A study of serum lactate level in malaria and its correlation with severity of disease

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ABSTRACT

Background: Since there is a high mortality due to malaria, there is a need of a parameter to identify patients at risk of developing complications, whereby intensive care is given to those patients who are at higher risk for complications and mortality. Aims: This study was undertaken to estimate serum lactate levels in patients with Plasmodium vivax, Plasmodium falciparum, and mixed malaria, and also to correlate it with various clinical and biochemical parameters and with the severity and prognosis of malaria. Methods: This was a cross-sectional, analytical, and observational study, which was conducted on 100 patients diagnosed with malaria and older than 14 years of age. Diagnosis of malaria was made by the gold standard method of peripheral blood smear examination and rapid tests. The blood sample for plasma lactate levels on admission was collected from a stasis free vein. The Student’s t-test for continuous normally distributed variables was used. For categorical data, the chi-square test was used and for the small numbers, Fisher’s exact test was used for small numbers. P < 0.05 was considered as a statistical significance at 95% confidence intervals. Results: In this study, there were 90% survivors and 10% of patients succumbed. Out of 90 survivors, 43 patients (47.7%) had some form of complicated malaria, whereas all patients who succumbed (10) had complicated malaria. All the patients who had jaundice, severe thrombocytopenia, renal failure, severe anemia, or hypotension (hypotension was confirmed clinically, but the remainder were confirmed by biochemical parameters such as liver functions, renal functions, platelet count, and hemogram) had hyperlactatemia in this study. All patients who died had a serum lactate level of >2 mmol/l. Conclusions: Hyperlactatemia had significant associations with complications of malaria. Raised serum lactate levels were significantly associated with mortality (P < 0.05).

Key words: Complications, hyperlactatemia, malaria, mortality

INTRODUCTION

Malaria is a widespread disease in the tropics, including India. Plasmodium vivax is the most prevalent species and Plasmodium falciparum is the most virulent one worldwide. Complicated malaria includes cerebral malaria, algid malaria, hematological abnormalities, metabolic acidosis, renal failure, hepatic dysfunction, pulmonary edema, hypoglycemia, and gram negative sepsis.

Recent reports of malaria cases in India showed that 8.8% of the total malaria cases and 4.1% of the total falciparum cases were reported from western India; hence, due to the widespread prevalence of malaria in this region, this study was conducted here.

The normal blood lactate concentration in unstressed patients is 0.4-1 mmol/l. Hyperlactatemia is defined as a mild-to-moderate (2-5 mmol/L) persistent increase in blood lactate concentration without metabolic acidosis,
whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >5 mmol/L) in association with metabolic acidosis.[5] The amount of lactate produced in any illness is said to correlate with the total oxygen debt, magnitude of hypoperfusion, and the severity of shock.[6] It is well known that in sepsis and septic shock, lactic acidosis can occur and hyperlactatemia is a marker of the severity of the stress response. Several studies on patients admitted to intensive care units have shown that median survival of patients with lactic acidosis and shock was less than the survival rate of those with absence of this state.[7] Malaria can cause lactic acidosis by tissue hypoperfusion and hypoxia, occlusion of microcirculation by parasites, production of lactate by parasite, and decreased hepatic blood flow.[8] Metabolic acidosis is a form of severe malaria according to the World Health Organization (WHO).[9]

However, in absence of overt acidosis, hyperlactatemia can occur in malaria, and be detected as a laboratory abnormality. Several studies have shown that presence of hyperlactatemia correlates adversely with prognosis in all types of malaria.[9–12] As there is high mortality due to malaria and a high prevalence of complicated malaria in India, there is an acute need to identify patients at risk of developing complications and to intensify care given to those patients, so that the mortality burden is reduced. This study aimed to establish if serum lactate levels and the presence of hyperlactatemia can be used as a parameter to determine outcome of malaria. In the study, serum lactate levels in all patients of *P. Vivax* and *P. falciparum* malaria were correlated with various clinical and biochemical parameters and with severity and prognosis of malaria.

**METHODS**

This cross-sectional, analytical, prospective, and observational study was conducted in a tertiary care center in western India over a period of two years.

Institutional ethical clearance was obtained from the college ethical committee and individual consent was taken from each patient.

