]. Any obtundation,delirium, or abnormal behavior should be taken very seriously. The onset may be gradual or sudden following a convulsion. The primary cause of coma is disruption of physiological barrier of the cerebral circulation [8]. This is brought about by alteration of the function of the endothelial cells which are normally highly impermeable but which become permeable to protein, especially albumin, and so allow leakage of fluid. The protein and water leak into the contiguous brain tissue, where they cause some local edema, and into the cerebrospinal space through the blood-brain barrier. Since the villi are similarly disturbed, the protein passes freely back into the blood stream, so that the cerebrospinal fluid protein content becomes only moderately raised. The leakage of protein and of the accompanying water causes local increase in plasma viscosity and eventually stasis with packing of erythrocytes into a homogeneous mass which is essentially similar to that which occurs in vessels in acute inflammation. The local circulation then slows and may come to a stop. Thus it may be the effect which finally induces coma in the patient [8]. The stasis is reversible for some time but eventually becomes irreversible. The ultimate outcome depends on two other factors: The degree of irreversible damage which has occured before therapy and the removal of the malaria parasites from the blood. The coma scale commonly used in adults is Glassgow Coma Scale[9]. Artemether treatment is associated with quicker clearance of parasites from the peripheral blood but slower resolution of fever, slower recovery from coma, and longer hospitalizations In patients with cerebral malaria, quinine treatment remained significantly associated with a more rapid recovery than artemether treatment.

Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with P. falciparum infections; is more common among adults than among children; and results from hemolysis, hepatocyte injury, and cholestasis[10,21]. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism. Occasional patients with falciparum malaria may develop deep jaundice. It can occur due to intravascular hemolysis, disseminated intravascular coagulation, glucose 6 phosphate dehydrogenase related hemolysis, antimalarial drug induced and, rarely, 'malarial hepatitis'. Histologically, the hepatitis or the actual inflammation in the liver has never been demonstrated. Jaundice has been found to be more common in falciparum as compared to vivax malaria. A diagnosis of malarial hepatitis can be made in a patient who fulfills the following criteria: Demonstration of *P. falciparum* infection. At least

threefold rise in transaminases, particularly alanine aminotranferase (ALT), demonstrated on two consecutive blood samples taken over 24 h apart with or without conjugated hyperbilirubinemia; absence of clinical and serological evidence to suggest drug or viral hepatitis; and finally clinical response to antimalarial drugs or autopsy evidence of disseminated falciparum infection. A variety of antimalarial medications are available. Resistance has developed to several antimalarial drugs, most notably chloroquine. The Antimalarial Drugs used in this study were artesunate & clindamycin in combination and quinine in the other group[13,16,19,20].

Aresunate is a artemisinin derivative. It ias a sesquiterpine lactone active against P.falciparum resistant to all other antimalarial drugs as well as sensitive strains. The endoperoxide bridge in its molecule appears to interact with heme in the parasite. Iron mediated cleavage of the bridge releases a highly reactive free radicle species that bind to *membrane* proteins, causes lipid peroxidation, damages endoplasmic reticulum, inhibits protein synthesis and ultimately lysis of the parasite. They are rapidly absorbed and converted into the active metabolite dihydro-artemesinin. Adverse effects include nausea, vomiting, abdominal pain, itching and drug fever. Abnormal bleeding, dark urine, S-T segment changes, Q-T prolongation, first degree A-V block, transient leucopenia and reticulipenia have been noted but subsides when the patient improves or drug is stopped.

