ACUTE CHANGES IN SERUM CORTISOL LEVELS FOLLOWING RUSSELL'S VIPER BITES IN MYANMAR

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Abstract. Forty-eight Russell's viper bite patients (40 males, 8 females), age ranging from 16-76 years were studied. Out of 48 patients, 14 were found to have a prolonged whole blood clotting time test (WBCT) (*ie* incoagulable blood) (Group I); 23 had a normal WBCT (*ie* clotted blood) (Group II); and 11 patients had a normal WBCT on admission which changed to non-clotting during the clinical course (Group III). Four patients from group I developed hypotension and 2 expired. The serum cortisol concentration (mean ± SEM) on admission among groups I and II were 639 ± 45.6 and 424 ± 33.2 nmol/l respectively. The blood cortisol level in 35 subjects (controls) were 370.7 ± 17.7 nmol/l (mean ± SEM). There was a significant rise of blood cortisol in patients with incoagulable blood when compared to controls at the time of admission to the hospital ($p < 0.05$); but there was no significant difference among those patients with clotted blood. A much higher mean serum cortisol level was observed in 4 patients with hypotension as compared to 10 patients without shock. These patients with hypotension according to our study shown to have a favorable response to steroid therapy and eventually recovered. Whether higher doses of steroid in addition to antiserum confer extra benefit in suppressing nonspecific venom effects on the pituitary and/or adrenal is not known.

INTRODUCTION

Snakebite is a major health problem in Myanmar and Russell's viper (RV) bite accounts for about 90% of cases. Oliguric acute renal failure is responsible for most deaths (*ie* 44%) and hypotension (38%) in systemically envenomed patients (Tin Nu Swe, 1994).

Circulatory shock with internal hemorrhage is a frequent finding in RV bite patients. Early shock may not be primarily cardiac in origin but is mainly due to vasodilatation with a profound decrease in peripheral vascular resistance. Delayed and sustained shock which may not be reversible by standard treatment is caused by hemorrhage and massive necrosis of the pituitary and/or adrenal. Acute massive hemorrhage in these organs has been confirmed by autopsy studies (Maung Maung Aye, 1976; Hla Myint *et al*, 1982; Than Than *et al*, 1989). Hypotension in these patients may be somewhat related to acute pituitary and/or acute pituitary-adrenal failure.

Hence, the present study was conducted with the aim of further clarifying the adrenal response in RV bite victims with reference to serum cortisol levels.

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MATERIALS AND METHODS

Patients

Fourty-eight cases of proven Russell's viper bite were studied at Tharyarwaddy township hospital, 130 km north of Yangon during the months November to January, 1990-1991, 1991-1992 and 1992-1993. The species of each snake was confirmed either by identifying the dead snake brought with the patient to the hospital or by detecting specific venom antigen by ELISA (Khin Ohn Lwin *et al*, 1982). Those patients aged below 12 and above 60 years, pregnant and lactating mothers were not included in this study.

Methods

A detailed history was taken and a complete physical examination conducted and the findings recorded. Local swelling was graded from 1-6 (Warrell, 1974). A simple whole blood clotting test (WBCT) was performed on admission and every 6 hours for 48 hours or until the blood becomes

incoagulable. The samples for serum cortisol were collected on admission and 2 hourly thereafter for 24 hours after admission. The blood samples were also drawn in the morning between 08.00-10.00 hours from 35 apparently healthy subjects as controls. Daily serum samples were frozen for serum cortisol measurements and venom antigen determination.

Serum cortisol was determined using commercially available RIA (double antibody cortisol kits) from Diagnostics Products Corporation Los Angeles, CA, USA. It is a competitive radioimmunoassay in which ^{125}I labeled cortisol competes with cortisol in the patient's sample for antibody sites. The lower detection limit is 8.28 nmol/l and both intraassay and interassay precision less than 10%. All analyses were performed in duplicate and Packard Auto Gamma Scintillation spectrometer model 5230 was used for radioactive measurement.

Treatment

All patients with incoagulable blood were treated with monospecific, refined equine RV antivenom. Fluid balance was strictly controlled. Those who passed less than 400ml of urine in 24 hours, despite rehydration, frusemide (up to 500 mg, intravenous bolus infusion) and dopamine infusion 2.5 μg/kg/minute was given and whose blood urea was rising were transferred to Yangon General Hospital for peritoneal dialysis. Hypotension (*ie* systolic blood pressure less than 90mm Hg for more than 10 minutes was managed by tilting the patient's head down and by giving intravenous dextran 40 (Rhcomacrodex), saline and/or fresh blood until initial central venous pressure (CVP) rose to between 0 and +5 cm of water. Unresponsive patients were given hydrocortisone 200-500 mg, intravenous bolus infusion followed by 100 mg, 6 hourly for 24 hours.

