Adrenal Insufficiency in Severe Falciparum Malaria: Its Outcome and Prediction by Discriminant Score

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ABSTRACT

Introduction: Severe falciparum malaria (SFM) is a complex syndrome which affect different organs of the body with variable severity. But adrenal insufficiency (AI) is a less described entity in SFM. The present study aimed at describing AI, its prediction with Discriminant Score (DS), effect of replacement of hydrocortisone in such cases.

Material and Methods: This study was conducted in two steps among two cohort of patients. In Step-1, AI has been detected by cortisol assay among 142 consecutive cases of SFM. Taking different clinical and biochemical variables, Discriminant Function Analysis was performed to find out a DS to predict AI. In Step-2 study DS has been validated in 74 new cases of SFM. Patients with AI have been replaced with Inj. hydrocortisone and compared with the patients without hydrocortisone of Step-1 study.

Results: Out of 142 cases of SFM, 50 (35.2%) patients had AI as defined by cortisol level <10ug/dl. DS of >0.35 could able to discriminate AI with sensitivity, specificity, and predictive value of 92.5%, 91.6%, and 85.7% respectively. The most common presentations are hypotension, hypoglycemia, and hyponatremia. After replacement of steroid the mortality was low (7.4%) compared to without replacement (18.0%).

Conclusion: The present study showed that AI is common in SFM and replacement of hydrocortisone is necessary in those patients for reduction of mortality. DS can be used to predict AI and patients with score >0.35 may be administered with low dose steroid.

Keywords: Severe Falciparum Malaria, Falciparum Malaria Outcome and Prediction, Discriminant Score

INTRODUCTION

Malaria is not always a simple febrile illness characterized by fever with chill, rigor and related symptoms. In approximately 1% of cases it may progress to severe malaria. Out of all species of Plasmodia that cause human malaria, P. falciparum has the potentiality to progress to severe malaria.[1] Cerebral malaria (CM) is the commonest form of complicated malaria encountered in clinical practice. Apart from CM, complicated malaria is also extended to other clinical forms of the disease like renal failure (RF), anaemia. Acute respiratory distress syndrome (ARDS), etc. At present there is a changing trend of severe falciparum malaria (SFM) in which CM with multi organ dysfunction syndrome (MODS) has been encountered more often than CM alone and the constellation of CM with jaundice and RF is very common.[2] Clinical features of adrenal insufficiency (AI) characterized by hypotension not responding to fluid therapy and pressuramine is not infrequent in SFM. Further, like sepsis, it also led to a MODS like state.[3]

SFM is a complex syndrome whose mechanism is thought to be related to sequestration of parasitized red blood cells in the capillaries of brain and other organs. Sequestration causes profound impairment of microcirculation leading to hypoxia and organ dysfunction.[4] Superimposition of shock over an existing hypoxic state may further deteriorate the condition. AI is one of the mechanisms of shock.[5] But treatment of shock and AI with steroid in severe malaria still controversial.[5]

Like sepsis, severe malaria being a stressful condition of the body stimulates the release of catecholamines and cortisol from the adrenal gland, and the later inhibits nuclear factor-kB and downregulates the production of proinflammatory cytokines. Inadequate production of cortisol in response to increased demand during stress due to Hypothalamic-pituitary-adrenal axis (HPA axis) dysfunction can lead to a state of relative adrenal insufficiency or failure (AI or AF) leading to refractory hypotension. There also exists a state of functional steroid resistance due to decreased number and function of steroid receptors.[6] As a result of AI there is unchecked release of proinflammatory cytokines which are key contributors to tissue hypoperfusion, organ injury, metabolic derangements like hypoglycemia, electrolyte abnormalities, and hemodynamic instability leading to adverse outcome. Relative mineralocorticoid deficiency also results in decreased tissue perfusion and further tissue injury. Therefore, supplementation of steroid in such patients may be an interesting therapeutic intervention.[7]

After the report of deleterious effect of high dose of dexamethasone in CM, there is no further research in this field.[8,9] On the contrary, similar reports in sepsis prompted a lot of subsequent works that changed the trend of steroid therapy from “high dose short duration” to “low dose long duration”; and from all (unselected) patients to selected

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patients.[10,11,12,13] Contrary to sepsis, patients of SFM were relatively younger, and usually did not have other ailments. Hence, logically, patients of SFM with AI are ideal candidates for replacement therapy.

