

# Study of serum cortisol level in severe falciparum malaria presenting with unexplained hypotension

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## ABSTRACT

**Background:** Hypotension in malaria can be due to various causes. One among them is relative adrenal deficiency. World Health Organisation (WHO) and Indian malaria guidelines do not allow the use of steroid in malaria patients. But it appears prudent to use systemic steroid in those subset of malaria patients having adrenal deficiency. So the aim of the study was to prove or disprove the existence of adrenal deficiency in malaria patients.

**Methodology:** This is a case control study which was conducted in two tertiary care centres, single blind and prospective in nature. SPSS 19 was used at the end of the study for all statistical analysis. Patient characteristics and outcome of interest is calculated with 95% confidence limits. The probability of  $<0.05$  is considered to be significant.

**Results:** Compared with control group the study group had significantly lower serum cortisol level at presentation ( $36.56 \pm 6.52 \mu\text{g/dl}$  vs.  $19.43 \pm 7.29 \mu\text{g/dl}$ ,  $p=0.006$ ). In the study group there is significant rise in serum cortisol level after recovery from hypotension ( $19.96 \pm 7.29 \mu\text{g/dl}$  vs.  $35.86 \pm 8.26 \mu\text{g/dl}$ ,  $p=0.01$ ). In control group there is slight decrease of serum cortisol level after recovery ( $36.85 \pm 6.42 \mu\text{g/dl}$  vs.  $34.72 \pm 9.12 \mu\text{g/dl}$ ,  $p=0.83$ ). **Conclusion:** Adrenal insufficiency may be the cause of unexplained hypotension in severe falciparum malaria. Administration of systemic corticosteroid in this subset of patients seems to be justified.

**Keywords:** Falciparum malaria, Hypotension, Serum cortisol

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## INTRODUCTION

Of the 34 million reported cases of malaria in South East Asian Region, India reports approximately two-third of all confirmed cases with 5 states accounting for more than 60% of these cases: Odisha, Chhattisgarh, Madhya Pradesh, Jharkhand and West Bengal.<sup>1</sup> Around 50% of the total malaria cases reported in India are due to Plasmodium falciparum.<sup>2</sup> There are many causes of hypotension in falciparum malaria and in some cases the exact cause cannot be recognised.<sup>3</sup> It is reasonable to think of adrenal gland affection in this subset of patients. Brookes et al (1969) found raised serum cortisol with normal diurnal variation in malaria patients of unspecified severity.<sup>4</sup> Serum cortisol

level has been reported to be higher in uncomplicated malaria than healthy controls by Wilson et al (2001).<sup>5</sup> Davis et al (1997) found that the basal serum cortisol in patients of severe falciparum malaria was significantly higher than those of uncomplicated cases.<sup>6</sup> Adding to the confusion Mohapatra et al (2005) observed that the mean serum cortisol level of uncomplicated malaria was higher than that of complicated malaria with hypotension.<sup>7</sup> Then there came the WHO guideline that corticosteroids are not to be used in malaria and they are in fact detrimental.<sup>8</sup> The objective of the present work is to focus on the group of patients presenting with unexplained hypotension in severe falciparum malaria and to analyse the functional status of the adrenals by estimating the serum cortisol.

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## MATERIALS AND METHODS

### Inclusion criteria

1. Age more than 15 yr.
2. Slide positive for *Plasmodium falciparum*.
3. Having systolic BP <80mm Hg.

### Exclusion criteria

1. Patients with other co-existing illness.
2. Other causes of hypotension like hypovolemia, septicaemia, pulmonary oedema, acidimia and low cardiac output.
3. Patients who had received corticosteroids in any form within 6 weeks.

After carefully considering the inclusion and exclusion criteria, all the patients were grouped into study and control group. Controls were those, which detected slide positive for falciparum malaria in peripheral smear but without hypotension. A total 80 patients were taken into consideration, half in control group and half in study group. Relevant parameters were compared using SPSS 19 software. Student's t test was used for nominal variables and chi square test was used for categorical variables. Patient characteristics and outcome of interest was calculated with 95% confidence limits. The probability of <0.05 is considered to be significant.

Detailed clinical evaluation of the patients was performed at the time of admission and daily thereafter. Serum Cortisol estimation was done at the time of admission and after hypotension was corrected with suitable anti malarial treatment and other supportive therapy like IV fluids and inotropes. Serum cortisol was estimated by Radio-immunoassay (RIA).

## RESULTS

The demographic profile of both study and control groups were similar ( $p=0.08$ ). We obtained maximum cases in the age group of 25-44 in both study and control group. Hypotensive patients more commonly presented with other complications (77.5%) as compared to the control group without hypotension (60%). Eighty five percent of cases presented within 7 days of symptoms and all of them presented within 10 days. Most of the cases in study group presented with heavy parasitemia (>15/1000 RBC) as compared to the control group. Eight patients died among the study group and 4 patients died among the control group. The mean serum cortisol at presentation among the cases was  $19.43 \pm 7.29 \mu\text{g/dl}$  and that of the control group was  $35.86 \pm 8.26 \mu\text{g/dl}$ . This difference is statistically significant ( $p= 0.006$ ). The mean serum cortisol level

after correction of hypotension among the study group increased to  $35.86 \pm 8.26 \mu\text{g/dl}$  and the rise was significant ( $p=0.001$ ). The mean serum cortisol level after treatment among the control group was  $34.72 \pm 9.12 \mu\text{g/dl}$  and this fall is not significant ( $p=0.06$ ). There was no difference in mortality among the study group among those patients with or without renal failure and hepatopathy. All the patients who died among the study group had at least some other WHO defined complication.

