

Endocrine dysfunctions may be sequelae of snake bite



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ABSTRACT

Background: At present snakebite has become a serious health problem in India. The actual incidence of mortality and morbidity related to the snakebite are not reported properly. Further, the most neglected part is the long term endocrine dysfunctions in survivors of snake bite.

Aims and Objectives: To evaluate serum fT₄, TSH, cortisol, prolactin, and testosterone levels in snake bite survivors after 3 and 6 months of snakebite. **Materials and Methods:** Forty-five survivors of russels viper bite patients were selected for the study according to inclusion and exclusion criteria. Admitted patients were treated accordingly and discharged in stable condition. The hormonal status were analysed and they have been followed up after 3 and 6 months. **Results:** Significant decrease in serum cortisol and prolactin were observed in survivors of russels viper bite patients particularly in them whose mean serum creatinine was more than 1.2 mg/dl and systolic blood pressure was < 110 mm of Hg and diastolic Blood pressure was < 70 mm of Hg. **Conclusion:** Measurement of long term hormonal status like serum cortisol and prolactin can be beneficial in survivors of hematotoxic snake bite patients.

Key words: Snake bite; Survivors; Endocrine dysfunctions; Serum creatinine; Blood pressure

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INTRODUCTION

Snakebites are well known serious public health problem in the tropical countries¹ and considered as occupational hazards among the agricultural workers.² Recent studies documented that in India, the death due to snakebite accounts about 50000 annually.³ An accurate measure of this global burden of snakebite remains elusive.^{4,5}

Many developing countries consider the snakebite as a neglected tropical disease.^{6,7} The incidence as well as mortality and morbidity associated with venomous snakes are only reflected by some sporadic reports. The neglected part also remains on survivors on envenomation.⁶ Related studies have documented the development of Sheehans like syndrome associated with chronic hypopituitarism following Russel viper envenomation.^{8,9} Bites by Russels viper can

cause, neurotoxicity, vasculotoxicity and myotoxicity.¹⁰ Toxicity due to viper bite causes the bleeding from mucocutaneous sites, hemolysis, acute kidney injury and shock.¹¹ Some studies evidenced that mortality increased by 1.3 to 2.2 fold in patients suffering from hypopituitarism, when compared with age and sex matched cohorts.¹² Snakebite is an uncommon cause of hypopituitarism stated by them.¹³ Chatterjee et al., observed hypopituitarism among the snakebite patients.¹⁴ Involvement of multiple endocrine glands can occur during acute stage or after several months of snake bite.¹⁵ Acute adrenal insufficiency was also observed by some authors after snakebite.¹⁶

By the review of above literatures, and limited studies observed at our region, we arranged the present study, to observe the prevalence of endocrine dysfunctions among survivors of Russels viper bite.

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MATERIALS AND METHODS

The current hospital based, cross sectional and observational study was conducted in the Department of Medicine and Department of Biochemistry of Calcutta National Medical College, Kolkata.

Selection of study group- The study group includes 45 survivors of hematoxic snake bite (age group between 14-60 years) patients admitted in Medicine ward matched with inclusion and exclusion criteria. Seven patients have not survived till the study period and eight patients did not attend the follow up programme. Admitted patients were managed in ward and discharged in hemodynamically stable condition. Further they have been followed up in Medicine Outpatient Department.

Informed consents were taken from patients and study was approved from Institutional Ethics Committee (IEC), according to the protocol of Helsinki declaration 1975, modified on 1983.

Investigation and management protocol followed- A clinical history taking and a complete physical examination were done in each case.

Inclusion criteria were all patients admitted with vasculotoxic snake bite within 72 hours.

The **exclusion criteria** included, Acute hypopituitarism developed after snakebite, patients with known endocrine disorder, known liver or kidney diseases, extremely poor general condition.

General examinations: All the participants were conscious, oriented. Pulse, respiration, temperature, blood pressure, pallor, and oedema were noted in them. Following investigations were performed at admission for all patients.

Blood- Whole blood clotting time (WBCT), haemoglobin, (S) creatinine, total and differential leucocyte count, platelet count, RBC count, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, and international normalised ratio (INR), kidney and liver function tests and (S) sodium and potassium.