Therefore, we have planned this prospective study in two steps to assess AI in SFM, its impact on the clinical course, to develop a Discriminant Function Score (DS) to predict the probability of AI, to determine the effect of replacement of hydrocortisone on the outcome, and to use DS for prediction of AI and steroid replacement in low resource settings where cortisol estimation is not possible.

MATERIAL AND METHODS

The present study was a hospital based prospective study, conducted at VSS Medical College, Burla now renamed as V.S.S Institute of Medical Science and Research, Burla, Sambalpur, Odisha from October 2012 to September 2018. Sambalpur is situated between the geographical coordinates of 21.5°N 83.87°E. Malaria is hyperendemic in this region, and transmission occurs throughout the year with a seasonal peak from July to October.

Ethical approval was obtained from the Institutional Ethics Committee (IEC) of VSS Medical College, Burla vide letter No. 14/12/ dated 14th Oct.2014. As the patients of SFM were comatose, written informed consent was obtained from the families of all patients before enrolment in the study.

Study Design: The present study was conducted in two steps. In step-1study we evaluated the AI, its prognostic impact on outcome of SFM, and development of DS to predict AI. In step-2 study we validated DS in new cases. After the completion of Step-1 study the IEC was convinced that replacement of hydrocortisone is necessary among the patients with AI in view of high mortality. Therefore, IEC has permitted to administer hydrocortisone as a part of replacement therapy of AI.

STEP-1

Step-1 study was designed as a cross sectional study of all patients of SFM. It is a prospective study in which 142 adult patients (18-65 years) of SFM were enrolled. For comparison of hydrocortisone level 40 patients of uncomplicated falciparum malaria (UFM) and 35 healthy controls were also enrolled.

The diagnosis of falciparum malaria was made with detection of asexual form of the parasite in the Giemsa stained peripheral blood smears or through Rapid Diagnostic Test. The parasitic count per µL was calculated by multiplying number of asexual form of parasites per 200 leukocytes with total leukocyte count. Smear was taken daily to know the parasite clearance with treatment. SFM was defined according to the WHO criteria whereas organ dysfunction was defined, and severity was assessed by MSS.[1,3]

At the time of enrolment, demographic information, clinical characteristics and investigations required for diagnosis of organ dysfunction were evaluated and recorded. The demographic information included sex, age, weight, region of residence, economic status. The clinical data included Glasgow Coma Scale (GCS), jaundice, renal failure, amount of urination, coma onset time (COT), duration of coma (DOC). COT has been determined from the time interval of initiation of fever to onset of coma. DOC has been calculated from onset of coma to onset of treatment with antimalarial drug. The base line biochemical investigations such as blood glucose, blood urea, serum creatinine, serum sodium, serum albumin, serum bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT) and complete blood count (CBC) including blood grouping were done in all cases at the time of admission or within 12 hours of admission. For estimation of hydrocortisone, blood was collected at the time of admission from the patients of SFM and at 6 A-8AM from patients of UFM and normal control.

We also conducted a cerebrospinal fluid analysis, abdominal ultrasound, chest X-ray, electrocardiogram, and serological markers for hepatitis to exclude the diseases mentioned in exclusion criteria.

All 142 patients were taken as developmental sample for Discriminant function (DF) analysis to develop DS to predict AI. For this we identified minimum number of variables that can be utilised for this purpose. To find out the cut-point to define normal and abnormal values we determined the co-efficient βs and 10 ug/dl is found out to define AI.

All patients were treated with injection Artesunate 2.4 mg/kg at 0 hrs., 12 hrs., 24 hrs. then once daily for 7 days or continued until they were able to tolerate drugs orally according to WHO guidelines.[1,14] Then Artesunate and sulfadoxine-pyrimethamine was given orally. Supportive treatment was given as per requirement. Patients with hypotension were treated with fluid replacement and vaso-pressures.

Patients with co-morbid conditions like diabetes mellitus, chronic renal failure, hypertension, coronary artery disease, valvular heart disease, chronic liver disease, alcoholic liver disease, associated infections (e.g. pneumonia, urinary tract infection, viral hepatitis, meningitis), and who lost follow up were excluded from the study.

Sub Study-2

In Step-2 study, 71 new consecutive patients of SFM were enrolled as validation sample to validate the DS. The methodology of Step-1 study had been followed in Step-2 sub-study. Patients with AI were treated with Hydrocortisone 50 mg IV start followed by 50 mg IV 6 hourly for 5 days in an open label and non - randomized manner. These patients were compared with the patients of AI of Step-1 study. The outcome, side effects, and duration of treatment were compared.

