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Outcome of severe falciparum malaria in an intensive care unit

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Abstract

***Objective*: Plasmodium falciparum infection is responsible for most malaria-related mortality and morbidity. We aimed at studying the initial clinical presentation and subsequent outcome of adult patients admitted to the ICU with severe falciparum malaria.**

***Design*: Prospective observational study.**

***Setting*: Intensive care unit of a 1300 bedded tertiary care hospital at Varanasi, India.**

***Patients and participants*: Patients aged more than 15 years fulfilling one or more of the WHO criteria for severe falciparum malaria were included.**

***Intervention*: All patients were managed as per the initial clinical presentation.**

***Measurements and results*: A total of 34 patients (23 males and 11 females) were included in the study. Twelve patients presented with coma, nine with shock, seven with generalized convulsions, four with ARDS, and the remaining two with spontaneous bleeding from multiple sites. Of these patients, seven survived from coma, two from shock, three from generalized convulsion, and one from ARDS. Twenty one patients died (12 from renal failure, five from multi-organ failure, and four from DIC) during their treatment in ICU, of whom 17 had on admission APACHE II score of >20. Of the 11 female patients, three were pregnant at the time of admission, all of whom died due to multi-organ failure.**

***Conclusion*: The most common mode of presentation of severe falciparum malaria was unarousable coma. Patients admitted to the ICU for neurological complications of malaria had a better prognosis than those admitted for other severe complications. APACHE II score can be a useful prognostic marker in cases of severe falciparum malaria. Renal failure was the most common cause of death in cases of severe falciparum malaria and was usually unresponsive to peritoneal dialysis.**

Key words: Falciparum malaria, ICU, severe.

Introduction

Malaria is one of the most common parasitic protozoal diseases of the human. It has an annual global incidence of about 300-400 million and about 2-3 million people die due to its complications. (1) India contributes to 80% of the total cases of malaria in South East Asia. (2) Being transmitted by the bite of female Anopheles mosquito, four species of the genus Plasmodium namely: P. ovale, P. vivax, P. malariae, and P. falciparum cause human malaria. Some rare routes of transmission are through blood transfusion or congenital transmission. Of the four species, infection caused by P. falciparum is responsible for most severe malaria-related morbidity and mortality. The major complications of severe falciparum malaria are cerebral malaria, pulmonary edema,

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acute renal failure, severe anemia, bleeding, acidosis, and hypoglycemia. (3) If untreated, severe falciparum malaria has nearly 100% mortality. Much has been reported regarding the intensive care management of severe falciparum malaria in endemic areas like India, but studies addressing the initial presentation and subsequent outcome are very few. So, we aimed at studying the initial clinical presentation and subsequent outcome of adult patients admitted to the intensive care unit (ICU) of a tertiary care hospital in India with one or more World Health Organization (WHO) criteria for severe falciparum malaria.

Materials and methods

Following approval from the institutional ethics committee, this prospective study was carried out in the ICU of a tertiary care hospital, over a period of 8 months. Patients aged more than 15 years, fulfilling one or more of the WHO clinical criteria for severe falciparum malaria (**Table 1**) (3-5) along with a positive rapid diagnostic test, and further, species (P. falciparum) identification by thin and thick blood smears at the time of admission to the ICU, once proven positive for P. falciparum, were included in the study. The initial parasitemia and the subsequent clearance after treatment were not observed.

On admission, APACHE II scoring and clinical examination was done, their initial mode of presentation and outcome was noted. Arterial blood gas analysis, random blood sugar estimation, complete blood count, liver function test, renal function test and coagulation study were done in all patients. Treatment was initiated for all patients as per WHO 2006 malaria treatment guideline: artesunate injection (for seven days) at a dose of 2.4 mg/kg, intravenously, at 0, 12, and 24 hours of admission, followed by daily administration of the drug at 2.4 mg/kg per oral, after the patients were able to take the drug orally. Mefloquine 25 mg/kg divided over two days was given to all the patients after completion of seven-day course of artesunate.

