Original Article

A STUDY OF CLINICAL PROFILE OF COMPLICATED MALARIA WITH SERUM LACTATE LEVELS AS A PROGNOSTIC MARKER

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ABSTRACT

Background : Malaria is of immense importance among tropical diseases in India. Pathophysiology of complicated malaria is multifactorial in origin involving tissue hypoxia, liver dysfunction, and impaired renal handling of bicarbonate. Acidosis is an important contributor to death from severe falciparum malaria. Metabolic acidosis results from abnormal microcirculatory perfusion and anaerobic glycolysis as a result of sequestration of parasitized erythrocytes and, also, cellular dysfunction consequent on release of host and parasite-derived toxic mediators.

Material and methods : The study was conducted at Victoria and Bowring & lady Curzon hospitals, attached to Bangalore medical college & research institute, Bangalore. A total of 40 patients with complicated malaria with respect to serum lactate levels measured serially every 24hours were studied.

Results : During our study, 24 out of 40 patients had lactate levels >19.8mg/dl. Out of these 24 patients,10 were given blood transfusion,3 were given platelet transfusion,9 were given inotropic support and 2 were dialysed as compared to patients with normal lactate levels who were 4,1,2 and 0 respectively; implying the fact that the incidence of complications are high in patients with hyperlactatemia. Also, 3 patients died during the study; all of them were from increasing levels of lactate levels on day 3 when compared to levels at the time of admission.

Conclusion : With this, it can be inferred that serum lactate levels are directly proportional to complications and mortality. Deaths can be prevented by intensive management of these patients with complicated malaria. However lactate levels did not have any correlation with other hematological parameters

Key words : Complicated malaria, Lactic acidosis, high mortality.

INTRODUCTION

Malaria is a protozoal disease caused by infection with parasites of the genus plasmodium and transmitted to man by certain species of infected female Anopheline mosquito. Four species of plasmodium: P.falciparum, P.vivax, P.ovale and P.malaria, cause infection in man. Almost all deaths are caused by Falciparum malaria.[1]

Metabolic acidosis is defined as a state of decreased systemic pH resulting from either a primary increase in hydrogen ion (H^+) or a reduction in bicarbonate (HCO_3^-) concentrations. In the acute state, respiratory compensation of acidosis occurs by hyperventilation resulting in a relative reduction in $PaCO_2$. Chronically, renal compensation occurs by means of reabsorption of HCO_3.[2]

Acidosis arises from an increased production of acids, a loss of alkali, or a decreased renal excretion of acids (see Metabolic Acidosis). The underlying etiology of metabolic acidosis is classically categorized into those that cause an elevated anion gap (AG) and those that do not. Lactic acidosis, identified by a state of acidosis and an elevated plasma lactate concentration is one type of anion gap metabolic acidosis and may result from

numerous conditions.[3]

The normal blood lactate concentration in unstressed patients is 1-1.5 mmol/L. Patients with critical illness can be considered to have normal lactate concentrations of less than 2 mmol/L. Hyperlactatemia is defined as a mild-to-moderate persistent increase in blood lactate concentration (2-5 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >4-5 mmol/L) in association with metabolic acidosis.[2,4]

Malaria is the most important of the parasitic diseases of humans with transmission in 107 countries containing 3 billion people and causing 1-3million deaths each year.[16] Although it has been eradicated from temperate zones, increasing number of travelers from temperate zone visit tropical countries, where the disease remains a major cause of morbidity and death.[17]

Malaria is of immense importance among tropical diseases in India. During 2003, about 1.65 million cases were reported with 943 deaths. There were 0.7 million cases of P.falciparum malaria.[18]

Hence Malaria is of immense social and economical importance among tropical diseases in India. There is a need to develop newer diagnostic aids and prognostic markers for prediction of the course and complications.

Pathophysiology of complicated malaria is multifactorial in origin involving tissue hypoxia, liver dysfunction, and impaired renal handling of bicarbonate. Acidosis is an important contributor to death from severe falciparum malaria.

