ORIGINAL RESEARCH PAPER

Medicine

STUDY OF ADRENAL INSUFFICIENCY IN SEVERE FALCIPARUM MALARIA WITH SHOCK

KEY WORDS: Falciparum Malaria, Shock, Adrenal Insufficiency, Corticosteroid

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ABSTRACT

Malaria remains a serious health problem in South East Asian Region (SEAR) with nearly 290 million people are estimated to be at high risk. India accounts for 77% of the regional total malarial cases. Most of deaths in malaria are due to severe falciparum malaria. Odisha is a unique state in the eastern region of India, which contributes 4% of the population and counting up to >40% of total falciparum malaria cases of India. Malaria is one of the most important public health disease in Odisha. In spite of such an important disease, there are many areas on severe falciparum malarias where research work is scanty. One among of them is detection of relative adrenal insufficiency in severe falciparum malaria. As there is limited work about the relative adrenal insufficiency in severe falciparum malaria with shock and its relation to mortality. This study has been undertaken with the following aims and objectives, firstly detection of relative adrenal insufficiency in severe falciparum malaria with shock and secondly to establish the relation of mortality with or without adrenal insufficiency in severe falciparum malaria. The present study has established that relative adrenal insufficiency is an important cause contributing to shock and increased mortality. Thus addition of corticosteroid saves life and must be used in the relative adrenal insufficiency. However the firm diagnosis of relative adrenal insufficiency depends upon estimation of basal serum cortisol level & post ACTH serum cortisol level. As corticosteroid reduces the mortality rate, it should be empirically used in critically ill severe falciparum malaria cases with shock.

INTRODUCTION:

Malaria is one of the most important disease of human which affect 300 to 500 million people in 100 countries. Malaria remains a serious health problem in South East Asian Region (SEAR) with nearly 290 million people are estimated to be at high risk. India accounts for 77% of the regional total malarial cases. Most of deaths in malaria are due to severe falciparum malaria.

Odisha being a unique state in the eastern region of India, contributes 4% of the population but counting >40% of total falciparum malaria cases of India. In contrast to the national scenario, in Odisha 85% of the reported malaria cases are due to *P. Falciparum*. It contributes to 26% of total death due to malaria of whole India. Almost all death in malaria is due to severe falciparum malaria. It is one of the most important public health disease in Odisha and so also in India.

In spite of such an important disease, there are many areas on severe falciparum malarias where research work is scanty. One among of them is detection of relative adrenal insufficiency in severe falciparum malaria. It is well known that there is high mortality in severe falciparum malaria due to its complications and one among of them is shock, which is akene to sepsis.

Recent studies have shown that critical illness including trauma, sepsis may also induce a hypoadrenal state. Clinical features of adrenal insufficiency and histological changes in adrenal glands occur in severe falciparum malaria. In view of complications such as hypoglycemia, hemodynamic instability, hypothalamic pituitary adrenocortical, (HPA) dysfunction would have important implications in Malaria. In severe falciparum malaria there is scanty and conflicting literature about the relative. The clinical state of patients and methods used in this studies leave open the possibility that HPA dysfunction might complicate severe falciparum malaria.

If the diagnosis of relative adrenal insufficiency has been established as shown by non- response to corticotropin stimulation, the patient has reduced risk of death if treated with hydrocortisone, 100mg every 6-8 hourly and tapered as patient achieves hemodynamic stability.

There is limited work about the relative adrenal insufficiency in severe falciparum malaria with shock and its relation to mortality. Under these background, this study has been undertaken with the following aims and objectives.

1. Detection of relative adrenal insufficiency in severe falciparum malaria with shock.
2. Relation of mortality with or without adrenal insufficiency in severe falciparum malaria.

MATERIALS & METHODS:

This study was conducted in the department of medicine S.C.B. Medical College, Cuttack, Orissa, a tertiary care hospital catering to the whole state of Orissa and neighbouring districts of west Bengal and Jharkhand.