During the hospital stay, patients were managed symptomatically. Comatose patients were managed with correction of dyselectrolytemia, maintenance of normovolemia, euglycemia and normocapnia (if mechanically ventilated), sedation (if required), and maintaining semi recumbent position. Patients with acute respiratory distress syndrome (ARDS) were managed with mechanical ventilation with positive end expiratory pressure (PEEP). We managed pulmonary edema with maintenance of euvolemia and blood oxygenation (mechanical ventilation, if required) along with diuretics. Blood samples were sent for culture, and fluid therapy (as per central venous pressure) along with dopamine was given to all the patients who presented with shock. Acute renal failure was managed with correcting electrolyte imbalance, maintaining euvolemia, diuretics, inotropic support in the form of dopamine, and peritoneal dialysis as per need. Patients with disseminated intravascular coagulation (DIC) were treated with fresh frozen plasma, platelet concentrates and packed red cell transfusion. For treatment of hypoglycemia, 25% dextrose solution was used. We used injection thiopentone (0.5-2 mg/kg) for controlling generalized seizure. Severe anemia was managed with packed red cell transfusion. Acidosis management was done as per the cause and injection sodium bicarbonate was used when plasma bicarbonate level was less than 15 mM/liter and blood pH was less than 7.2.

Results

A total of 34 patients (23 males and 11 females) were included in the study. Of the 11 females, three were pregnant at the time of admission. **Table 2** shows the initial mode of presentation and on admission mean APACHE II score of the patients. At the time of admission, 12 patients presented with coma (Glasgow Coma Scale <9), nine patients with shock, seven with generalized convulsions, four with ARDS, and the remaining two with spontaneous bleeding from multiple sites. Of the 12 comatose patients, seven (58.33%) survived and five (41.67%) died due to renal failure. Seven (77.78%) out of nine patients presented with shock died - four had renal failure, two had DIC, and one patient had multi-organ failure. Of seven patients presented with generalized seizures, three (42.85%) survived and the rest four died (57.15%) - three had renal failure and one patient died of multi-organ dysfunction. Among the four patients presented with ARDS, three (75%) died due to multiple organ failure. None of the patients who presented with bleeding from multiple sites survived (**Table 3**).

Twenty one patients (61.76%) died during their treatment in ICU, of whom 17 (80.95%) had an APACHE II score of >20 at the time of admission. Out of the 21 patients who did not survive, 12 died from renal failure, five from multi-organ failure, and four from DIC (**Table 3**). Peritoneal dialysis was done in eight of the 12 patients of renal failure, among them six died. Out of the 11 female patients, three were pregnant at the time of admission, all of whom died due to multi-organ failure.

Discussion

Severe infection with P. falciparum is life-threatening and requires early diagnosis. It should be best managed in an ICU where clinical deterioration can be detected early and hence can be managed appropriately. Our study aimed at describing the initial clinical presentation and subsequent outcome of adult patients admitted to the ICU with one or more WHO criteria for severe falciparum malaria. Considering the high incidence of renal failure and DIC in the studied population, they have been categorized as separate entities from multi-organ failure that is, dysfunction of more than one organ, requiring intervention to maintain homeostasis. An early detection and organ support in the form of renal replacement therapy is advised.

The most frequent mode of presentation to the ICU in our study was unarousable coma followed by circulatory collapse and/or shock. In our study, 58.33% patients with unarousable coma and 42.85% patients with generalized seizures on admission survived. This finding was consistent with previous study reports in which patients admitted to the ICU for neurological complications of malaria had a better prognosis than those admitted for other severe complications. (6,7) So, this group of patients has a fair chance of survival with earlier and aggressive intensive care management. Renal failure was the most common cause of death in our study. Metabolic acidosis due to renal failure and lactic acidosis is a major cause of death in severe falciparum malaria. (8) We tried to avoid metabolic acidosis by using dopamine in the management of renal failure and shock as evident from previous studies. (9,10)

Studies have shown a significantly lower mortality with hemofiltration compared with peritoneal dialysis in sepsis or malaria-related renal failure. (11,12) The greater mortality of the patients of renal failure in our study could be attributable to the use of peritoneal dialysis instead of hemofiltration. The treatment of severe malaria should aim for a fast reduction in parasitemia. Treatment with quinine is associated with complications like hypoglycemia, hypotension and cardiac arrhythmia (3) which can be detrimental in already critically ill patients. Artemisinin compounds are highly effective and devoid of major side effects. (12,13) Artesunate has the combined advantage of rapid action, smaller infusion volumes, lesser toxicity and a mortality reduction. (14) In our study we have used artesunate in all patients to have a faster elimination of parasite and to avoid the complication related to quinine. Multi-organ failure has poor prognosis in cases of severe falciparum malaria. Previous studies have shown benefits of exchange transfusion in management of multi-organ failure in severe falciparum malaria. (15,16) However, exchange transfusion was not performed in our study as it was shown to be expensive, time consuming and hazardous. (17,18) In our study all the pregnant women with severe falciparum malaria died in spite of all possible efforts. Pregnant women (particularly during the second and third trimester) are prone to severe P. falciparum infection. Severe falciparum malaria in pregnancy is associated with high level parasitemia with anemia, hypoglycemia and pulmonary edema, (19,20) and thus contributing toward greater mortality in this group of patients.