A hundred patients older than 14 years old who were admitted to intensive care unit and general medicine wards with a diagnosis of malaria made by standard method of peripheral blood smear examination demonstrating the parasite, were selected for the study. Patients having a past history of systemic illnesses like hypertension, diabetes, chronic renal failure, tuberculosis, nephritic syndrome, acute or chronic viral hepatitis and chronic liver disease, and those taking medication that was likely to affect liver and renal function tests, were excluded from this study.

Patients who fulfilled inclusion criteria were thoroughly interrogated with regards to presenting complaints like fever, chills, jaundice, oliguria, hematuria, swelling over body, breathlessness, bleeding tendencies, altered sensorium, convulsions etc. On admission, vital parameters like temperature, pulse rate, blood pressure, and respiratory rate were recorded. Signs such as pallor, icterus, edema, bleeding were noted. Systemic examination was done. Investigations including peripheral smears, complete blood counts, platelet count, urea and creatinine, bilirubin, liver enzymes, and blood sugar tests were done.

The diagnosis of malaria was made by the gold standard method of peripheral blood smear examination by demonstration of asexual form of plasmodium. The thin smear was prepared from a finger prick, methanol fixed, and stained with diluted Giemsa using buffered water at pH 7.2 seen under oil immersion, and a minimum of hundred fields were examined before declaring the slides negative. Optimal test detecting the plasmodium lactate dehydrogenase (rapid diagnosis) was also used in all patients. Parasite density index was calculated for all patients being included. A blood sample for plasma lactate level on admission was collected from a stasis free vein, without using a tourniquet. The sample was collected in a fluoride ethylene diamine tetra acetic acid (EDTA) bulb and was immediately sent for processing on an ice pack for estimation of plasma lactate levels. Plasma was separated by centrifugation within 30 min.

The kit used for estimation of plasma lactate levels was the Randox Kit manufactured by (Randox Laboratories Ltd, 55 Diamond Road, Crumlin, Co. Antrim, United Kingdom, BT29 4, QY). Lactate levels were estimated using biochemistry analyzer TRACE 30 v4.1. Hyperlactatemia was defined as serum lactate levels more than 2 mmol/l.

**Statistical analysis**

Data collected was systematically tabulated and analysis was done using standard statistical software SPSS version 15.0. The Student’s t-test for continuous normally distributed variables was used. For categorical data, the chi-square test was used and Fisher’s exact test was used for small numbers. For the variables not normally distributed, Wilcoxon’s Mann-Whitney test was used. *P* < 0.05 was considered as statistical significant at 95% confidence intervals. Multivariate analysis was done using multilinear regression analysis for various complications of falciparum malaria and outcome. It was also used for comparison with lactate levels.

**RESULTS**

Out of the 100 patients of malaria, 50% had *P. vivax*, 35% had *P. falciparum*, and 15% had mixed infection. The
majority, 33%, of patients were 21-30 years old. Males were 67% of the patients and 33% of patients were females. It was observed that higher the serum lactate levels, more was the duration of stay of the patient in hospital. In this study, 90% of patients survived and 10% of patients succumbed. Out of the 90 survivors, 43 patients (47.7%) had some form of complicated malaria, whereas all patients who succumbed (10) had complicated malaria. Out of the total 100 study subjects, 53% had complicated malaria while 47% were uncomplicated cases.

Twenty six percent of patients of *P. vivax* malaria, having hypotension had hyperlactatemia. 14% of *P. falciparum* patients and 20% of mixed malaria patients with hypotension had hyperlactatemia [Table 1]. The majority (91.3%) of patients of all types of malarias having hypotension had hyperlactatemia versus 8.7% who had normal lactate levels.

Out of the 78 patients who had severe thrombocytopenia, 10 succumbed. 76% of patients with *P. vivax* and severe thrombocytopenia (<50000) and 88% of *P. falciparum* patients with same range of platelets had hyperlactatemia. All of the patients with mixed malaria and severe thrombocytopenia had hyperlactatemia. In all, 89.7% of patients of all types of malarias who had severe thrombocytopenia had hyperlactatemia versus 10% having normal lactate levels. The patients with mild thrombocytopenia and normal platelet count had mostly normal serum lactate levels. Hence, this difference was statistically significant ($P = 0.001$) [Table 2]. Hemoglobin levels less than 5 gm/dl were found in 10% of patients, all of them had hyperlactatemia.