Urine microscopy, urine albumin.

The radiological investigations included X-ray chest, ultrasonography of the abdomen.

Patients were treated conservatively. 10 vials of Antivenom Serum (AVS) given initially and clinical

assessment done periodically. After 6 hours WBCT measured again and 20 vials of AVS was administered accordingly. Hemodialysis was done for selected patients whose creatinine levels were higher, hypervolemia and hyperkalaemia. Inotropic support was given to patients who developed shock like features. After the recovery, patients were discharged with hemodynamically stable condition and further asked to follow up in OPD and were assessed clinically.

Dialysis: Six (20%) patients required hemodialysis as part of treatment while 24 (80%) didn't. The following investigations were done at 3 and 6 months follow up to find out any endocrinological abnormalities:

(S) fT₄, TSH, Cortisol, Prolactin, and Testosterone.

Measurements of Biochemical parameters: (S)fT₄ was measured by competitive enzyme immunoassay (Tosoh India),¹⁷ (S) TSH was measured by solid phase enzyme linked immunosorbent assay (Accu DiagTM TSH, USA).¹⁸ (S) cortisol was analysed by competitive enzyme immunoassay (Monobind Inc, USA).¹⁹ (S) prolactin was estimated by solid phase enzyme linked immunosorbent assay (AccuDiagTM-Prolactin).²⁰ Furthermore (S) testosterone was measured by competitive enzyme immunoassay (Calbiotech, India).²¹

Patients were divided into subgroups according to age, sex, haemoglobin, creatinine, systolic and diastolic blood pressure, WBCT, dialysis and AVS treatment for comparison and followed up for 3 and 6 months for study.

Data collection and processing for statistical analysis: Statistical analysis was aimed

- To assess the significance of difference between the mean values of serum cortisol, prolactin and testosterone between 3 and 6 months follow up in complete study population.
- To find out the same significance among viper bite patients with serum creatinine >1.2 mg/dl on admission and with systolic blood pressure <110 and/or diastolic blood pressure <70 mm of Hg on admission.
- Data was collected after estimation of biochemical parameters and processed for calculation of mean and standard deviations as well as for rest of the statistical analysis.
- Outcome measures are tabulated as results.

Statistical methods: Continuous variables were expressed as mean (Std deviation) and the differences were accomplished by comparison via unpaired t test or one-way ANOVA as

appropriate. A significant difference was considered as $p < 0.05$. Data was analysed using SPSS 20 software.

RESULTS

Table 1 has shown the demographic profile and biochemical parameters of snake bite patients included in the present study. The following features were observed on admission.

Thirty snake bite patients were included in the present study. Among them 11 patients had haemoglobin level < 10 gm/dl and 19 patients had > 10 gm/dl (S) creatinine was < 1.2 mg/dl only in 5 patients whereas the same was > 1.2 mg/dl in 25 patients. Systolic blood pressure was < 110 mm of Hg in 12 patients whereas the same was more than 110 mm of Hg in 18 patients. 16 patients were having diastolic blood pressure < 70 mm of Hg whereas 14 patients had > 70 mm of Hg. Platelet count was < 1 lakh/cmm in 13 patients whereas the same was more than 1 lakh in 17 patients. 6 patients were undergone hemodialysis. All patients required antivenom on admission (Table 1).

Table 1: Showing demographic profile and biochemical parameters of Russel viper bite patients