The mortality of severe falciparum malaria in our setup was high (61.76%) as compared to developed countries. This could be due to delayed referral of the cases to us and lack of awareness about the disease in general population. Although the patient population in our study was small the results may provide a useful approach for focusing the management to the category of patients with favorable outcome (i.e., patients with neurological symptoms) in the resource-limited ICUs and preferring hemofiltration to peritoneal dialysis for management of renal failure in cases of severe falciparum malaria.

Conclusion

Thus we conclude that the most common mode of presentation

of severe falciparum malaria was unarousable coma. Patients admitted to the ICU for neurological complications of malaria had a better prognosis than those admitted for other severe complications and should be managed early and aggressively. Severe falciparum malaria had a grave outcome during pregnancy. Renal failure was the most common cause of death in cases of severe falciparum malaria and was usually unresponsive to peritoneal dialysis.

Table 1. WHO criteria for recognizing severe falciparum malaria

Defining criteria (1990 Criteria)	Finding
Cerebral malaria (unarousable coma)	Unarousable coma not attributable to any other cause in a patient with falciparum malaria with a Glasgow Coma Scale score ≤9. Coma should persist at least 30 minutes after a generalized convulsion to make the distinction from transient post-ictal coma
Severe normocytic anaemia	Normocytic anemia with hematocrit <15% or hemoglobin <5 g/dL in the presence of parasitemia >10,000 parasites per μL
Renal failure	Urine output <400 mL in 24 hours in adults, or 12 mL per kg in children, failing to improve after rehydration, and with serum creatinine >265 μmol/L (3 mg/dL)
Pulmonary edema, ARDS	
Hypoglycemia	Whole blood glucose <2.2 mmol/L(<40 mg/dL)
Circulatory collapse, shock	Hypotension (systolic blood pressure <50 mmHg in children 1-5 year-old; <70 mmHg in adults) with cold, clammy skin or a core-to-skin temperature difference >10 °C
Spontaneous bleeding, DIC	Spontaneous bleeding from gums, nose, GI tract, or other sites, with laboratory evidence of disseminated intravascular coagulation
Repeated generalized seizures	≥3 convulsions observed within 24 hours despite cooling
Acidaemia or acidosis	Arterial pH <7.25, plasma bicarbonate <15 mmol/L
Malarial hemoglobinuria	Need to exclude hemoglobinuria due to antimalarial medications and to G6PD deficiency
Additional criteria(from 2000)	**Finding**
Impaired consciousness but arousable	Impaired consciousness less marked than unarousable coma, can localize a painful stimulus
Prostration and extreme weakness	Patient unable to sit or walk, with no other obvious neurological explanation
Hyperparasitemia	>5% parasitized erythrocytes or >250,000 parasites/μl (in nonimmune individuals)
Jaundice	Total bilirubin >50 μmol/L (>3 mg/dL)
Hyperpyrexia	Rectal temperature >40 °C

Table 2. Frequency of WHO defining criteria and APACHE II scores in the 34 patients with severe P. falciparum malaria at the time of admission to intensive care unit

Criteria	n (%)	APACHE II score (mean±SD)
Cerebral malaria (unarousable coma)	12 (35.29)	23.5±5.12
Circulatory collapse, shock	9 (26.47)	23±3.16
Repeated generalized seizures	7 (20.58)	23.4±4.31
Pulmonary edema, ARDS	4 (11.76)	29.5±4.79
Spontaneous bleeding, DIC	2 (5.88)	34±2.82

Table 3. Cause of death, initial mode of presentation, and APACHE II score in 21 patients

Cause	n (%)	n (mode of initial presentation)	APACHE II score	
			No. of patients with >20	No. of patients with <20
Renal failure	12 (66.66)	5 (comatosed)	3	2
		4 (shock)	3	1
		3 (generalized convulsion)	2	1
Multiple organ dysfunction	5 (14.28)	1 (shock)	1	0
		3 (ARDS)	3	0
		1 (generalized convulsion)	1	0
DIC	4 (19.04)	2 (DIC)	2	0
		2 (shock)	2	0

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