All the patients diagnosed to be Severe Falciparum Malaria in shock as per WHO criteria-2006 admitted to medicine ward of S.C.B. Medical College, Cuttack, Odisha will be taken in to study and detailed clinical examination were performed by using a standard proforma.

Inclusion Criteria :

- Age > 15 yrs
- All cases of severe falciparum malaria in shock [slide +ve/Rapid diagnostic test(ICT or optimal)/quantitative buffy coat test(QBC)+VE]

Exclusion Criteria:

- All pts with Diabetes mellitus, chronic renal failure, Addison's disease , chronic steroid therapy and any cardiac disease, UTI were excluded from the study

DIAGNOSIS AND INTERVENTION :

Malaria diagnosis is confirmed by thick and smear or OptiMAL test or immune-chromatographic test or quantitative buffy coat test. Hypo-adrenal state was confirmed corticotropin stimulation test. The serum cortisol level was measured by Rapid ACTH stimulation test. Blood sample was collected before & 30(T30), 60(T60), 90(T90) mins after corticotropin (250mcg) [IV SYNACTHEN] injection. The maximum increase in cortisol level was calculated as the

difference between T0 and the highest cortisol value at T30, T60, T90 and hypoadrenal state was confirmed if post stimulation cortisol rise d"9 microg/dl.

INVESTIGATION :

Haematological Examination-

- Haemoglobin estimation- by Sahli's method
- Total Leucocyte Count
- Differential Count
- Total Platelet Count

Urine Examination-

- For Sugar , Albumin, RBC , Pus cells , Casts

Biochemical tests-

Done by using standard kits in Autoanalyzer

- Blood sugar estimation
- Liver function tests- serum bilirubin (Direct, total), SGOT,SGPT, alkaline phosphatase
- Renal function tests-Blood urea, Serum creatinine
- Serum electrolytes- Serum Na+, K+
- Serum cortisol Estimation

Other tests-

ECG , Blood culture, Urine culture.

Study Procedure:

On admission detailed history of the patient is obtained. Thorough physical examination and laboratory investigations are done as per the proforma attached herewith after taking in to account of inclusion and exclusion criteria.

Outcome:

The outcome is binary i.e death or discharge. Patients are examined at least 8 hourly till full recovery or death.

TREATMENT & FOLLOW UP:

- The patients were given parenteral Artesunate or quinine in standard does as per WHO guidelines-2006.
- Those patients having relative adrenal insufficiency were given hydrocortisone intravenously 100mg 6-8 hourly for first 24 hr, then 50 mg 6 hourly and then if possible 60 mg daily by mouth.
- Few patients having relative adrenal insufficiency are followed after 2 weeks and basal serum cortisol level was measured.

Statistical Analysis :

- Patient characteristics and outcomes of interest were calculated with 95% confidence interval.
- SPSS-16 software was used for all statistical analysis.
- Linear variables were compared using 't'- test for independent variables.
- Chi-square test was used for testing significance of difference between two proportions.
- The probability P < 0.05 is considered to be significant.

RESULTS AND DISCUSSION:

A total of 31 cases were enrolled for the study. Out of 31 cases, there were 11 male and 20 female adult patients. There were 21 Patients with relative adrenal insufficiency and 10 patients without adrenal insufficiency. The observations of the study were as follows.

Table No-1: Occurrence Of Relative Adrenal (RADR) Insufficiency With Respect To Age Group

Days of fever (in days)	With RADR insuff.		Without RADR insuff.		Total	
	No of cases	%	No of cases	%	No of cases	%
<20	4	19	3	30	7	22.6
20-30	7	33.4	4	40	11	35.5
30-40	4	19	2	20	6	19.4
40-50	5	23.8	0	0	5	16.1
50-60	0	0	1	10	1	3.2
>60	1	4.8	0	0	1	3.2
Total	21	100	10	100	31	100
Mean ±SD	33.09 ± 12.8		28.3 ± 12.2		31.54 ± 12.6	

- There is no Significant occurrence of relative adrenal insufficiency with respect to any specific age group. However age group of 20-30 is more vulnerable.
- The mean age among pts with adrenal insufficiency is 33.09+12.8 years in comparison to 28.3 ± 12.2 in females.

