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Original Research Article

Endocrine Dysfunctions in Survivers of Russell's Vipers Envenomation: A Six Months Follow up Study

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Abstract

Background: Presently snakebite has become a serious health problem in India.The actual incidence of mortality and morbidity related to the snakebite are not reported properly. Furthermore, the most neglected part is the long term endocrine dysfunction in survivors of russel viper envenomation. ***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 those patients whose mean serum creatinine was more than 1.2 mg/dl and systolic blood pressure is more than 110 mm of Hg and diastolic Blood pressure is more than 70 mm of Hg. ***Conclusion:*** Measurement of long term hormonal status like serum cortisol and prolactin can be beneficial in survivors of russel viper bite patients.

Keywords: Russel viper bite, survivors, endocrine dysfunction, serum creatinine, blood pressure.

INTRODUCTION

Snakebites are considered as a serious public health problem in the tropics [1] as well as occupational hazards among the agricultural workers [2]. Recent studies indicated that the death due to snakebite accounts about 50000 annually in India [3]. An accurate measure of the global burden of snakebite envenoming remains elusive [4, 5].

WHO considers the snakebite as a neglected tropical disease [6, 7].

The incidence, mortality and morbidity associated with venomanous snakes are only reflected by some sporadic/isolated reports. Particularly the neglected part remains on survivors on envenomation [6]. Accumulated studies have evidenced the development of Sheehans like syndrome associated with chronic hypopituitarism following Russel viper envenomation [8, 9]. Bites by Russels viper can cause vasculotoxicity, neurotoxicity and myotoxicity. Hypopituitarism is a rare sequelae of vascular snake bite [10].

Envenomation due to viper bite cause the bleeding from mucocutaneous sites, hemolysis, acute kidney injury and shock [11].

Some studies documented that mortality increased by 1.3 to 2.2 fold in hypopituitarism patients, compared with age and sex matched cohorts [12]. Snakebite is an uncommon cause of hypopituitarism stated by them [13]. Chatterjee et al found 86 hypopituitarism patients that snake bite is an important aetiological factor [14]. During acute stage or after several months of snake bite, involvement of multiple endocrine glands can occur [15]. Acute adrenal insufficiency was also observed by some authors [16].

By the review of above literatures, and limited data obtained at our region, we arranged the present study, to observe the prevalence of endocrine dysfunction among survivors of Russell's viper bite.

Aims of the Study

Following investigations were done at 3 and 6 months follow up in survivers of russell's viper envenomation to find out any endocrinological abnormalities.

- Serum fT4

- Serum TSH
- Serum Cortisol
- Serum Prolactin
- Serum Testosterone.

MATERIALS AND METHODS

Study Design

This hospital based, cross sectional, non interventional study was conducted in the Department of Medicine and Department of Biochemistry of Calcutta National Medical College, Kolkata from December 2016 to November 2017.

Selection of Case Group

The study group includes 45 survivors of hematotoxic snake bite (age group between 14 – 60 years) patients admitted in Medicine ward matched with inclusion and exclusion criteria. The following age group were selected as the biochemical parameters may alter with increasing and decreasing age.

Seven patients have not survived the study period and eight patients did not attend the follow up programme. Admitted patients were managed in word and discharged in hemodynamically stable condition. Further they have been followed up in Medicine Outpatient Department after 3 and 6 months of discharge.

Informed consents were taken and study was approved from Institutional Ethics Commiitee (IEC). Investigation and management protocol followed- A clinical history taking and a complete physical examination were done in each case.

Inclusion Criteria

- Patients admitted with vasculotoxic snake bite within 72 hours.

Exclusion Criteria

- Acute hypopituitarism develops after snakebite.
- Patients with known endocrine disorder.
- Known liver or kidney diseases.
- Extremely poor general condition.

General examinations: All the patients were conscious, oriented. pulse , respiration, temperature, blood pressure, pallor, and oedema were noted.

Following investigations were performed at admission for all patients.

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), urine microscopy, urine albumin, kidney and liver function tests and (S) sodium and potassium.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 given accordingly.

Hemodialysis given to selected patients with increasing creatinine levels, volume overload, hyperkalemia. Inotropic support given to patients who developed shock like features.

After the recovery patients were discharged with hemodyamically stable condition and further asked to follow up in OPD and assessed clinically.

Dialysis: 6 (20%) patients required hemodialysis as part of treatment while 24(80%) didn't.

Antivenom on admission: 10 patients (15%) required 10 vials, 6 (20%) needed 20 vials, 5 patients (16.7%) received 30 vials and 4(13.3%) received 40 vials.