Quinine is the levorotatory alkaloid obtained from cinchona bark. Quinine is an erythrocytic schizonticide for all species of plasmodia. Most of the chloroquine and multidrug resistant strains are still sensitive to it. Quinine has no effect on preerythrocytic stage and on hypnozoits of relapsing fever, but kills the vivax gametes. Quinine is rapidly and completely absorbed orally. It 70% bound to plasma proteins. CSF concentrations are low,a large fraction of dose is metabolized in the liver by CYP3A4 and excreted in the urine with a t1/2 0f 10-12 hrs. Adverse effects : 'Cinchonism' which consists of ringing in the ears, nausea, vomiting, headache, mental confusion,v ertigo, difficulty in hearing and visual defects. Diarrhea, flushing and marked perspiration may also occur. Hypoglycemia and hemolysis especially in pregnant women and falciparum malaria may occur. Few individuals may develop idiosyncratic/ hypersensitivity reaction to quinine. Clindamycin is a lincosamide antibiotic which acts by inhibiting protein synthesis by binding to 50s ribosome. Oral absorption of clindamycin is good. It penetrates most skeletal and soft tissues. Side effects are rashes, abdominal pain, urticarial but diarrhea is the main problem.

The objective of the study, hence, is to compare the prognostic indicators such as: Hb levels, serum lactate levels, liver function tests, blood sugar levels and glassgow coma scale, in patients of severe falciparum malaria on treatment with Artesunate combination therapy (artesunate plus clindamycin) and Quinine.

MATERIAL AND METHODS:

The study was carried out in the Post Graduate Institute Of Medicine, G.S.V.M. Medical College, Kanpur during the period of December 2011 to October 2013. The cases included were of severe falciparum malaria selected from medicine indoor wards, fulfilling following inclusion criterias (table 1). Exclusion criteria were, malaria caused by species other than P.falciparum and patients with co-morbid conditions such as type 2 diabetes, chronic kidney disease, hemolytic anaemia, respiratory and cardiovascular disorders, acute or chronic liver disease, seizure disorder, patients on antiarrythmics, pregnant females or other infectious diseases.

Patients included in the study group presented with the history of fever usually above 40 centigrades associated with chills and rigors, headache, myalagia and abdominal discomfort, generalized seizures, jaundice.baseline blood pressure, pulse rate, respiratory rate, temperature, urine output ,blood sugar were taken for all the patients. Detailed neurological, abdominal, cardiovascular and respiratory system examination was done. Investigations such as thick and thin blood smear**,** clinical findings with rapid diagnostic test, haemoglobin with general blood picture**,** urine routine and microscopy**,** ecg **,**liver function test **,**prothrombin time, activated partial thromboplastin time, bleeding time, clotting time **,**renal function test & arterial blood gas analysis was done. The patients diagnosed as cases of severe falciparum malaria were be divided into two treatment groups: group A- patients receiving Artesunate combination therapy (artesunate plus clindamycin) and group B- patients receiving Quinine. The patients while on treatment were monitored for 5 laboratory parameters i.e. haemoglobin, liver function test,glassgow coma scale,serum lactate levels & blood sugar levels. Patients were monitored on day of admisssion, 48 hrs ,

Table 1: Major Manifestations in Severe Falciparum Malaria.

Major	Manifestations
Unarousable coma/cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Acidemia/acidosis	Arterial pH <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as labored deep breathing, often termed "respiratory distress"
Severe normochromic, normocytic anemia	Hematocrit of <15% or hemoglobin level of <50 g/L (<5 g/dL) with parasitemia level of >100 ,000/L
Renal failure	Urine output (24 h) of <400 mL in adults or <12 mL/kg in children; no improvement with rehydration ; serum creatinine level of >265 mol/L (>3.0 mg/dL)
Pulmonary edema/adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by overhydration
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/disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h; signs of continued seizure activity sometimes subtle (e.g., tonic-clonic eye movements without limb or face movement)
Hemoglobinuria[a]	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Other	
Impaired consciousness/arousable	Unable to sit or stand without support
Extreme weakness	Prostration ; inability to sit unaided[b]
Hyperparasitemia	Parasitemia level of >5% in nonimmune patients (>20% in any patient)
Jaundice	Serum bilirubin level of >50 mmol/L (>3.0 mg/dL) if combined with other evidence of vital-organ dysfunction

72 hrs and 7th day.