Statistical analysis

Data analysis was performed with SPSS on an IBM computer. Data are expressed as mean ± SEM. Comparisons between the study groups were made using Mann-Whitney U test for unpaired samples (two-tailed). Differences in serum cortisol concentrations in relation to time after admission were assessed using Wilcoxon's Signed Rank test (two-tailed). Differences were considered significant if $p < 0.05$.

Ethical considerations

The study was approved by the Medical Ethics Committee of the Department of Medical Research, Yangon, Myanmar.

RESULTS

Forty-eight proven RV bite patients (40 males, 8 females) with an age ranging from 16-76 years were studied. The study consisted of the following 3 groups.

i) those patients with a normal whole blood clotting test (WBCT) on admission and during the entire clinical course (group I).

ii) those with a prolonged WBCT (*ie* nonclotting) on admission and during the clinical course (group II).

iii) those patients with a normal WBCT on admission which changed to non-clotting during the clinical course (group III).

Comparison of patients' characteristics, clinical features and complications in these 3 clinical groups are shown in Table 1. These 3 groups are comparable because that there is no difference in age and time interval between bite on admission. Hypotension observed in 4 patients among those patients with incoagulable blood (group II), developed within 24-48 hours after admission. Three of them received intravenous corticosteroids of which 2 recovered and the remaining patient developed oliguric acute renal failure and expired. There was a significant rise of blood cortisol level in patients with incoagulable blood (group II) when compared to those patients with clotted blood (group I) at the time of admission to the hospital. But there was no difference in mean serum cortisol level of those patients with clotted blood (group I) when compared to controls. The mean peak serum cortisol level observed at 6 hours after admission (*ie* 10 hours after being bitten by the snakes) in patients with incoagulable blood (Fig 1). The rise was maintained up till 10 hours after admission then it decreased thereafter.

A sustained rise of mean serum cortisol level since the time of admission up till 24 hours was noted in 4 systemically envenomed patients with hypotension (Fig 2). There was a significant rise of

Table 1

Patients' details.

Ser No.	Patients characteristics	Russell's viper bite patients with		
		coagulable blood (group I) n = 23	incoagulable blood (group II) n = 14	coagulable blood changed to in-coagulable blood (group III) n = 11
1.	Average age (yr)	30	27	36
2.	Sex ratio (male : female)	21 : 2	11 : 3	8 : 3
3.	Time interval between bite and admission (hr)	2 hrs 13mins	2hrs 46 mins	2hrs 14mins
4.	Initial venom antigen level (ng/ml) (mean ± SEM)	6.5 ± 2.5	61.4 ± 4.8	26.3 ± 5.1
5.	Local swelling			
	Grade 0-2	21 (91%)	6 (43%)	8 (73%)
	Grade 3 and >	2 (9%)	8 (57%)	3 (27%)
6.	Bleeding froms site of bite	1 (4%)	9 (64%)	2 (18%)
7.	Systemic bleeding*	Nil	10 (71%)	4 (36%)
8.	Hypotension	Nil	4 (29%)	Nil
9.	Oliguria	Nil	11 (79%)	2 (18%)
10.	Oliguric acute renal failure	Nil	4 (29%)	Nil
11.	Peritoneal dialysis	Nil	4 (29%)	Nil
12.	Expired	Nil	2 (14%)	Nil

* refers to bleeding from gum, nose, hematemesis and/or melena, conjunctival hemorrhage, hematuria, etc.