In adult patients, acidosis results from metabolic, circulatory, and renal dysfunction, whereas in children, metabolic factors appear to predominate.

Metabolic acidosis results from abnormal microcirculatory perfusion and anaerobic glycolysis as a result of sequestration of parasitized erythrocytes and, also, cellular dysfunction consequent on release of host and parasite-derived toxic mediators. Arterial bicarbonate and venous and cerebrospinal fluid concentrations of lactate have been shown to be powerful prognostic indicators in patients with severe malaria.

Hence there is a need to assess the respective roles of respiratory status, renal dysfunction, and glycolytic abnormalities in acidosis in severe malaria and specifically in the pathogenesis of cerebral malaria.

According to the *World malaria report 2011*, there were about 216 million cases of malaria (with an uncertainty range of 149 million to 274 million) and an estimated 655 000 deaths in 2010 (with an uncertainty range of 537 000 to 907 000).

Malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the South African Region.

Most deaths occur among children living in Africa where a child dies every minute from malaria.

MATERIALS AND METHODS

A total of 40 patients more than 18 years of age diagnosed to have complicated malaria over a period of 2 years admitted in Victoria hospital and Bowring and Lady Curzon Hospitals attached to BMCRI, Bangalore were included in our study. This is a prospective study. All study subjects were identified positive for Plasmodium falciparum parasite on peripheral smear examination with conventional microscopy.

Serum lactate levels were done by quantitative PAP/PCP Method. Repeat lactate levels were done in patients with clinical features of metabolic acidosis, icterus, tachypnea, ARDS, shock, severe anaemia every 24 hours for 3 times. Other investigations included CBC, RFT, LFT, Dengue serology, Leptospira antibody, ECG, Chest X ray, USG abdomen, CSF analysis wherever applicable.

All patients were treated with parenteral Artesunate and primaquine single-day dosage. Some patients had to be treated with Packed cell / whole blood transfusion, IV fluids, Dialysis, Platelet transfusion.

Data was expressed on excel spread sheet and statistical analysis was performed.

p-values <0.005 were considered as significant.

INCLUSION CRITERIA

All patients above 18 years of age whose peripheral blood smear positive for Plasmodium falciparum parasite and also satisfying at least one or more parameters of crieteria for complicated malaria as per WHO guidelines for complicated malaria 2000.

EXCLUSION CRITERIA

1. Diabetic patients on metformin therapy
2. HIV patients on Anti Retroviral Therapy
3. Chronic Renal Failure patients
4. Congestive Cardiac Failure patients
5. Chronic liver disease
6. Acute febrile illness mimicking malaria (MP-ve) as in Leptospirosis , Dengue fever & sepsis
7. Known patients with G-6 P D deficiency

STATISTICAL METHODS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made.

Assumptions

1. Dependent variables should be normally distributed,
2. Samples drawn from the population should be random; Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Pearson correlation between lactate levels with clinical variables is done to find the relationship.

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

A total of 40 patients above 18 years of age who were diagnosed to have complicated malaria over a period of 2 years were studied. The mean age of patients was 35.87±14.83

Out of 40 patients studied, it included 75% males and 25% females.

10 clinical parameters were studied. Of them majority 70% patients presented with prostration, followed by icterus 37.5%, 17.5% each presented with ARDS and syncope. 15% patients presented with decreased urine output.

3 patients presented with bleeding from the gums, nose. 2 patients with seizures, none of the patients presented with coma or hemoglobinuria Pulse rate, blood pressure, temperature, respiratory rate were studied.

25 patients had tachycardia and 15 patients had normal rate.

20patients had systolic blood pressure <70 mmHg and rest of the patients had systolic blood pressure more than 70 mmHg. 62.5% of the patients studied did not have postural hypotension and 12.5% patients had postural

hypotension. However, postural hypotension could not be tested in 10 patients in view of their inability to stand and had altered sensorium and prostration. 30 patients had fever and 10 patients did not have fever at the time of presentation.