RESULTS:

Total 100 patients were enrolled in the study and they were divided into two groups. Group A receiving ACT (Artesunate Combination Therapy) and the other group B receiving Quinine. Each group contained 50 patients(table2). Out of the 100 patients enrolled in the study, 54 were males and 46 were females (Table 3). Of all the patients enrolled in the study 22 patients were of the age group <25 years, 10 were in the ACT receiving group A and 12 were in the Quinine receiving group B. 37 patients were in the age group of 25-50 years, 20 were in the ACT group A and 17 were in the Quinine group B.35 patients were in the age group of 50-75 years, 16 were in the ACT receiving group A and 19 were in the Quinine receiving group B and 6 patients were in the age group of >75 years , 4 in the ACT group A and 2 in the Quinine group B (Table 4). Most of the patients

Table 2: Patient distribution in the two groups.

Total number of patients examined	Number of patients receiving ACT (A)	Number of patients receiving Quinine (B)
100	50	50

Table 3: Table showing gender distribution.

Gender	ACT receiving group (A)	Quinine receiving group (B)
Male	30	24
Female	20	26

Table 4: Table showing age distribution.

Age distribution	ACT receiving group (A)	Quinine receiving group (B)
<25 years	10	12
25-50 years	20	17
50-75 years	16	19
>75 years	4	2

Table 5: Clinical signs in Malaria.

Clinical signs	Patient distribution	%
Pallor	90	90
Icterus	50	50
Hepatomegaly	25	25
Splenomegaly	60	60
Altered sensorium	49	49
Decreased urine output	10	10

enrolled in the study presented with the clinical signs of pallor, icterus, hepatosplenomegaly, altered sensorium and decreased urine output (Table 5). The prognostic indicators observed were Glassgow Coma Scale, plasma lactate levels, plasma glucose levels, Hb levels and liver function tests.

Patients with GCS score <11 were 30 out of which 14 were in group A and 16 were in group B. Out of this 3 in the group A and 5 in the group B expired. Remaining 19 patients had GCS score <15 but >11. Patients with plasma lactate levels >5 mmol/l were 87, 43 were in group A and 44 were in group B. Patients with Hb levels <5 gm% were 22, 10 were group A and 12 were in group B. Patients with serum bilirubin levels >50µmol/l were 50, 26 in group A and 24 in group B. Of all the enrolled patients SGPT was raised in all the 100 patients and SGOT was deranged in 98 patients. PT was deranged in 65 patients out of which 30 were in group A and 35 were in group B. Serum Alkaline phosphatase was elevated in 90 patients out of which 42 were in the group A and 48 were in the group B. Serum protein was deranged in 70 patients out of which 36 were in group A and 34 in group B.(Table 6). Laboratory details on admission for the patients of severe falciparum malaria on act or quinine for treatment enrolled in a study comparing the prognostic indicators (Table 7). Outcome measures for treatment of the patients enrolled in the study (Table 8)

Out of the 21 patients who experienced hypoglycemic episodes 6 were group A and mean ± s.d. for this group was 0.12±0.33 and 15 patients were in group B and mean±s.d. for this group was 0.30±0.46; the p value for this was 0.027 which was statistically significant. In the study 21 patients expired 7 patients were in group A and mean±s.d. was 0.14±0.35 and 13 patients were in group B and mean±s.d. was 0.26±0.44 ; the p value for this was 0.13 which was statistically not significant. Time for normalization of serum lactate levels was slightly lower for group B and mean±s.d. was 17.08±17.49 whereas for ACT receiving group A mean±s.d. was 15.12±23.25 ; the p value for this was 0.63 which was statistically not significant. Coma Recovery Time (CRT) was slightly lower for group A and mean±s.d. for this group was 13.72±28.53 whereas mean±s.d. for the group B was 14.66±33.24 ; the p value for this was 0.87 which was statistically not significant. The time

Table 6: Distribution of patients of severe falciparum malaria on treatment with ACT and quinine according to prognostic indicators.