STATISTICAL ANALYSIS

Data were analyzed using SPSS-11 and expressed as mean and standard deviation. The quantitative data among the survivors and non-survivors of patients of severe malaria with or without AI were compared with Kruskal-Wallis one-way ANOVA. Probabilities ≤ 0.05 was considered significant. DF analysis was performed to find out the variables affecting the prognosis of AI and to identify

the minimum number of variables that can be utilised for prediction AI among new cases. All the variables considered for DF analysis were mentioned in the Table-3. DF analysis had been done in the following steps. In step-1, the initial analysis was done to determine the group means and standard deviation of each variable with one-way ANOVA & Wilk's lambda (U-statistics). In step-2, the variables were analysed simultaneously, and potentially useful variables were selected by stepwise selection, which combine the features of forward selection and backward elimination. In the next step, canonical DF coefficient of the variables were calculated to derive an equation of the form $DF=B_0X_0+B_1X_1+B_2X_2\ldots B_pX_p$ for prognostication where DF is discriminant function, Xs are the values of independent variables, and Bs are coefficients estimated from the data

RESULTS

Study-1

During the study period 142 patients of severe malaria were admitted to the hospital. Of them 50 (35.2%) patients had AI at the time of admission. Majority (80.0%) patients with AI had MODS and constellation of jaundice, renal failure, and cerebral malaria was common (Table-1). Out of all clinical features hypotension, hypoglycemia, hyponatremia, high parasitic count, and MODS were found more among patients with AI (Table-2). There were 3 independent risk factors

Types of Malaria	Severe malaria with AI N=50	Severe malaria without AI N=92	Total N=142	P value
A.Cerebral	10 (20.0%)	30 (32.0%)	40	<0.01
B.MODS	40(80.0%)	62 (67.4%)	102	<0.01
Renal+Cerebral	7(14.0%)	11(11.9 %)	18	,0.01
Jaundice+Cerebral	7(14.0%)	7(7.6 %)	14	<0.01
Anaemia+cerebral	3(6.0%)	3(3.2%)	6	<0.01
Cerebral+Jaundice+Renal	23 (46.0%)	41 (44.5%)	64	<0.01
C.Death	9(18.0%)	10 (10.8%)	19	<0.001

Table-1: Step-1 Study

Symptoms and Sign	With AI (n=50, 35.2%)	Without AI (n=92, 64.7%)	Total (n=142)	p Value
General Symptoms				
A. Fever	42 (84.07%)	90 (97.8%)	132(92.9%)	<0.01
1. Intermittent	25 (50.0%)	50 (54.3%)	75(52.8%)	<0.01
a. Tertian	15 (30.0%)	29(31.5%)	44(30.9%)	0.14
b.Quotidian	10 (20.0%)	21(22.8%)	31(21.8%)	<0.01
2. Continuous	17 (34.0%)	40 (28.1%)	57(40.1%)	<0.01
B. Other Symptoms				
1. Headache	38 (76.0%)	75(81.5%)	113(79.5%)	<0.01
2. Vomiting/Nausea	38 (76.0%)	75(81.5%)	113(79.5%)	<0.01
3. Abd. Pain	10 (20.0%)	30(32.6%)	40(28.1%)	<0.05
4. Myalgia	35 (70.0%)	78(84.7%)	113(79.5%)	0.15
5. Prostration	30 (60.0%)	85(59.8%)	115(80.9%)	0.1
6. Fainting attack	45(90.0%)	36(39.1%)	81(57.1%)	<0.05
8. Sub conjuctival haemo.	8 (16.0%)	25(21.2%)	33(23.2%)	<0.05
II. Organ Specific symptoms				
A. CNS				
1. Unconsciousness	50 (100.0%)	92 (100.0%)	**142** (100.0%)	NS
2. Convulsion	5(10.0%)	18(19.5%)	23(16.1%)	<0.001
4. Retinal haemorrhage	5(10.0%)	10(10.8%)	15(10.6%)	NS
B. Renal				
1. Oliguria	30(60.0%)	58(63.1%)	88(61.9%)	<0.001
2. Black urine	5(10.0%)	18(19.5%)	23(16.1%)	<0.001
C. Gastro intestinal				
1. jaundice	29(58.0%)	46(50.0%)	75(52.8%)	<0.001
2 Abd.pain	15 (30.0%)	35(38.1%)	50(35.2%)	<0.01
3. Hepatosplenomegaly	40(80.0%)	85(59.8%)	125(88.0%)	<0.05
D. Haematological				
1. Bleeding	2(4.0%)	21(22.8%)	23(16.1%)	<0.001
2. Anaemia	41(82.0%)	52(56.5%)	93(65.4%)	<0.05
E. Hypotension	36(72.0%)	42(45.6%)	78 (54.9%)	<0.01
Comparison made using X2 test				