Fifty percent of patients of *P. vivax* malaria having jaundice had hyperlactatemia, while the values for *P. falciparum* and mixed malarias were 60% and 86%, respectively. 95.16% of patients of all types of malarias having serum bilirubin >1.3 mg/dl had hyperlactatemia versus 4.8% having normal lactate levels [Table 3]. 42% of *P. vivax* patients having alanine transaminase (ALT) >40 had hyperlactatemia while the values for falciparum and mixed malaria patients were 54% and 73%, respectively. Those having normal liver functions mostly had normal serum lactate values and hence this difference was statistically significant ($P 0.018$).

All patients (of all types of malaria) with serum creatinine >1.6 mg/dl had hyperlactatemia. Patients with a normal serum creatinine mostly had normal values of serum lactate and the difference in the two groups was statistically significant ($P = 0.00736$) [Table 4]. Hyperlactatemia was present in 56% of patients with *P. vivax* positive malaria who had blood urea level of >40 mg/dl while 68% of *P. falciparum* positive and

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**Table 1**: Association of systolic blood pressure in malaria patients with lactate level

| Malarial species | Lactate level (mmol/lit) | Systolic B. P. ($\leq$ 90 mm of Hg) | Systolic B. P. ($>$ 90 mm of Hg) |
|-----------------|------------------------|-------------------------------------|---------------------------------|
| *P. vivax* (P.V) | <2                     | 1                                   | 9                               |
|                 | $>$2                   | 13                                  | 27                              |
| *P. falciparum* (P.F) | <2             | 1                                   | 4                               |
|                 | $>$2                   | 5                                   | 25                              |
| Mixed (P.V./P.F.) | <2                     | 0                                   | 0                               |
|                 | $>$2                   | 3                                   | 12                              |
| Total           | 23                     | 77                                  |

**Table 2**: Association of platelet counts of malaria patients with lactate level

| Malarial species | Lactate level (mmol/lit) | Platelet count (<50000/μl) | Platelet count (50000-150000/μl) | Platelet count (>150000/μl) |
|-----------------|-------------------------|-----------------------------|----------------------------------|-------------------------------|
| *P. vivax* (P.V) | <2                     | 5                           | 4                               | 1                            |
|                 | $>$2                   | 33                          | 7                               | 0                            |
| *P. falciparum* (P.F) | <2             | 2                           | 2                               | 0                            |
|                 | $>$2                   | 24                          | 6                               | 0                            |
| Mixed (P.V./P.F.) | <2                     | 0                           | 0                               | 0                            |
|                 | $>$2                   | 13                          | 0                               | 2                            |
| Total           | 78                     | 19                          | 3                               |

**Table 3**: Association of serum bilirubin of malaria patients with lactate level

| Malarial species | Lactate level (mmol/lit) | S. bilirubin (<1.2 mg/dl) | S. bilirubin (1.3-3.0 mg/dl) | S. bilirubin (>3 mg/dl) |
|-----------------|-------------------------|---------------------------|-------------------------------|--------------------------|
| *P. vivax* (P.V) | <2                     | 9                         | 1                             | 00                        |
|                 | $>$2                   | 15                        | 18                            | 7                         |
| *P. falciparum* (P.F) | <2             | 3                         | 1                             | 1                         |
|                 | $>$2                   | 9                         | 7                             | 14                        |
| Mixed (P.V./P.F.) | <2                     | 0                         | 0                             | 0                         |
|                 | $>$2                   | 2                         | 3                             | 10                        |
| Total           | 38                     | 30                        | 32                            |
86% of mixed malaria patients had an elevated urea level. Hence, most patients who had complications of malaria had lactate levels >2 mmol/l; in most cases it was statistically significant.

All patients who died had a serum lactate level of >2 mmol/l. All 10 patients (100%) had platelet counts of <50000/μl. Blood urea was >40 mg/dl in 8 patients (80%) and creatinine was >3 mg/dl in 4 patients (40%). Hypotension and jaundice were present in 6 patients (60%). Severe anaemia was observed in 4 patients out of 10 (40%) [Table 5]. Among the survivors, the mean lactate level in those cases without any complications was 3.16 ± 1.41 mmol/l but that in survivors who had complications was 4.63 ± 1.3 mmol/l. The mean serum lactate level in survivors was 3.86 ± 1.54 mmol/l, while the same in non-survivor group was 6.72 ± 0.39 mmol/l, which was statistically significant (P = 0.0319). Hence, raised serum lactate levels were significantly associated with mortality.