Parameters	Description
Age	Between 14-60 years. 12(40%) are < 30 yrs, 18(60%) patients > 30 yrs.
Gender	18 males and 12 females have completed the study.
Hemoglobin on admission	11(36.7%) have haemoglobin < 10 gm/dl on admission. 19 (63.3%) have > 10 gm/dl.
Serum Creatinine on admission	5(16.7%) patients have < 1.2 mg/dl on admission when 25 (83.3%) have > 1.2 mg/dl
Systolic blood pressure on admission	12 patients (40%) with < 110 mm of Hg, 18 patients (60%) with > 110 mm/Hg
Diastolic blood pressure on admission	16(53.3%) having < 70 mm of Hg. 14 patients (46.7%) having > 70 mm of Hg.
Whole blood clotting time on admission	16(53.3%) were detected to have < 20 secs and 14(46.7%) with > 20 secs
Dialysis	6 (20%) patients required hemodialysis as part of treatment while 24(80%) didn't required
Antivenom on admission	10(33.3%) required 10 vials, 6 (20%) needed 20 vials, 5 (16.6%) patients got 30 vials and 4(13.3%) received 40 vials
Platelet count	13 patients having < 100000 /cmm, 17 patients having > 100000 /cmm
(S) Sodium	All patients having > 140 meq/L
(S) Potassium	All patients having > 4 meq/L
(S) Fasting plasma glucose	All patients having > 75 mg/dl

The present study (Table 2) has clearly shown the significant decrease of serum cortisol ($p = 0.0014$) and prolactin ($p = 0.0001$) levels between 3 and 6 months follow up in whole cohort whereas serum testosterone didn't show any significance ($p = 0.34$). The same trend was found among cohorts (Table 3) with (S) Creatinine > 1.2 mg/dl (For serum cortisol $p = 0.0241$, serum prolactin $p = 0.0065$ serum testosterone $p = 0.46$, and cohorts (Table 4) with systolic blood pressure < 110 , and/or diastolic blood pressure < 70 mm of Hg (For serum cortisol p value was 0.0367, serum prolactin p value was 0.0187, serum testosterone $p = 0.71$).

DISCUSSION

Multiple endocrine gland dysfunctions, namely adrenal insufficiencies and hypopituitarism are commonly encountered events in practice. The incidents and causative factors are variable from region to region.¹⁴ Among the different causes, post snake bite endocrine gland insufficiencies are of significant entities in tropical countries like India.¹⁵ The present study shows significant decrease of (S) cortisol and prolactin levels between 3 to 6 months follow up in whole study population. Vasculotoxicity after viper bite occurs due to activation of coagulation enzymes by viper venom, abnormal platelet activity and direct endothelial damage. These factors may result in microthrombi formation and shock which ultimately results in pituitary insufficiencies and adrenal failure.^{16,22} Amalnath D et al.,¹⁶ found panhypopituitarism associated with adrenal insufficiencies in snake bite patients with vasculotoxic complications. The various pathways proposed for pituitary damage following vasculotoxic snakebite include pituitary vessels thrombosis, most probably a part of disseminated intravascular coagulation (DIC), spasm and thrombosis of pituitary vessels leading to ischemic pituitary infarction. Decreased platelet function and secondary fibrinolysis resulting pituitary haemorrhage.¹⁰ Proby et al.,²³ observed the haemorrhagic necrosis of anterior pituitary after viper bite. Furthermore, some studies^{8,24} evidenced adrenal haemorrhage in addition to pituitary haemorrhage following russel viper bite.

Present study showed significant fall of (S) prolactin and cortisol in 3 to 6 months follow up patients with (S) creatinine more than 1.2 mg/dl and SBP < 110 mm of Hg and/or DBP < 70 mm of Hg at admission.

Some authors suggested about presence of microthrombi and histological evidences indicating acute tubular necrosis in kidney in addition to haemorrhagic necrosis of anterior pituitary gland in patients with

Table 2: Hormonal profile at 3 and 6 month follow up in whole cohort

Biochemical parameters	After 3 months (Mean ± SD)	After 6 months (Mean ± SD)	95%CI	Significance
(S) Cortisol (µg/dl)	9.22±2.03	7.67±1.50	0.62-2.47	p=0.0014*
(S) Prolactin (ng/ml)	10.54±2.64	7.07±1.84	2.29-4.64	p=0.0001*
(S) Testosterone(ng/ml)	7.15±1.92	6.70±1.72	-0.49-1.39	p=0.34

*indicates significant

Table 3: Hormonal profile at 3 and 6 month follow up with Serum Creatinine>1.2 mg/dl on admission