Table-2: Clinical Presentation of Patients of Severe Falciparum Malaria with and without AI

Variables	Severe malaria with AI		Severe malaria without AI		Probability* With/withoutAI
	Survivors	Non- survivors	Survivors	Non- survivors	
Sample size	41	9	82	10	
Male: Female	30:11	6:3	62:25	3:2	
Age (Years)	38.5±4.0	41.7±16.2	33.4±11.5	45.8±11.8	0.011/ 0.01
Coma onset time (hour)	109.0±41.2	57.7±48.7	57.3±33.3	33.7±20.1	0.0001/0.05
Duration of coma (hour)	38.4±22.3	90.0±28.0	78.8±42.3	93.2±31.8	0.0001/0.01
Glasgow coma scale score	7.5±2.6	4.6±2.3	5.7±3.0	4.6±1.0	0.0001/0.05
Heart rate (No. of beats/ minute)	117.4±13.7	121.4±10.4	107.9±10.6	104.5±27.0	0.0001/0.01
Mean blood pressure (mmHg)	87.4±8.9	81.1±15.1	108.2±5.2	110.6±4.5	0.0001/0.001
Temperature (^{0}F)	102.0±2.9	103.1±2.7	101.7±1.8	103.0±2.4	0.002/0.001
Respiration rate (No./ minute)	17.4±23.9	27.5±6.5	14.3±4.2	25.4±3.6	0.078/0.5
Urine output (ml/24 hour)	1050.0±353.2	816.1±388.0	2060.0±411.1	961.5±229.2	0.0001/0.01
Blood glucose (mg/dL)	71.4±21.2	57.464.5	76.2±16.1	56.2±14.5	0.217/0.12
S. bilirubin (mg/dL)	5.5±3.2	6.9±3.2	3.6±4.3	4.5±0.2	0.0001/0.001
S. albumin (gm/dL)	4.5±0.7	4.2±1.1	5.1±0.7	5.1±0.5	0.01/0.01
Blood Urea (mg/dL)	44.4±27.5	54.3±24.9	23.3±16.0	21.2±6.4	0.0001/0.02
S.Creatinine (mg/dL)	1.8±1.5	2.5±1.4	0.39±0.3	0.5±0.3	0.0001/0.012
S. Sodium (mEq/L)	130.9±7.7	125.1±25.4	131.6±5.2	129.6±6.6	0.0001/0.01
Hematocrit (%)	34.8±8.7	33.0±7.1	30.5±5.3	30.9±4.8	0.002/0.001
Hemoglobin (gm/dL)	8.2±2.4	6.4±2.2	9.2±3.2	7.5±2.8	0.001/0.001
Total leukocyte count (thousand/ µL)	8306.7±2714.0	9675.0±3684.9	8782.0±1133.7	9038.5±1470.6	0.245/0.24
Platelet count (1x10^5/µL	2.0±1.6	1.4±0.6	1.6±0.6	1.4±0.4	0.0001/0.01
Parasitic count (thousand/µL	4112.9±1967.3	4252.9±1999.4	4125.9±1989.4	4110.8±1865.3	0.721/0.65
Cortisol (µg/dl)	18.7±8.2	8.3±0.9	35.6±8.9	22.2±4.5	
* Probability of survivors and Non-survivors of AI					

Table-3: Baseline characteristics of patients of severe malaria with and without RAI (Step-1 Study)

Variable	Wilk's Lambda	F	Significance
Sex	0.99	0.24	0.61
Age	0.98	0.78	0.39
Coma onset time (hour)	0.74	23.70	0.011
Duration of Coma (hour)	0.44	91.27	0.0001
Glasgow Coma Score	0.76	22.37	0.0001
Heart Rate (beat/min.)	0.97	1.74	0.002
Mean B.P. (mmHg)	0.96	1.58	0.214
Temperature (^{0}F)	0.96	2.62	0.001
Resp. Rate (No/minute)	0.99	0.001	0.972
Urine output (ml/24 hr)	0.91	7.01	0.019
Blood Glucose (mg/dL)	0.96	2.37	0.127
S. bilirubin (gm/dL)	0.99	0.34	0.557
S. albumin (gm/dL)	0.97	1.48	0.226
B. urea (mg/dL)	0.97	2.36	0.128
S. Creatinine (mg/dL)	0.97	2.36	0.128
S. Sodium (mEq/Lt.)	0.97	2.06	0.154
Hematocrit (%)	0.98	0.98	0.769
Hemoglobin (gm/dL)	0.97	1.74	0.191
Total Leukocyte count (thousands/µL)	0.99	0.24	0.625
Cortisol			
Platelet Count (1x10^5/µL)	0.95	3.22	0.076
Parasite Count (thousands/L)	0.99	0.08	0.769