Though 37 out of 40 patients had respiratory rate of more than 16 per minute, only 7 patients had ARDS and rest had tachypnea due to metabolic acidosis due to hyperlactatemia as evident by serum lactate levels.

Common clinical signs in decreasing order of frequency were pallor 37.5%, icterus 7.5%, edema 7.5%, cyanosis and mucosal bleed 5% each. None

of the patients had lymphadenopathy, tender muscles and skin rash.

On examination, majority of the patients had significant findings on per abdominal examination followed by central nervous system examination and respiratory system examination.

On per abdominal examination 15 patients had hepatospleenomegaly, 22 had spleenomegaly alone and 1 patient was pregnant at the time of examination.

On central nervous system examination, 11 were in altered sensorium, 8 were drowsy and 2 were restless at the time of presentation.

On respiratory system examination, 9 patients had features suggestive of ARDS.

On CVS examination, 4 patients had flow murmur.

As per crieteria of WHO for complicated malaria 2000, 12.5% of patients had Hb <5gms%, 15% had leucocyte nt of less than 4000cells/mm3, 7.5% had hematocrit <15%, 35% patients had platelet count below 50000/mm3

4 out of 40 patients had random blood sugar levels of less than 50mg/dl satisfying the crieteria of WHO.

20 patients had normal blood glucose levels and others were worked for diabetes and two patients were known diabetics not on metformin earlier.

55% patients in our study had normal blood urea levels and 40% patients had blood urea levels.

12.5% patients had creatinine levels more than 3mg/dl at the time of presentation again suggestive of renal failure.

15% patients had impaired renal function tests in the form of creatinine levels between 1.5-3.0mg/dl.

In all these patients chronic renal failure was ruled out by relevant investigations.

20 out of 40 patients had hyponatraemia and 20 patients had normal sodium levels.

5 out of 40 patients had hypokalaemia though asymptomatic. 2 patients had hyperkalaemia mainly because of acute renal failure and rest of the 29 patients had normal potassium levels.

14 out of 40 patients had bilirubin of more than 2.5mg/dl meeting the crieteria for complicated malaria guidelines 2000 by WHO. 11 patients had normal bilirubin levels.

32.5% Of patients had elevated alkaline phosphatase levels however values did not cross 2 times the upper limit of normal. 55% of patients had SGOT levels above the normal limit but did not cross 3 times the upper limit of normal.

Though 12.5% of patients had SGPT levels above 2 times the normal limit, only one patient had SGPT levels elevated upto 20 times of ULN.

Outcome	Number of patients	%
Recovered	36	90.0
DAMA	1	2.5
Expired	3	7.5
Total	40	100.0

Table 1: Distribution of Outcome of patients studied

In our study, 90% (n=36) of patients recovered.
7.5% (n=3) expired and
2.5% (n=1) got discharged against medical advice.

Lactate levels	Number of patients	%	BT	PT	IS	DIALYSIS
<19.8 mg/dl	16	32.0	4	1	2	0
>19.8 mg/dl	24	63.2	10	3	9	2
Total	40	100.0	14	4	11	2

Table 2: Distribution of lactate levels of patients studied

BT: Blood Transfusion; **PT:** Platelet Transfusion; **IS:** Inotropic support

Out of 40 patients studied, 24 patients had lactate levels more than 19.8mg/dl at any given point of time and 16 patients had normal lactate levels. 14 out of 40 were given blood transfusion, 4 out of 40 were given platelets, 11 were given inotrope support and 2 were dialysed.

Lactate levels	Day 1 (n=40)	Day 2 (n=40)	Day 3 (n=40)	Outcome Death	Dama
<4.5 mg/dl	-	-	-		
4.5-19.8 mg/dl	10(25.0%)	8(20.0%)	22(55.0%)	Nil	Nil
>19.8 mg/dl	20(50.0%)	10(25.0%)	6(15.0%)	3	1
Not recorded	10(25.0%)	22(55.0%)	12(30.0%)	Nil	Nil

Table 3: Distribution of lactate levels in three days of patients studied

In our study 25% (n=10) patients had normal lactate levels at the time of admission and 50% (n=20) had high lactate levels on day1.