Table No –2: Basal Cortisol Level In Relation To Relative Adrenal (RADR) Insufficiency

Basal cortisol level (mcg/dl)	With RADR insuff.		Without RADR insuff.		Total	
	No of cases	%	No of cases	%	No of cases	%
<5	0	0	0	0	0	0
5-25	4	19	3	30	7	22.6
25-35	5	23.8	5	50	10	32.3
35-45	6	28.6	2	20	8	25.8
45-55	4	19	0	0	4	12.9
?55	2	9.6	0	0	2	6.4
Total	21	100	10	100	31	100
Mean ± SD	38.37 ± 14.5		27.34 ± 8.9		34.81 ± 13.8	

Chi- Square p – 0.317

- There is no Significant Correlation between basal serum cortisol level and relative adrenal insufficiency.
- The mean basal serum cortisol level in patients with adrenal insufficiency is 38.37 ± 14.5 in comparison to 27.34 ± 8.9 in females.

Table No-3: Correlation Of Organ Failure With Occurrence Of Relative Adrenal (RADR) Insufficiency

ORGANS	With RADR insuff.		Without RADR insuff.		Total		Chi-square P
	No of cases	%	No of cases	%	No of cases	%	
CEREBRAL	11	52.4	4	40	15	48.4	0.519
RENAL FAILURE	15	71.4	2	20	17	54.8	0.007
ARDS	2	9.5	1	10	3	9.7	0.967
HEPATOPATHY	15	71.4	6	60	21	67.7	0.525

- It is seen that the cases with relative adrenal insufficiency is significantly associated with Acute Renal Failure (P=0.007) in comparison to case without adrenal insufficiency. 71% of cases with adrenal insufficiency developed Acute Renal Failure while in both group the occurrence of other organ damage is almost same

Table No – 4: Correlation Mods With Relative Adrenal (RADR) Insufficiency

NO OF ORGANS	With RADR insuff.		Without RADR insuff.		Total
	No of organs	%	No of organs	%	No of organs
Only shock	2	50	2	50	4
1	5	55.6	4	44.4	9
2	6	66.7	3	33.3	9
3	6	85.7	1	14.3	7
4	2	100	0	0	2
Total	21		10		31

- As the no of organ damage is increasing, the occurrence of relative adrenal insufficiency is increasing
- No of organ damage is increasing, more chance of

occurrence of relative adrenal insufficiency

Table No- 5: Mortality In Relation To Relative Adrenal (RADR) Insufficiency

Adrenal status	No of cases	No of death	%
With RADR insuff.	21	7	33
Without RADR insuff.	10	0	0
Total	31	0	22.6

Chi – Square P – 0.03

- There is significant correlation between mortality and relative adrenal insufficiency (P=0.03)
- There is more occurrence of death in patients with adrenal insufficiency (33%) in comparison to patients without adrenal insufficiency (0%)

Table No-6: Multiorgan Dysfunction And Death With Respect To Relative Adrenal (RADR) Insufficiency

No of organs	With RADR insuff.			Without RADR insuff.			Total		
	No of cases	No of Death	%	No of cases	No of Death	%	No of cases	No of Death	%
Only shock	2	0	0	2	0	0	4	0	0
1	5	0	0	4	0	0	9	0	0
2	6	2	33.3	3	0	0	9	2	22.2
3	6	3	50	1	0	0	7	3	42.8
4	2	2	100	0	0	0	2	2	100
Total	21	7	33.3	10	0	0	31	7	22.6

- Among all cases with relative adrenal insufficiency, Four organ involvement had highest mortality i.e 100%

Table No – 7: Correlation Of Mods With Respect To Mortality

No of organs	No of cases	No of death	%
≤ 2	22	2	9.09
>2	9	5	55.6
Total	31	7	22.6

Chi-Square P – 0.005

- From this table, it's clear that the more no of organs (>2) affected, more the chance of mortality (55.6%) in comparison to mortality (9.09%) in patients with less no of organs (≤2) affected which is significantly related. (P=0.005)