Table-4: Wilk's lambda (U-statistics) and Univariate 'F' ratio in Discriminant analysis (Step-1 Study)

for a patient of developing AI in SFM. They were 1) High parasite count >5000/µL (OR=1.8 [95%CI=1.1-2.8], p = 0.01) 2) presenting with multi organ failure (OR=1.9[95%CI 1.2-3.1], p=0.002), 3) hyponatremia (OR=4.4[95%CI=1.4-14.3],p=0.002). The death was higher (18.0%) among patients with AI compared to patients without AI (10.8%, p<0.01). The base line characteristics were presented in Table-1 and -2.

Study Variables and Equation

Increased age, short COT, prolonged DOC, low GCS

Variable	Walk's Lambda	F	Co-efficient#	Probability
Duration of Coma (in hr.)	0.44	91.27	0.38	0.0001
GCS Score	0.76	22.37	0.21	0.0001
Heart rate No. of beats/minutes)	0.97	1.74	0.02	0.002
Temperature (^{0}F)	0.96	2.62	0.11	0.001

# Canonial discriminant function co-efficient for obtaining the equation. 	
Constant = -15.8
Equation :
DS = 0.38 (duration of coma in hr) – 0.21 (GCS Score) + 0.02 (heart rate per minute) + 0.11 (temperature 0F) – 15.8
DS > 0.35 Probability of AI
DS < 0.35 No AI				

Table-5: Summary of discriminant analysis for prediction AI (Step-1 Study)

Group	Cortisol Means±SD	P value*
1. Normal Control N=35	22.2±4.5 µg/dl	
2. Uncomplicated falciparum malaria N=40	37.2±5.9µg/dl	<0.001
3. Severe malaria without RAI N=92	35.6±8.9µg/dl	<0.05
4. Severe malaria with RAI N=50	8.7±4.2µg/dl	<0.001
Compared to normal control		

Table–6: Mean Plasma Cortisol Level: Step-1 Study

Types of Malaria	Severe malaria with AI N=50 (Step-1 study with Standard Therapy)	Severe malaria with AI N=27 (Step-2 study with Steroid Therapy)	P value
Cerebral	10 (20.0%)	5(18.5%)	NS
MODS	40(80.0%)	22(81.4%)	NS
Renal+Cerebral	7(14.0%)	3(11.1%)	NS
Jaundice+Cerebral	7(14.0%)	3(11.1%)	NS
Anaemia+cerebral	3(6.0%)	2(7.4%)	NS
Cerebral+Jaundice+Renal	23 (46.0%)	14(51.8%)	<0.01
C. Death	9(18.0%)	2(7.4%)	<0.001

Table-7: Comparison of Organ Dysfunction and outcome of Steroid Therapy (Step-2 Study)

score, tachycardia, high temperature, low urine output, and low mean blood pressure were the variables, which were significantly different among survivors and non-survivors of severe malaria with and without AI (Table-3). All variables that passed the tolerance test (minimal tolerance level of 0.001) were entered to obtain the equation. Hence, four variables e.g. DOC, GCS score, heart rate per minute and temperature (°F) have been selected by DF analysis to obtain an equation to identify patients of SFM with AI with a score (DS) (Table-4 and-5). The equation was: DS = 0.38 (DOC in hr.) – 0.21 (GCS score) + 0.02 (heart rate per minute) + 0.11 (temperature ^{0}F) – 15.8. The probability of AI was considered when the score was more than 0.35, probability of absence of AI was considered with the score less than 0.35. When the prior probabilities were based on the sample proportion of cases in each group, the groups were classified correctly up to 93.1%.

The level of cortisol was mentioned in Table-6. Cortisol level was higher among patients with UFM than healthy controls (22.2±4.5 µg/dl) p<0.001). Among SFM, cortisol level varied from 4.1 to 42.5 µg /dl. The cortisol level below 10.0 µg / dl has been defined as AI and was found in 50 patients with mean 9.7±4.2µg/dl and is significantly lower than patients without AI, 35.6±8.9µg/dl (p<0.001). In 5 cases of SFM the cortisol level was more than 40.0 µg /dl and in one patient it was 4.1µg/dl similar acute adrenal crisis.