Criteria	Total	ACT receiving group (A)	Quinine receiving group (B)
Glassgow coma scale <11	30	14 (28%)	16 (32%)
Serum lactate levels >5mmol/l	87	43	44
Plasma glucose levels <2.2mmol/l (40 mg/dl)	10	8	2
Hb< 5gm%	22	10	12
Liver function test			
Serum bilirubin levels >50µmol/l	50	26	24
SGPT/SGOT	100/98	50/49	50/49
PT	65	30	35
Se ALP	90	42	48
Se protein (total/albumin)	70	36	34

Table 7: Laboratory details on admission for the patients of severe falciparum malaria on ACT or quinine for treatment enrolled in a study comparing the prognostic indicators.

Variable	All (n=100)	ACT (50)	Quinine (40)	p value
Median glassgow coma scale score (range)	15 (3-15)	15 (3-15)	13 (3-15)	0.30
Serum lactate level, medial mmol/l (range)	4.3 (0.3 -27.3)	4.8 (1.0 -20.1)	3.8 (0.3 27.3)	0.65
Plasma glucose levels, mean mmol/l	8.5 (7.7 -9.3)	8.2 (7.2 -9.3)	8.4 (7.4 -9.5)	0.07
Hb median (range)	7.0 (2-11.8)	7.6 (2-11.8)	6.8 (2.4 -11)	0.37
Liver function test				
Total serum bilirubin levels, median µmol/l (range)	51 (9-646)	54 (8-646)	54 (11 -453)	0.98
SGPT/SGOT	115/75 (71-158)/ (52-98)	153/116 (55 -251)/ (4-228)	149/77 (46-351)/ (4-300)	0.02/0.34
Se ALP	310 (100 - 800)	320 (100 -556)	300 (120 -800)	0.54
Se Protein T/A	6.3/2.2 (5 -8)/ (1.5-3.5)	6.3/2.3 (5 -8)/ (1.5 -3.5)	6.5/2.2 (5 -8)/ (1.5 -3.5)	0.46/0.57
PT	18 (10 -23)	17 (10 -23)	16 (11 -20)	0.68

Normal plasma glucose levels 3.5-5.5 mmpl/l; Normal serum lactate levels <2mmol/l; Normal Hb levels >11 gm%; Normal serum bilirubin levels 3-17µmol/l, Normal serum Alkaline Phosphatase level 20-140 IU/l,Normal range of PT 10-14 seconds, serum proteins/ albumin- 7-9/3.5-5.5, PT/OT- <40

to death for group A was longer as compared to group B. the mean±s.d. for group A was 90.86±140.26 whereas mean±s.d. for group B was 41.77±40.15 the p value for this was 0.24 which was statistically not significant. There was no significant difference in the time for normalization of LFT in both groups A and B. The mean±s.d. for group A was 53.72±29.42 whereas mean±s.d. for group B was 51.68±40.43 ; the p value for this was 0.77 which was statistically not significant.

Table 8: Outcome measures for treatment of the patients enrolled in the study.

Variables	All	ACT (A)	Quinine (B)	p value
Hypoglycemic episodes, no. of patients	21	6 (12%)	15 (30%)	0.027
Time to plasma lactate levels <2 mmol/l, median h (range)	12 (1-120)	18 (2-72)	12 (1-120)	0.63
Coma recovery time , median h (range)	17 (1-188)	17 (1-125)	18 (1-188)	0.87
No. of patients who died	20	7	13	0.13
Time to death, median h (range)	42 (3-408)	48 (29-408)	21 (3-144)	0.24
Time for normalization of LFT h (range)	72 (24-160)	72 (24-120)	72 (24-160)	0.77
Hb levels	7.0 (2-11.8)	7.6 (2-11.8)	6.8 (2.4-11)	0.37

Table 9: Reported adverse events in the patients treated with primary regimen of quinine and of the patients treated with primary regimen of quinine.