Subsequently,20% (n=8) had normal lactate levels and 25% (n=10) had high lactate levels on day2.

On day 3,55% (n=22) had normal lactate levels and 15% (n=6) had high lactate levels.

3 of these 6 patients died and 1 patient got discharged against medical advice.

Clinical variables	Lactate levels		P value
	<19.8 mg/dl (n=14)	>19.8 mg/dl (n=24)	
Age in years	33.00±15.82	37.79±14.15	0.323
Hemoglobin %	11.46±3.02	7.50±2.70	<0.001**
Total count	6626.88± 4592.37	9494.17± 5332.53	0.087+
Hematocrit	34.45±8.16	27.18±8.98	0.013*
MCH	27.73±3.79	27.67±4.03	0.961
MCV	84.38±9.48	85.85±10.26	0.655
MCHC	32.71±2.55	31.82±2.05	0.234
Platelet count	96233.48± 90225.91	129708.33± 108462.17	0.325
RBS mg/dl	106.23±34.38	99.82±53.47	0.702
Blood urea mg/dl	48.00±43.27	72.09±69.96	0.232
S creatinine mg/dl	1.45±1.10	1.35±0.97	0.754
Sodium	131.93±5.12	133.29±4.85	0.430
Potassium	4.24±0.74	4.21±0.92	0.916

Table 4: Correlation of clinical variables according to Lactate levels

DISCUSSION

Total of 40 patients with complicated malaria were studied. The mean age of patients was 35.87±14.83 years,[35] moreso between 18-37 years.[39]This study includes 30males and 10 females. In present study, males were commonly involved due to the fact that most of the patients had recent history of travel to endemic areas.[35,36,37]

The commonest clinical manifestations were fever with chills, prostration (70%), jaundice (37.5%), syncope(17.5%).

Commonest clinical findings were tachycardia (62.5%),hypotension(50%), tachypnea (92.5%), pallor (45%), icterus (37.5%), spleenomegaly (55%), hepatospleenomegaly (37.5%), altered sensorium (32.5%).[38] A clinical spectrum of fever, spleenomegaly and pallor is always associated with malaria; hypotension, tachypnea, icterus, altered sensorium implying complicated malaria.

In this study 24 out of40 patients had lactate level more than 19.8mg/dl. Incidence being 60%.[30,40] Lactic acidosis and hypoglycemia are the most common metabolic complications. Type B Lactic acidosis more commonly seen in complicated malaria. It often manifests as deep breathing, often termed "respiratory distress" and is a sign of poor prognosis. It results from accumulation of organic acids. Hyperlactatemia commonly co-exists with hypoglycemia as seen in our study too. In adults, co-existing renal impairment compounds the acidosis as evident in our study. Some unidentified organic

acids are also important contributors to acidosis. Hyperlactatemia can lead to respiratory arrest as it is often followed by circulatory failure refractory to volume expansion or inotropic support.[17] Lactic acidosis is caused by combination of anaerobic glycolysis in tissues where sequestrated parasites interfere with microcirculatory flow, hypovolemia, lactate production by parasites and failure of hepatic and renal lactate clearance.

The mechanism of hyperlactatemia is complex. In plasmodium falciparum infection, membrane protuberance appears on the erythrocytic surface towards the end of 24 hoursof asexual cycle. These "knobs" extend high molecular weight antigenically variant, strain specific adhesive protein (PfEMP1) that mediate attachment to receptors on venules and capillary endothelium an event termed 'cytoadherence'. Several vascular receptors are identified of which intracellular adhesion molecule 1 is probably the most important in the brain and CD36 in most other organs. Thus infected erythrocytes stick inside the small blood vessels. At the same stage, these Pf infected RBC's may also adhere to uninfected RBC's to form rosettes. The process of cytoadherence, rossetting and agglutination are central to the pathogenesis of lactic acidosis.[17]