Study-2

In study-2 we have included 71 patients to validate the DF and to predict the AI. Out of them 27 (38.0%) patients had AI. The DF predicted AI in 23 (32.4%) patients. Hence, the resultant DS could predict the outcome with high sensitivity (92.5%) and specificity (91.6%) with a predictive value of 85.7%.

Inj. Hydrocortisone 50 mg IV followed by 50 mg IV 6 hourly for 5 days had been administered to all 27 patients with AI along with antimalarial drugs and other supportive treatment. The outcome that is mortality, duration of use of vasopressures, and side effects of glucocorticoids have been assessed.

Normalization of BP was observed in 24 (88.8%) patients of which 5 (18.5%), 6(22.2%), 8(29.6%), 2(7.4%), and 3(11.1%) patients became normotensive within 24, 48, 72,96, and 120 hours respectively. 3 (21.2%) patients did not respond and vasopressures were added. 1 patient recovered on 7th day and 2 (7.4%) patients who did not respond died.

The comparison and types of SFM of patients with without AI were mentioned in Table-7. The mortality among the patients with steroids was 7.4% (2 of 27), which was lower ($p<0.01$) than the mortality without steroid i.e.18.0% (9 of 50) We did not come across with any side-effects like bleeding, vomiting due to steroid therapy.

DISCUSSION

Unlike sepsis, AI in adult malaria is a less described entity. The present research revealed that AI in adult SFM is common and is associated with hypotension, MODS, hyponatremia, hypoglycemia and high mortality. Replacement of hydrocortisone is necessary in such patients and it reduces the mortality without any side effect. Further a DS has been derived to predict AI without steroid estimation in low resource settings and can be used for steroid replacement.

The adrenal gland produces an estimated 5.7 mg/m2 (about 10mg/dl) of cortisol per day (corresponding to 20-30 mg of hydrocortisone) with peak at 4-8 am and low at 6 pm, which can increase 5 to10 fold during the time of stress and the maximal production of cortisol during stress is 60-100mg/m2/day (150-300 mg of hydrocortisone or 30-60mg of prednisolone/day).[15,16]

Adequate adrenocortical function is crucial for survival of patients with critical illness. Most critically ill patients, as a homeostatic adaptation exhibit an elevated plasma cortisol level, reflecting activation of the HPA axis.

In the 1st part of the study we found that cortisol level was higher than normal among patients with UFM and CM, which agrees with previous studies that showed increased cortisol level in UFM and CM as a normal response to stress as in cases of sepsis.[17] In UFM, this has been attributed to a prolonged cortisol half life and stimulatory effect of cytokines on the adrenal cortex, with a consequent protective effect against hypoglycemia. Further, a raised setpoint for cortisol inhibition of Adreno Cortico-Trophic Hormone (ACTH) secretion has also been observed.[18] Cortisol level was also found elevated among UFM patients with pregnancy and it has been postulated that higher total cortisol level cause loss of malaria immunity rather than being concomitant with malaria infection.[19]

However, in 5 (3.5%) cases we got very high level of plasma cortisol and in 35.2% cases we got low level of cortisol i.e. < 10.0 µg/dl of cortisol described as AI and in one patient we got very low level of cortisol like adrenal crisis. These findings are in consistent with sepsis which showed that during severe illness cortisol level may rise very high, and concentration of cortisol above 50µg/dl had been observed and higher cortisol level was associated with high mortality.[20] However, in our series we did not found any association of high mortality with high cortisol level in patients with SFM, whereas high mortality was associated with AI.

In critical illness the HPA axis is usually activated, resulting in increased cortisol production. This enables the human organism to cope with sepsis, trauma, and other stress. On the other hand, there may be sub-normal production of corticosteroids due to HPA dysfunction or cortisol resistance giving rise to functional or relative adrenal inefficiency. Critical illness with low basal cortisol <30mcg/dl and incremental response < 9 µg/dl predicted poor outcome postulating a possible role of glucocorticoid replacement. However, random cortisol level of below 8.0µg/dl in acute illness is a strong presumptive evidence of AI.[21,22] There is no consensus to define the lower limit of cortisol in critically ill patients, but it may range from 10-20µg/dl.[20] Clinical features along with response to hydrocortisone has been considered as an important parameter for diagnosis of AI.[23] The diurnal variation is frequently disrupted during critical illness and surgery.[15,16] Therefore, instead of basal cortisol estimation random cortisol is helpful for recognition of AI in critical cases.[24] Hence, for the present study we defined AI when random cortisol level was below 10.0 g/dl depending on the cutoff value obtained.