Primary treatment	Quinine (n=50) (B)	Artesunate (n=50) (A)	p value
Hypoglycemia	15 (30%)	6 (12%)	0.027
Hearing disturbances	12 (24%)	0	0.0004
Visual disturbances	1 (2%)	0	0.33
Hepatotoxicity	1 (2%)	0	0.33
Prolongation of QTc- interval	3 (6%)	0	0.09
Acute renal failure	2 (4%)	0	0.17
Other	2 (4%)	3 (6%)	0.58

Other adverse reactions include idiosyncratic reactions, skin rashes. Patients in group B receiving Quinine experienced more number of adverse effects as compared to patients of ACT receiving group A. out of these occurrence of hypoglycemia and hearing disturbances were statistically most significant.

DISCUSSION:

One hundred patients were recruited between December 2011 and October 2013. 50 were randomly assigned to group A who received artesunate combination therapy and 50 were assigned to group B who received quinine treatment. To avoid treatment delay, patients were recruited and randomized before the results of all laboratory investigations were available. Clinical and laboratory parameters on admission, including variables considered a prior to be key prognostic indicators in adults, did not differ significantly between the quinine and artesunate groups for all patients and for the subset of patients with severe malaria. The median admission GCS score was lower in the quinine group; 32% of the patients in that group had cerebral malaria, compared with 28% in the artesunate group.

The overall mortality was 20% (20 of 100 patients; table no.7 and 10). The p-value for this was 0.13 which was statistically not significant. The causes of death were usually multifactorial.The more rapid initial parasite clearance may translate to reduced mortality in severe adult malaria. The overall median time between the initiation of antimalarial treatment and death was 42 h (range, 3–408 h). This was significantly shorter for quinine-treated group B patients (21 h; range, 3–144 h) than for artesunate-treated group A patients (48 h; range, 29–408 h) (table no.7 and 13),but the p-value for this was 0.24 which was statistically not significant.

The overall median coma recovery time for patients who presented with a GCS score of 15 was not significantly different between the 2 treatment groups. The mean for CRT (Coma Recovery Time) in the patients with GCS11or less in group A was 13.72 and those taking Quinine in group B was 14.66 (p=0.8797); this difference was statistically not significant. This delay in the CRT was probably

attributed to the neurotoxicity of the Artemesnin compounds[5].

There were significant differences between the artesunate and quinine-treated patients in the frequency of hypoglycemia (6 of 50 in group A vs. 15 of 50 patients in group B), the mean±s.d. for group A was 0.12±0.33 and for group B was 0.30±0.46; p-value was 0.027 which was statistically significant. In Falciparum malaria quinine-induced insulin secretion may precipitate hypoglycemia, but other factors including the large glucose requirements of the malaria parasites may also contribute[11]. Hypoglycemia is a frequent complication of falciparum malaria and it reflects severe disease and is associated with poor prognosis. Impaired gluconeo-genesis may also contribute to the pathogenesis of hypoglycemia[20]. Treatment with Quinine was associated with significantly more episodes of post admission hypoglycemia when compared with ACT[6]. There was no evidence to indicate a dose relationship between Quinine and occurrence of hypoglycemia[14]. Hematocrit profiles did not differ significantly between the 2 treatment groups. There was no significant changes found in the Hb levels in both the study groups A and B during the treatment period of 7 days (table no. 7). Delayed hemolysis was a complication only in hyperparasetaemic patients treated with Artesunate but not in patients treated with Quinine. The aetiology of delayed hemolysis remains unknown.the fact that only hyperparasaetimic patients develop hemolysis may point to the contribution of a mechanism called 'pitting'[18]. The pathophysiological process that contributes to SMA(severe malarial anaemia) involve direct and indirect destruction of parasitized and non-parrasitized RBCs, inefficient and/or suppression of erythropoiesis and dyserythropoiesis[15]. One important cause of impaired erythroid response with SMA is dysregulation in the innate immune response. Phagocytosis of the malarial pigment hemozoin (Hz) is a central factor for promoting dysregulation in innate inflammatory mediators. Fewer patients became hypoglycemic in the artesunategroup (12%) than in the quinine group (30%). Patients treated with quinine consistently developed cinchonism and had a significantly higher frequency of hypoglycemia. One patient had a probable adverse reaction to artesunate.