Following investigations were done at 3 and 6 months follow up to find out any endocrinological abnormalities:

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

Methods of 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 (AccuDiag^{TM} 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(AccuDiag^{TM}-Prolactin) [20].

Furthermore (S) testosterone was measured by competitive enzyme immunoassay (Calbiotech, India) [21].

All hormonal immunoassays were measured by ELISA Reader (Tecan ELISA microplate reader)

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

Data Collection and Processing For Statistical Analysis:

Statistical analysis was aimed

- To asses the significance of difference between the mean values of serum cortisol, prolactin and testosterone between 3 and 6 months follow up in complete cohort.
- 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.

Statistics

- Statistical universe- Survivers of russell's viper bite envenomation.
- Method of selecting the subjects- According to inclusion and exclusion criteria.
- Method of allocating the subjects in different groups- Same subjects were evaluated at 3 and 6 months follow up.

Statistical Methods

Continuous variables were expressed as mean± Std deviation and the differences were accomplished by comparision via unpaired t test or one way ANOVA as appropriate. A significant difference were considered as $p<0.05$. Exact p values were depicted. Data was analysed using SPSS 20 software.

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 >10gm/dl.
Serum Creatinine on admission	5(16.7%) patients have <1.5 mg/dl on admission when 25 (83.3%) have >1.5mg/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

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

*indicate 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

*indicate 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

*indicate significant

RESULTS

Results of the present study have clearly shown the significant decrease of serum cortisol and prolactin levels between 3 and 6 months follow up in whole cohort whereas serum testosterone didn't show any significance (Table-2). The same trend were found among cohorts with (S) Creatinine >1.2 mg/dl and cohorts with systolic blood pressure <110, and/or diastolic blood pressure<70 mm of Hg.

Primary outcome: Fall of (S) cortisol and prolactin levels between 3 to 6 months follow up of survivers of russell's viper bite envenomation but (S) testosterone level did'nt follow the same trend.

Secondary outcome: Particularly the same trend was obvious when serum creatinine level was >1.2 mg/dl and systolic blood pressure < 110 mm of Hg and/or diastolic blood pressure is < 70 mm of Hg.

DISCUSSION

Multiple endocrine gland dysfunction, namely hypopituitarism and adrenal insufficiencies are commonly encountered events in practice. The incidents and causative factors are variable in different regions [14]. Among the causes, post snake bite endocrine gland insufficiencies are of significant entities in tropical countries like India [15]. Present study shows significant decrease of (S) cortisol and prolactin between 3 to 6 months follow up in whole cohort. Vasculotoxicity follows viper bite occurs due to activation of coagulation enzymes by viper venom, abnormal platelet function 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 deficiencies in snake bite patients with vasculotoxic complications. The various pathology proposed for pituitary damage follows 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. Impaired platet function and secondary fibrinolysis result pituitary haemorrhage [10].

Proby *et al.*, [23] observed the haemorrhagic necrosis of anterior pituitary following viper bite. Furthermore some studies [8, 24] documented adrenal haemorrhage in addition to pituitary haemorrhage following Russel viper bite.

Present study shows significant fall of (S) prolactin and cortisol in 3 to 6 months follow up patients with (S) creatinine more than 1.5 mg/dl and SBP < 110 mm of Hg and/or DBP < 70 mm of Hg at admission.

Some reports obtained 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 russels viper bite [8, 23, 24]. Few authors explained 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]. Since one previous stud [16] already stated the pituitary insufficiency resulting from microthrombi formation and shock with hypotension. Russels viper vonom produces activation of Factor V with fibrinolysis leading to DIC, resulting haemorrhage, hypovolumia and deposition of thrombin in microvasculature and glomerular capillaries and microangiopathic haemolytic anaemia and subsequent acute kidney injury (AKI).

A direct cytotoxic action of snake venom may also act on kidney to develop AKI [25] Hypotension after snakebite is attributable to various venom activities including permeability that causes extravasation of plasma and toxins acting on cardiac muscle, vascular smooth muscle and other tissues. Several mechanisms causes shock following envenomation, these include fright, abnormal capillary permeability (Capillery leak syndrome) with relative intravascular hypovolumia, venom induced activation of kininogens, ACE inhibitors and bradikinin potentiating peptides, direct myocardial suppression, massive bleeding thromboembolism and anti snake venom induced anaphylactic reactions [26].

Present study shows 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 catecholemines and Angiotensin II, decreased rennin generation and increased prostacyclin production.

Pituitary necrosis due to russels 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 did'nt 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 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 vipers 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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