DISCUSSION

The prevalence of complicated malaria has significantly increased in the last decade. Due to this increase, a reliable indicator of the severity of malaria is needed so that efficient intensive care can be provided to severely affected patients. The most common etiology of hyperlactatemia in severe malaria is probably the increased anaerobic glucose metabolism due to generalized microvascular sequestration of parasitized red blood cells (RBCs) that decreases blood flow to tissues.[13]

Not many studies have been conducted from this part of India to correlate hyperlactatemia as an indicator of severity of malaria.

In the present study, a significant number of patients of complicated and severe P. vivax, falciparum, and mixed malaria had hyperlactatemia. The serum lactate levels showed a significant association with most of the complications of malaria like anaemia, thrombocytopenia, jaundice, and renal failure. Raised serum lactate levels were significantly associated with mortality (P < 0.05).

In a study by Waller et al., hyperlactatemia was shown to be an independent indicator of a fatal outcome of severe malaria in African children.[9] In a study by Day et al., hyperlactatemia was present in 35% of patients and was associated significantly with metabolic acidosis.[14] Acidosis in turn was significantly associated with a fatal outcome. In a study by English et al. on children, patients having complications, like coma and respiratory distress, had a higher serum lactate level.[10] In a study by van Genderen et al., admission plasma lactate levels were significantly higher in travelers with severe falciparum malaria than in those with uncomplicated malaria. That study suggested that a timely determination of plasma lactate levels on admission may provide the clinician with a useful tool for estimating disease severity.[11] In a study by Krishna et al., mean venous blood lactate concentrations were almost twice as high in fatal cases (7.1 mmol/L vs. 3.6 mmol) and were correlated with levels of tumor necrosis factor and interleukin 1-alpha.[12]

### Table 4: Association of serum creatinine in patients of malaria with lactate level

| Malarial species | Lactate level (mmol/lb) | S. creatinine (≤1.6 mg/dl) | S. creatinine (1.7-3 mg/dl) | S. creatinine (>3 mg/dl) |
|------------------|-------------------------|-----------------------------|-----------------------------|--------------------------|
| P. vivax (P.V)   | <2                      | 10                          | 0                           | 0                        |
|                  | >2                      | 22                          | 17                          | 1                        |
| P. falciparum (P.F) | <2                | 5                           | 0                           | 0                        |
|                  | >2                      | 12                          | 9                           | 9                        |
| Mixed (P.V./P.F.) | <2                      | 0                           | 0                           | 0                        |
|                  | >2                      | 3                           | 5                           | 7                        |
| Total            | 52                      | 31                          | 17                          | 17                       |

### Table 5: Death of patients and lactate level

| Diagnosis  | Serum Lactate Level | TLC (<4000) | Hb (<5) | Platelet (<50000) | BP (<90) | Bilirubin (>3) | PT (>15) | S. Creatinine (>3) | B. Urea (>40) |
|------------|---------------------|-------------|---------|-------------------|---------|----------------|---------|------------------|---------------|
| PV         | <2                  | 0           | 0       | 0                 | 0       | 0              | 0       | 0                | 0             |
| (P. Vivax) | >2                  | 1           | 1       | 2                 | 2       | 2              | 0       | 1                | 2             |
| PF         | <2                  | 0           | 0       | 0                 | 0       | 0              | 0       | 0                | 0             |
| (P. Falciparum) | >2          | 2           | 2       | 6                 | 2       | 2              | 2       | 2                | 5             |
| PV+PF (Mixed) | <2              | 0           | 0       | 0                 | 0       | 0              | 0       | 0                | 0             |
|                | >2                  | 1           | 1       | 2                 | 2       | 2              | 1       | 1                | 1             |
| Total        | 4                   | 4           | 10      | 6                 | 6       | 6              | 3       | 4                | 8             |
In this study, the serum lactate levels showed a significant association with most of the complications of malaria like anemia, thrombocytopenia, jaundice, and renal failure. Raised serum lactate levels were significantly associated with mortality ($P < 0.05$).

Hence, serum lactate levels can be independently used as an indicator of severity of complications and mortality. Those having hyperlactatemia can be observed more carefully for complications and care can be intensified in these patients so that morbidity and mortality is effectively reduced.

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