Table No – 8: Mortality In Relation To Hydrocortisone Therapy In Relative Adrenal Insufficiency

Adrenal insufficiency	No of cases	No of Death	%
Hydrocortisone therapy	16	3	18.8
Without hydrocortisone therapy	5	4	80
Total	21	7	33.3

Chi-Square P – 0.01

- There is significant correlation between mortality with hydrocortisone therapy in patients with adrenal insufficiency (P = 0.01)
- There is more chance of mortality (80%) if patients with adrenal insufficiency are not treated with hydrocortisone therapy.

Table N0 -9 : Correlation of Duration Recovery of Shock with Relative Adrenal (RADR) Insufficiency in Survivors

Shock recovery (in days)	With RADR insuff.		Without RADR insuff.		Total	
	No of cases	%	No of cases	%	No of cases	%
3	1	7.14	3	30	4	16.7
4	12	85.72	5	50	17	70.8
5	1	7.14	2	20	3	12.5
Total	14	100	10	100	24	100
Mean ± S.D	4 ± 0.39		3.9 ± 0.73		3.95 ± 0.6	

Chi-Square P= 0.161

- There is no significant correlation between days of recovery from shock with relative adrenal insufficiency (P= 0.161)
- The mean days of recovery from shock is patients with relative adrenal insufficiency is 4 ± 0.39 and in patients without adrenal insufficiency is 3.9 ± 0.73.

Table No -10: Correlation Of Recovery Shock With Hydrocortisone Therapy In Relative Adrenal Insufficiency

	With hydrocortisone therapy		Without hydrocortisone therapy		Total	
	No of cases	%	No of cases	%	No of cases	%
3	1	7.7	0	0	1	7.14
4	11	14.6	1	100	12	85.72
5	1	7.7	0	0	1	7.14
Total	13	100	1	100	14	100
Mean ± S.D	4 ± 0.4		4		4 ± 0.39	

Chi-Square P= 0.914

- The mean days of recovery of shock in patients treated with hydrocortisone therapy (in survived patients with relative adrenal insufficiency) is 4 ± 0.4 days and in patients not treated with hydrocortisone therapy is 4 days and there is no statistical significance (P=0.914)

Table No – 11: Comparative Analysis of Physical and Clinical Parameter with Respect to Relative Adrenal (RADR) Insufficiency

Parameters	Adrenal status	n	Mean	SD	't' test for equity significance
Age (yrs)	Y	21	33	12.8	0.33
	N	10	28.3	12.2	
Duration of fever before admission (days)	Y	21	4.3	1.6	0.959
	N	10	4.3	1.9	
Total leucocyte count (/cmm)	Y	21	9.466	1997.4	0.100
	N	10	8.280	1336.4	
Serum urea (mg%)	Y	21	119	44.5	0.065
	N	10	86	42	
Serum creatinine(mg%)	Y	21	4.8	2.4	0.022
	N	10	2.6	2	
Serum bilirubin(mg%)	Y	21	5.6	3.8	0.52
	N	10	7.2	7.6	
Haemoglobin (gm%)	Y	21	7.8	2.2	0.232
	N	10	8.9	2.2	

- There is significant difference in the level of serum creatinine level between case with relative adrenal insufficiency and without relative adrenal insufficiency and without relative adrenal insufficiency (P=0.022).

Table No – 12: Correlation of Post ACTH Stimulation Cortisol Rise with Occurrence of Relative Adrenal (RADR) Insufficiency

Rise in cortisol level above basal level after administration of ACTH	With RADR insuff.		Without RADR insuff.		Total
	No of cases (n=21)	%	No of cases (n=10)	%	No of cases
< 9	21	100	0	0	21

≥ 9 - 19	0	0	5	100	5
≥19 - 29	0	0	4	100	4
≥ 29 - 40	0	0	1	100	1

- From this table, it is clear that all patients with relative adrenal insufficiency have post stimulation rise in cortisol level < 9 mcg/dl. Maximum no of patients without relative adrenal insufficiency have post stimulation rise within 9 – 19 mcg/dl.