Biochemical parameters	After 3 months (Mean ± SD)	After 6 months (Mean ± SD)	95%CI	Significance
(S) Cortisol (µg/dl)	8.64±2.78	7.01±2.67	0.22-3.03	P=0.0241*
(S) Prolactin (ng/ml)	10.82±3.03	8.67±2.87	0.62-3.67	P=0.0065*
(S) Testosterone (ng/ml)	7.01±2.77	6.53±2.4	-0.85-1.83	P=0.46

*Indicates significant

Table 4: Hormonal profile at 3 and 6 month follow up with Systolic blood pressure <110 and/or diastolic blood pressure <70 mm of Hg on admission

Biochemical parameters	After 3 months (Mean ± SD)	After 6 months (Mean ± SD)	95%CI	Significance
(S) Cortisol (µg/dl)	12.21±3.97	10.26±3.03	0.12-3.77	p=0.0367*
(S) Prolactin (ng/ml)	13.42±3.23	11.46±3.04	0.3390-3.5810	p=0.0187*
(S) Testosterone (ng/ml)	5.32±1.87	5.50±1.97	-1.1727-0.8127	p=0.71

*Indicates significant

russels viper bite.^{8,23,24} Few authors documented the deposition of microthrombi in microvasculature was due to activation of procoagulant enzymes contained in viper venom.¹⁰ Increased serum creatinine, indicator of renal disturbances might be a direct consequences of DIC leading to prerenal failure.¹⁰ Study conducted elsewhere¹⁶ stated the pituitary insufficiency results from microthrombi formation and shock with hypotension. Russels viper venom causes activation of Factor V with fibrinolysis leading to DIC, resulting haemorrhage, hypovolemia and deposition of thrombin in microvasculature as well as glomerular capillaries and microangiopathic haemolytic anaemia and subsequent acute kidney injury (AKI). A direct cytotoxic action of snake venom may also develop AKI.²⁵

Hypotension after snakebite is attributable to various venom activities including increased capillary permeability that causes extravasation of plasma and toxins acting on cardiac muscle, vascular smooth muscle and other tissues.

Several mechanisms cause shock following envenomation, these include fright, abnormal capillary permeability (Capillary leak syndrome) with relative intravascular hypovolemia, venom induced activation of kininogens, ACE inhibitors and bradykinin potentiating peptides, direct myocardial suppression, massive bleeding and thromboembolism as well as anti snake venom induced anaphylactic reactions.²⁶

The present study observed cortisol deficiency at 6 months follow up in patients with hypotension at admission. Glucocorticoid deficiency leads to hypotension by decreasing vascular responsiveness as the steroids having permissive action on catecholamines and Angiotensin II, decreased rennin generation and increased prostacyclin production.

Pituitary necrosis due to Russel viper envenomation may be a two stage process, in the first stage pituitary stimulation and enlargement occurs due to direct effects of venom, capillary leak syndrome and hypotension. In the second stage, major bleeding may cause relative ischemia to the swollen pituitary stalk causing pituitary necrosis. This is likely to be aggravated by microvascular thrombosis due to DIC.²⁷

The present study shows the fall of (S) cortisol and prolactin levels between 3 to 6 months follow up but (S) testosterone level didn't follow the same trend. This reflects partial hypopituitarism following snakebite.²⁸

Furthermore, manifestations of hypopituitarism may become obvious after a long period of months or years after the snakebite event, rather called chronic hypopituitarism.²⁹ A study conducted in Burma shows a gap of six months to twenty years between the snake bite event and onset of hypopituitarism.^{29,30}

Hypopituitarism after snakebite is rare and often insidious in onset. Diagnosis is delayed since often patients present with non-specific symptoms like nausea, vomiting, lethargy and weight loss due to cortisol deficiency.²⁸

CONCLUSION

Hypopituitarism followed by snakebite is often a missed clinical entity and compromise the life of survivors of Russel viper's envenomation. A high degree of clinical suspicion is required to diagnose the condition. Hormonal evaluation should be undertaken if clinically appropriate.

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Authors contribution:

KK-Concept and design of the study, prepared full draft of manuscript, statistically interpreted and analysed; **SM**- Reviewed the literature and prepared the manuscript.

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