In this study patients of AI had hypotension, hypoglycemia, hyponatremia, poor response to vasopressure, MODS, and high mortality compared to without AI.

Patients with SFM may have normal to subnormal cortisol response to stress and there may be primary and secondary AI. Primary AI which occurs due to affection of adrenal cortex can happen in SFM as a result of necrosis or impaired circulation due to sequestration of parasites. ACTH stimulation testing have also shown that primary AI contributes to inappropriately low serum cortisol level in sepsis.[25] Secondary AI due to defect at pituitary can also occur in SFM. Basal plasma level of ACTH within or below the control range and blunted ACTH response to Corticotropin Releasing Hormone (CRH) even in those with normal basal cortisol, suggested a pituitary contribution to AI in SFM.[26] The mechanism of pituitary contribution may be due to altered set point for cortisol inhibition of ACTH or may be due to erythrocyte sequestration within the hypothalamic-pituitary portal system. The parasite produces a peptide like mammalian somatostatin, which inhibits ACTH secretion *in vitro* and this may explain the role of pituitary in AI of SFM.[27] Radio-immuno-assay detected about 150 molecules of somatostatin per parasite, hence its effect on plasma cortisol may be enormous.[26] The pituitary contribution had been further corroborated by the observation of depressed thyrotroph and thyroid gland dysfunction in severe malaria.[28] This study supports previous studies that have linked biochemical parameters such as raised s. bilirubin, s. creatinine, blood urea and anaemia with poor prognosis.[1] In addition, we have identified that short COT, prolonged DOC, thrombocytopenia, oliguria, and low albumin as other factors contributing to a poor prognosis for patients of SFM. We used DF analysis on twenty different variables on day-1 to develop an equation to predict the outcome of new cases. The risk of AI could be predicted primarily by those variables

reflecting changes in level of consciousness (DOC and GCS score), with a significant contribution from temperature and heart rate. Thus, four factors: DOC, GCS, heart rate and temperature (°F) were found to contribute significantly in group separation and prognostication.

In the second part of the study 27 patients of SFM with AI has been treated with hydrocortisone. With treatment, hypotension was improved within 5 days in majority (88.8%, 24 0f 27) of cases. There were 2 (7.4%) deaths which was significantly lower than patients without steroid therapy.

Though there is no definite definition of AI, response to hydrocortisone has been considered as an important parameter for diagnosis of AI[23] In sepsis low dose of steroid has been advocated instead of high dose of steroid. It is evident that glucocorticoid dose should not exceed >200mg/day and mineralocorticoid supplementation with fludrocortisone is not necessary in patients with secondary AI or in those with primary AI receiving more than 50 mg of hydrocortisone due to its potent mineralocorticoid action at high dose.[22]

We have used 50 mg hydrocortisone 6 hourly for 5 days. With steroid, there was good recovery with low mortality. There were no adverse side effects like haemorrhage as described in high dose steroid. There are many studies in sepsis where low dose steroid is found beneficial. It is notable that recently in animal model steroids found to improve cerebral malaria.[29] Cortisol interacts at all levels of immune system exerting suppressive and permissive effects. In addition, cortisol administration improves haemodynamic parameters, corrects hypoglycaemia and electrolyte abnormalities, improves brain oedema.

CONCLUSION

The present study showed for the first time that AI can occur in SAF and low dose corticosteroid as a replacement therapy is beneficial in this sub-group of patients. Therefore, even if high dose of dexamethasone has no more been recommended in CM by WHO, there is a place of low dose steroid as a replacement therapy among patients of SFM with AI. In the absence of cortisol estimation, DS will be useful for discriminating patients with AI and steroid therapy.