## DISCUSSION

Both the control and study group are similar from the demographic point of view ( $p=0.08$ ). In both the groups the most common age group of presentation was 25-44 years. Sharma *et al* (2007) also observed that 61.4% of malaria cases belong to 15-39 age group.<sup>9</sup> Getahun *et al* (2006) also had reported that 59% of their cases were in the age group of 15-29.<sup>10</sup> So this study is no different to conclude that most of the cases of malaria present at a younger age group. In a study by Mohapatra *et al* (2005) the authors concluded that most of the complications develop within 5 days of development of fever.<sup>11</sup> Our study was no different as we observed that 85% of our cases in study population presented within 7 days of fever. Nearly 55% of cases in the study group had heavy parasitemia >15/1000 RBC in comparison to only 12% in the control group. It appears that the degree of parasitemia has something to do with hypotension.

Eight patients from the study group and 4 patients from the control group succumbed during the treatment. Among those 8 patients who died in the study group all had associated other complications like that of cerebral, renal failure, hepatopathy, anaemia or something other. No death is seen among patients of hypotension without any other added complications. So it is prudent to opine that though hypotension itself is not responsible to increase the mortality, but when added to another complication, it dramatically increases the mortality. Five patients among those 8 deaths in the study group had hypotension lasting more than 48 hours; (co-efficient of co-relation among the duration of hypotension and mortality is 0.68). So we may conclude there is a positive co-relation among the duration of hypotension and mortality. Even after searching extensively we could not get any prior documentation of relation among the duration of hypotension and mortality. Those 4 patients who died from the control group 3 of them had multiorgan failure along with cerebral malaria and the other had only cerebral malaria.

It is a well known fact that the serum cortisol level should increase at the time of stress to combat the crisis. Severe falciparum malaria is a great stress to the body and we expect the serum cortisol level to rise. In the setting of

critical illness, serum cortisol  $<15 \mu\text{g}/\text{dl}$  is accepted as adrenal insufficiency, where as  $15\text{-}34 \mu\text{g}/\text{dl}$  is considered as relative adrenal insufficiency and  $> 35 \mu\text{g}/\text{dl}$  is considered as normal.<sup>11</sup> Wilson et al (2006) while studying the uncomplicated malaria cases observed that serum cortisol level was higher than healthy controls.<sup>5</sup> Davis et al (1997) found that the basal serum cortisol in patients of severe falciparum malaria was significantly higher than those of uncomplicated cases.<sup>6</sup> Mohapatra et al (2005) observed that the mean serum cortisol level of uncomplicated malaria was  $46.3 \pm 7.5 \mu\text{g}/\text{dl}$  and that of complicated malaria with hypotension was  $34.8 \pm 8.5 \mu\text{g}/\text{dl}$ .<sup>7</sup> Our study population was only that subset of hypotensive patients where no other cause of hypotension could be attributed like that of hypovolemia and decreased cardiac output. The mean serum cortisol at presentation among the control group was  $35.86 \pm 8.26 \mu\text{g}/\text{dl}$  and after treatment it decreased marginally to  $34.72 \pm 9.12 \mu\text{g}/\text{dl}$  and the difference was not significant ( $p=0.06$ ) explaining that the serum cortisol level was elevated at the onset suggesting acute stress. While comparing the serum cortisol level at presentation among the study and control group, the study group had decreased level and the difference was significant ( $p=0.006$ ) which probably can be explained by relative hypoadrenergic state though the relative adrenal insufficiency has a cut off value of  $15 \mu\text{g}/\text{dl}$ . The mean serum cortisol at presentation among the study group was  $19.43 \pm 7.29 \mu\text{g}/\text{dl}$  and after the correction of hypotension it significantly increased to  $35.86 \pm 8.26 \mu\text{g}/\text{dl}$  ( $p=0.001$ ). This shows that the increase in serum cortisol level after return of blood pressure to normalcy may be due to regain of the adrenal function. There was no statistical difference in those patients of hypotension who also had renal failure or hepatopathy. Probably this indicates that both of these factors do not affect the cortisol production in this subset of patients. Davis et al (1997) found that the cortisol metabolism was slower in severe falciparum malaria with hepatopathy.<sup>12</sup> They observed that there is a significant co relation between serum bilirubin and serum cortisol level but not with serum transaminases, albumin or serum creatinine.<sup>6</sup> We did not observe such correlation between hepatopathy and our study group.

## CONCLUSION

The serum cortisol level among the patients of unexplained hypotension is significantly lower than those of control

and the level increases significantly with treatment. Even if the absolute serum cortisol appears normal in malaria patients, it may be considered subnormal considering the severe stress of malaria. Hypotensive patients present with more complications than normotensive malaria patients. Hypotension alone is not associated with increased mortality, but when combined with other complications the mortality is exacerbated. Administration of systemic steroid in this subset of patients with unexplained hypotension appears to be justified in addition to inotropic support and anti malarial treatment. More study is required with more number of cases with more stringent criteria to generalise this observation of us.

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### Authors Contribution:

**SP, KP** - conceived and designed the study, analyzed and interpreted the data, searched the literature and made the first draft of the manuscript; **DD,SK, BNM & TK** - searched the literature and helped the manuscript preparation. All authors reviewed and approved the final manuscript

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