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Original Research Article

Evaluation of myotoxicity and neuropathy in hemotoxic snake bite envenomation in a tertiary care center

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ABSTRACT

Background: Snakebite is a significant health problem in India, particularly in rural areas. Hemotoxic snakebites can cause myotoxicity, leading to acute kidney injury and other complications due to extensive muscle injury. This study aimed to investigate the clinical severity of myotoxicity in hemotoxic snakebite patients and its effect on AKI.
Methods: A prospective observational study was conducted among 50 patients with hemotoxic snakebite admitted to a tertiary care center in Odisha. Clinical manifestations, serum creatine phosphokinase levels and nerve conduction studies were evaluated.
Results: The majority of patients were males (74%) in the 30-39 age group. Russell's viper was the most common species responsible for envenoming (60%). Elevated serum CPK levels were found in 80% of patients, indicating muscle damage. Local necrosis was associated with significantly higher mean CPK levels (555.78±353.51 U/l). AKI was observed in 46% of patients, with serum creatinine levels correlating with AKI severity. Nerve conduction studies revealed abnormalities in two-thirds of cases, including axonal neuropathy and motor-sensory deficits.
Conclusions: Myotoxicity is a significant complication of hemotoxic snakebite, contributing to AKI and other systemic manifestations. Serum CPK levels may serve as a useful biomarker for predicting tissue damage severity. Early identification, continuous monitoring and supportive care are crucial in managing snakebite victims. Further research is needed to validate these findings and refine the use of serum CPK in clinical decision-making.

Keywords: AKI, CPK, Myotoxicity, Necrosis, Snakebite

INTRODUCTION

Snake bite mortality is very high in India (40,900 to 50,900 annually). Besides Andhra Pradesh and Madhya Pradesh, Odisha is the 3rd highest mortality rate. Annual snake bite deaths were 2200 in Odisha in 2005.[1] Coagulopathy, neuromuscular paralysis, acute kidney injury and local effects are the most important clinical syndromes of snake envenoming.[2] *Daboia russelii* and *Echis carinatus* are the most commonly found in India. From these two species *Daboia russelii* is the most commonly found in Odisha.

Myotoxicity is an important effect of snake envenoming and can manifest locally or systemically. Local muscle necrosis is a component of the local necrotic effects. Systemic myotoxicity ranges in severity. Clinical evidence of myotoxicity, including local and generalized myalgia, muscle tenderness and dark red or black coloured urine suggestive of myoglobinuria had been reported in cases of Russell's viper envenoming in Sri Lanka.[3,4] Elevation of plasma and urinary myoglobin concentrations were reported in 19 Russell's viper bite patients from Sri Lanka further suggesting the existence of myotoxicity in Sri Lankan Russell's viper patients.

Loss of functioning of muscles cells due to myotoxicity can aggravate co-existing weakness due to neuromuscular block caused by neurotoxins as seen in haemotoxic snakebite. Especially rhabdomyolysis can cause secondary acute kidney injury and itself can result in life threatening hyperkalemia due to extensive muscle cell damage.[5] Myotoxins are related to neurotoxins (phospholipase A2) and they bind to the muscle fibres, causing progressive destruction of muscle cells with release of breakdown products. This process takes hours to become evident by the time already irreversible damage has been done.

Myotoxins are particularly abundant in snake venom and can promote myoglobinuria as well as acute renal failure. They are classified into 3 groups small myotoxins, cardiotoxins and phospholipase A2 (PLA2) myotoxins. PLA2 are the most important among them. Three types of PLA2 myotoxins, commonly referred as Asp49, Ser49 and Lys49 PLA2 have been characterised in viperid venoms. Despite structural similarity, the latter two lacks catalytic activity and are referred as 'PLA2 Like' peptides. It is important to note that the enzymatic activity and the myotoxic activity of PLA2 myotoxins are independent of each other.