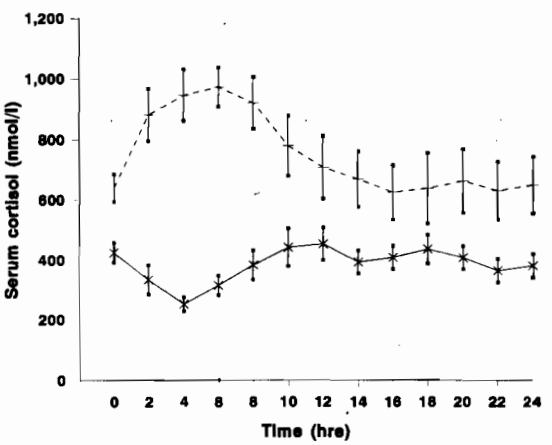

Fig 1–Serum cortisol levels (mean ± SEM) of Russell's viper bite patients.
* clotted; + nonclotted

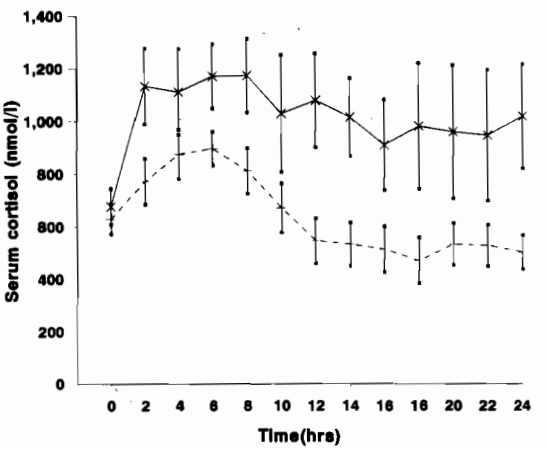

Fig 2–Serum cortisol levels (mean ± SEM) in patients with systemic envenoming by Russel's viper
* nonclotted with shock; + nonclotted without shock.

serum cortisol level in these two groups when compared to controls at the time of admission to the hospital.

DISCUSSION

Russell's viper venom (RVV) contains two potent procoagulant enzymes activating Factors V, IX and X with eventual production of stabilized fibrin (Macfarlane, 1974). The dose of venom related to body weight injected into humans is insufficient to cause clot formation in the heart which is the cause of death in rodents which are the snake's natural prey. However, there was evidence of disseminated intravascular coagulation (DIC): incoagulable blood and depletion of clotting factors and small fibrin thrombi found in pituitary venous sinusoids, pulmonary vessels, glomeruli capillaries and adrenal vessels has been reported (Tun Pe *et al*, 1987).

Abnormal changes in blood cortisol concentration during acute episode in 9 RV bite victims with hypotension has been reported (Tun Pe *et al*, 1987). It was further documented by Proby *et al* (1989). Our study also showed similar changes in blood cortisol concentration in systemically envenomed RV bite patients and more so in 4 patients who developed hypotension during the clinical course (Fig 1). The initial serum cortisol concentration at the time of admission to the hospital in patients with incoagulable blood were found to be significantly increase as compared to controls or patients with non DIC (Fig 1). These abnormally high values were observed only in patients with DIC (*ie* incoagulable blood) but not in those who do not developed DIC (*ie* clotted blood) (Fig 1).

It is clear that ACTH production failure and hence cortisol deficiency contributes to death in the acute phase, by aggravating shock and by hypoglycemia. Similar damage to the adrenals themselves may also occur since adrenal hemorrhage has been found at necropsy in patients following RV bite (Than Than *et al*, 1989). Interpretation of these abnormalities (especially high blood cortisol levels) is difficult and is complicated by the effects of acute illness per se on hormone levels. However, a direct relationship between the release of cortisol and disease severity has been documented (Baxter, 1981). Hence, it may be possible for the high serum cortisol levels observed in RV bite patients with DIC as compared to those without DIC, since the former patients had much higher venom antigen levels and also increase in clinical severity (Table 1). A dose dependent release of GH, TSH and ACTH from dispersed rat anterior pituitary cells in culture (*in vitro* test) has been demonstrated and reported (Hart, 1989). This might partly explained the occurrence of high values of cortisol concentration but whether these effects contribute to its known actions *in vivo* remains to be established. Nevertheless, one could not exclude the possibility of requiring such high cortisol concentration to overcome the acute crisis in these patients.

The use of intravenous glucose and corticosteroids in these patients has been advocated since impaired consciousness hypoglycemia and hypotension following RV bite may be caused by pituitary failure (Tun Pe *et al*, 1987). Three patients with hypotension in our study were shown to have a favorable response to steroid therapy administered at the onset of hypotension (*ie* within 24-48 hours). Whether higher doses of steroids in addition to antiserum confer extra benefit in suppressing non specific venom effects on the pituitary and/or adrenal is not known.

Our study also demonstrated the possibility that anterior pituitary and/or adrenal failure with cortisol insufficiency could occur in RV bite victims and thus provides some information concerning the need for corticosteroids in the treatment of RV envenoming with shock.

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