In our study 14 (35%) patients had platelet count less than 50000/cu.mm. The mechanism of thrombocytopenia is uncertain. Immune mediated lysis, sequestration in spleen and a dyspoietic process in the marrow with diminished platelet production have all been postulated. Abnormalities in platelet structure and function have been described as consequence of malaria and in rare instances platelets can be invaded by malarial parasites themselves.[41,42]

In our study, 11(27.5%) patients had renal failure. Renal impairment is common among adults with complicated malaria. The pathogenesis of renal failure is unclear; but may be related to erythrocyte sequestration interfering with renal microcirculatory flow and metabolism. Clinically and pathologically this syndrome manifests as acute tubular necrosis, although cortical necrosis never develops. In survivors urine flow resumes in a median period of four days and serum creatinine levels return to normal.[17] In our study,2 patients were dialysed who had associated hyperlactatemia and recovered after dialysis.[43]

In our study 14 (35%) patients had bilirubin of >2.5mg/dl, 32.5% had elevated alkaline phosphatase, 55% had increased SGOT& SGPT in 12.5% of patients. This is similar to series of Ramachandran et al[45] and Gupta et al[46], S.Bag et al.[47] Rise of serum bilirubin in falciparum malaria patients is considered to be due to hemolysis of peripheral parasitized RBC and impairment in bilirubin transport because of reticulo endothelial blockage and disturbances of hepatocyte microvilli.[48] Thus, conjugated, unconjugated and mixed type of hyperbilirubinemia observed in the present study might be due to forementioned reasons. Fatty changes, liver cell necrosis, nuclear vacuolation and liver congestion have been observed in falciparum malaria infection.[49] Hence it is reasonable to say that the rise in level of transaminases in the present series could be due to liver cell damage. It is unlikely to be due to viral hepatitis because in all our cases studied, jaundice disappeared quickly after treatment of malaria.

Study conducted by T A Taylor et al The strong association of altered acid-base status with disease severity and mortality was independent of other previously identified predictors of illness and death in malaria.[50]

A study by M. English et al demonstrated that Severe malaria caused a predominantly

High -anion gap metabolic acidosis in at least 43% of children. Children with coma and respiratory distress (CM+RD) had greater evidence of renal dysfunction, lower mean pH and higher mean plasma osmolality than those with respiratory distress (RD) or coma.[51]

In a study conducted by Maitland K et al demonstrated metabolic acidosis as a central feature of severe malaria and is the best independent predictor of a fatal outcome in both

adults and children.[52]

Piero Olliaro showed that, despite the diverse presenting syndromes across the different age groups, depth of coma and severity of acidosis were the most important prognostic factors, independent of age.[53]

Andrej Trampuz et al showed in their study that metabolic acidosis and hypoglycemia are common systemic complications of severe malaria.[54]

Tsiri Agbenyega et al in their study demonstrated the positive correlation between duration of coma and the lactate disposal rates is consistent with the hypothesis that microvascular obstruction, due to sequestration of infected erythrocytes, is an underlying mechanism that is common to the development of both cerebral malaria and lactic acidosis.[55]

Tim Planche et al in their study suggested that severe malaria has many manifestations, of which coma and lactic acidosis are the best independent predictors of a fatal outcome.[56]

CONCLUSION

Severe lactic acidosis is a good predictor of poor prognosis.

Higher the lactate levels in serum more the incidence of complications than the patients with normal lactate levels.

If hyperlactatemia persists for more than three days despite adequate therapy, mortality rate increases upto 10%.

SUMMARY

Malaria continues to be a huge social, economical and health problem particularly in tropical countries. Complicated malaria is a major cause of morbidity and mortality. Early diagnosis and prompt treatment of complications reduces the global burden of malaria and thereby reducing the mortality and morbidity. High serum lactate levels are better predictors of outcome and helps in early diagnosis of complicated malaria and intensive management of patients with lactic acidosis prevents mortality. However, the level at which hyperlactatemia causes mortality is not known pointing towards the role of unknown factors. Hence further studies need to be conducted on lactate levels in complicated malaria to quantify the values.

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