Time for normalization of serum lactate levels was slightly lower for quinine treated group B but the P value for this was 0.63 which was statistically not significant. Hyperlactatemia, metabolic acidosis (SBD, >3.3), and acidemia (pH <7.35) were strongly positively associated with a fatal outcome[11].The SBD(serum base deficit) was the single best clinical or laboratory predictor of fatal outcome. The two main independent contributors to metabolic acidosis were plasma creatinine, as a measure of renal dysfunction, and venous plasma lactate, together accounting for 63% of the variance in SBD. There was no significant difference in the time for normalization of LFT in both groups A and B (table 7 and 14). The p-value for this was 0.77 which was statistically not significant. Jaundice is common in severe malaria and may be multifactorial[10]. Hepatocellular jaundice in malaria should be more appropriately labeled as malarial hepatopathy rather than malarial hepatitis. Clinical relevance of malarial hepatopathy also lies in the fact that the more severe presentation with cerebral malaria can be misdiagnosed as fulminant hepatic failure.The incidence of adverse events was more in group B patients receiving Quinine. Hypoglycemia was reported in 15 out of 50 patients in group B whereas only 6 patients developed hypoglycemia who were on ACT. The p-value for this was 0.027 and this was statistically significant. In group B 12 patients reported hearing disturbances whereas no such events occurred in group A. The p-value for this was 0.0004, which was statistically significant. 1 patient in group B developed visual disturbance and 1 patient developed hepatotoxicity, no such events occurred in group A, the p-value for this was 0.33, which was statistically not significant. Prolongation of QTc-interval was noted in 3 patients of group B and p-value for this was 0.09. 2 patients in group B developed acute renal failure during the course of treatment whereas no such events occurred in group A and p-value for this was 0.17. idiosyncratic reactions and rashes occurred in 2 patients in group B and 3 patients in group A and p-value for this was 0.58 which was statistically not significant.

The main obstacle to malaria control is the emergence of drug resistant strains of Plasmodium falciparum[13]. The combination of an Artimisinin derivative and a partner drug with unrelated mode of action has shown a remarkable double effect: preventing the emergence and spread of drug resistance and interrupting the transmission of Plasmodium falciparum. Increasing resistance of Plasmodium falciparum malaria to antimalarial drugs is posing a major threat to the global effort to 'Roll Back Malaria' [19]. One strategy advocated for delaying the development of resistance to the remaining armory of effective drugs is the wide scale deployment of artemisinin-based combination therapy.

CONCLUSION:

The present study suggests that Artesunate is an effective alternative to quinine in the treatment of severe malaria. The mortality cases i.e. the number of patients who expired was less and time to death was large in patients of group A as compared to group B, but the difference was not statistically significant. Among ACT receiving group A patients, incidence of post-treatment hypoglycemia was lower as compared to the Quinine receiving group B patients and this difference was found to be statistically significant. The Coma Recovery Time (CRT) was less for group A patients who received ACT as compared to group B patients, but this difference was not statistically significant. Time to normalization of plasma lactate levels was lower for the Quinine receiving group B patients as compared to the ACT receiving group A patients, but this difference was not found to be statistically significant. The time for normalization of LFT was slightly lower for group B in comparison to group A, but the difference was also not statistically significant. No significant variation was found in the Haemoglobin levels in both the study groups during the course of treatment. The incidence of adverse events was more in group B patients receiving Quinine, and the occurrence of hypoglycemia and hearing disturbances was found to be statistically significant.

LIMITATIONS OF THE STUDY:

Small number of cases in this study is its limitation and further studies are required to confirm the above findings.

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