REFERENCES

1. Guidelines for the treatment of Malaria, 3rd Edition. World Health Organization, 2015; 3rd edition: 1-62. www.who.int.
2. Mohapatra MK. The natural history of complicated falciparum malaria-a prospective study. J Asso Phys Ind, 2006;54:848-853
3. Mohapatra MK & Das SP. The malaria severity score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults. J Asso Phys Ind, 2009;57:119-126.
4. Miller LH, Baruch DI, Marsh K, Doumbo K. The pathogenic basis of malaria. Nature,2002;415:673-679.
5. Mohapatra MK, Padhiary KN, Sahu RP, Padhy N, Murmu M, Karua PC. Relative adrenal failure in complicated falciparum malaria. Is there a benefit from stress doses of hydrocortisone? International conference of Malaria, New Delhi, 2005, 67.
6. Drucker D, Shandling M. Variable adrenocortical function in acute medical illness, Crit Care Med, 1985;13:477-479
7. Marik PE. Steroid in sepsis: yes, no or may be? J Thorac Dis, 2018;10 (Suppl):s1070-s1073
8. Warrell DA, Looareesuwan S, Warrelll MJ, Kasemsarn P, Intarapraset R, Bunnag D, Harinasuta T. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. N Eng J Med, 1982; 306:313-319.
9. Wyler DJ. Steroids are out in the treatment of cerebral malaria:What's next? J Inf Dis, 1988;158:320-324.
10. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high dose methyl prednisolone in the treatment of severe sepsis and septic shock. N Eng J Med, 1987; 317:653-658.
11. Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high dose glucocorticoid therapy on mortality in patients with clinical signs of sepsis. N Eng J Med,1987; 317:659-665.
12. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Eng J Med,2018;378:797-808.
13. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahler O, Bercker S, et al. Immunologic and hemodynamic effects of low dose hydrocortisone in septic shock. Am J Respir Crit Care Med, 2003;167:5120520.
14. Guidelines for diagnosis and treatment of malaria in India 2014, National Institute of Malaria Research, New Delhi, 2014; 3rd ed: 1-13.
15. Coursin DB, Liddy B, Wood KE. Corticosteroid replacement in critical illness. Clin Pulm Med, 2003;10: 278-288
16. Jung C, Inder WJ. Management of adrenal insufficiency during the stress of medical illness and surgery. Med J Aus, 2008;188:409-413.
17. Shwe T, Khin M, Min H, Hla Kk, Win YY, Htwe K, Thu TM. Serum cortisol levels in patients with uncomplicated and cerebral malaria. Southeast Asian J Trop Med Pub Health,1998;29:46-9.
18. Wilson M, Davis TM, Binh TQ, Long TT, Danh PT, Robertson K. Pituitary-adrenal function in uncomplicated falciparum malaria. Southeast Asian J Trop Med Pub Health, 2001;32:689-95.
19. Vleugels MP, Brabin B, Eling WM, de Graff R. Cortisol and Plasmodium falciparum imfection in pregnant women in Kenya. Trans Royal Soc Trop Med & Hyg, 1989;83:173-177.
20. Shenker Y, Skatrud JB. Adrenal insufficiency in critically ill patients. Am J Resp Crit Care Med,2001;163:1520-1523.
21. Macia BC, Begona POM, Pilar PCM, Asuncion ARM, Castono FG, Venta OR. Serum cortisol concentration in acute non-critical ill patients, measured in three periods of the day. Med Clin (Barc), 2001;15:254-56.
22. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab. 2006;91:3725-3745.
23. Beishuizen A, Thijs LG. Relative adrenal failure in intensive care: an identifiable problem requiring

treatment? Best Pract Res Clin Endocrinol Metab, 2001; 15: 513-31.
24. Annane D. Resurrection of steroids for sepsis resuscitation. Minerva Anaesthesiologica. 2002; 68: 127-31.
25. Davis TME, Thu TA, Binh TQ, Robertson K, Dyer JR, Danh PT, et al. The hypothalamic-Pituitary-Adrenal axis in severe falciparum malaria: Effects of cytokines. J Clin Endocrinol Metab,1997; 82: 3092-33.
26. Pan JX, Mikkelsen RB, Wallach DF, Asher CR. Synthesis of a somatostatin like peptide by plasmodium falciparum. Mol Biochem Parasitol, 1978;25:107-111.
27. Hofland LJ, Lamberts SWJ, Feelders RA. Role of somatostatin receptors in normal and tumoral pituitary corticotropic cells. Neuroendocrinology, 2010; 92 (suppl-1):11-16.
28. Davis TME, Supanaranond W, Pukrittayakamee S, Krishna S, Hart GR, Burrin JN, et al. The pituitary-thyroid axis in severe falciparum malaria: evidence for depressed thyrotroph and thyroid gland function. Trans R soc Trop Med Hyg. 1990; 84:330-335.
29. Vandermosten L, Pham T, Knoops S, Geest CD, Lays N, Molen KV, Kenyon CJ, Verma M, etal. Adrenal hormones mediate disease tolerance in malaria. Nat Commun, 2018; 4525doi.1038/s41476-018-06986-5.

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