Table No – 13: Follow Up Of Cases With Relative Adrenal Insufficiency

No of cases	One	Two	Three
Basal Serum cortisol level	63.4	34.8	12.9
Poststimulation cortisol rise	0	7.2	6.7
After two weeks	18.6	14.7	10.4

- From this data it is evident that the serum cortisol level of the patients with relative adrenal insufficiency during illness become normal after two weeks.

SUMMARY AND CONCLUSION:

Malaria is an important public health problem in India and more so in Odisha. The study aims to recognize relative adrenal insufficiency in severe falciparum malaria with shock. Shock is a serious complication in severe falciparum malaria resulting in increased mortality. The present study conducted in the Dept. of Medicine, SCB Medical College & Hospital, Cuttack had thirty one patients with severe falciparum malaria (as per WHO guidelines 2006) with shock who were hospitalized, were enrolled into study. The main objective of the study was to ascertain the differences between the cases with relative adrenal insufficiency and cases without adrenal insufficiency. At the end of the study, S.P.S.S. Software is used with the 95% confidence limit to analyze the data.

Though basal serum cortisol level is slightly raised in all cases. But it has no relation with occurrence of relative adrenal insufficiency (P=0.317). Basal serum cortisol level remain high above normal in 81% cases with relative adrenal insufficiency and 70% case without adrenal insufficiency. Organ dysfunction is common presentation in both the study groups. Among all organs, Renal failure is significantly associated with relative adrenal insufficiency (P=0.007) followed by cerebral, hepatopathy, respiratory insufficiency.

Multiorgan dysfunction is not significantly associated with relative adrenal insufficiency (P=0.107). However if number of organ damage is increasing, then there is increase in chance of occurrence of relative adrenal insufficiency and so also mortality. Also in the settings of relative adrenal insufficiency, if multiorgan dysfunction is present, then there is high chance of mortality (100%). The number of organ damage is significantly related with the mortality in cases with adrenal insufficiency (P=0.015). Also the occurrence of relative adrenal insufficiency is significantly associated with mortality (P=0.03) [33% death in cases adrenal insufficiency Vs 0% in cases without adrenal insufficiency]

There is high chance of mortality in cases with relative adrenal insufficiency & not treated with hydrocortisone therapy (80%) in comparison to less chance of mortality in cases with hydrocortisone therapy (18.8%). It is statistically significant (P=0.01. Duration of recovery is not significantly related with relative adrenal insufficiency. The mean days of recovery in patients with relative adrenal insufficiency is 4 ± 0.39 in comparison to 3.9 ± 0.73 in patients without relative adrenal insufficiency.

There is no significant difference between two groups who survived regarding age (P=0.33), total leucocytes count (P=0.1), Serum urea (P=0.065), Serum bilirubin (P=0.52), Hb (P=0.232). The serum creatinine level among cases with relative adrenal insufficiency is significantly higher than case without adrenal insufficiency (4.8 ± 2.4 Vs 2.6 ± 2) and this is statistically significant (P=0.007).

In the study, maximum no of patients (5 out of 10), those without relative adrenal insufficiency have post-stimulation rise within 9-19 mcg/dl (50%). After 2 weeks, the basal serum cortisol level of patients with relative adrenal insufficiency which were elevated at the time of illness were found to be within normal range.

The present study has established relative adrenal insufficiency as an important cause contributing to shock and increased mortality. Addition of corticosteroid saves life and must be used in the relative adrenal insufficiency. However the firm diagnosis of relative adrenal insufficiency depends upon estimation of basal serum cortisol level & post ACTH serum cortisol level. But because of profound effect of relative adrenal insufficiency on mortality and effect of corticosteroid on reduction in mortality, it should be empirically used in critically ill severe falciparum malaria cases with shock.

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