Myotoxic PLA2s cause muscle damage primarily by destruction of sarcolemma.[5] In a previous study in 2016 says Sri Lankan Russell's viper (*Daboia russelii*) envenoming had been reported to cause mild and non-life-threatening myotoxicity in humans, which was not reported for other Russell's vipers.[5] There are several gaps in our understanding of the myotoxicity associated with Indian viper envenoming. It is unclear whether viper bites cause severe myotoxicity and whether any resultant myotoxicity can be treated with Indian Polyvalent antivenom. The present study aims to investigate the clinical severity of myotoxicity in haemotoxic envenomation and effect of ASV over myotoxicity.

Objectives

Evaluation of myotoxicity in haemotoxic snake bite patients. To evaluate the effect of myotoxicity over acute renal failure. To evaluate neuropathy in hemotoxic snake bite.

METHODS

Study type

This study was a prospective observational study.

Study place

SCB Medical College and Hospital, Cuttack, Odisha

Study duration

The study period was from January 2017 to January 2018.

Inclusion criteria

Patients with history of snake bite with signs and symptoms compatible with envenomation like local swelling, Bleeding manifestations, 20 min whole blood clotting test abnormal and age >15 years were taken.

Exclusion criteria

Patients with pre-exiting coagulopathy, on anti-coagulants and anti-platelet drugs, with pre renal disease and chronic liver disease. Patients with risk factors like diabetes, Hypertension, connective tissue diseases, chronic infection, malignancy and patients who doesn't give consent for participation.

All the issues including ethical issues pertaining to the study was evaluated by the Institutional Review Board and clearance for the same was obtained for the study.

Informed consent was taken in all cases. All the clinical features were recorded. All hemotoxic snake bite cases with features of envenomation were treated as per WHO guidelines.[6]

Clinical data collection and blood collection

Clinical examination of all patients was undertaken on admission to hospital, at 12 hours and 24 hours post-bite and then every 24 hours until discharge.

In particular, muscle pain and tenderness, in the bitten limb (local myotoxicity) and the other limbs (generalized myotoxicity), dark coloured urine, CNS evaluation were assessed as part of the clinical examinations. Blood samples were collected from patients on admission at 24 hours post-bite and daily thereafter.

Investigations include 20 min Whole blood clotting time, CBC, peripheral smear, liver function tests, urea, creatinine, urine microscopy, Sr. CPK, electromyography test, nerve conduction test. In the present cohort, the majority of patients received antivenom and a small proportion of these received their first dose of antivenom at a primary care hospital, before being transferred to the study hospital.

The decision to administer antivenom was made solely by the treating physician, based on clinical and laboratory evidence of systemic envenoming.[12] Patients were administered between 10 to 20 vials of antivenom, which is the standard dose.

Antivenom was administered in normal saline and infused over 1h. If an acute adverse reaction to antivenom occurred, the infusion was stopped for 5 to 10 min and the patient treated with adrenaline, antihistamines and corticosteroids, as per the treating clinicians.

Statistical analysis

The study used various statistical analyses to evaluate the clinical severity of myotoxicity in hemotoxic snakebite patients and its effect on acute kidney injury. Descriptive statistics were used to describe categorical variables, such as demographic characteristics and clinical manifestations. The Mann-Whitney U test, a non-parametric test, was used to compare two independent groups, evaluating relationships between serum CPK levels and local necrosis, as well as local muscle tenderness. The Kruskal-Wallis test, another non-parametric test, assessed the relationship between serum creatinine levels and AKI severity, as well as serum CPK levels and AKI stages.

RESULTS

The majority of victims are males predominantly within 30-39 years of age group. Russell's viper bite is the most common. Most common clinical manifestations were fang marks (100%), local swelling (100%), local myalgia (96%), generalized myalgia (80%), local muscle tenderness (90%), generalized muscle tenderness (80%), neurological (24%), bleeding from bitten part (22%) and local necrosis (18%). Serum CPK elevation is more frequent and higher in who presents early. However, due to variability and overlap, this difference is not statistically significant. Mann–Whitney U test shows significant raised serum CPK in patients with local necrosis. Serum CPK remained high as long as local muscle tenderness was present but was insignificant as suggested by Mann–Whitney U test. Kruskal–Walli's test shows significant increase in serum creatinine with AKI severity.

But serum CPK levels do not significantly correlate with AKI severity despite a rising trend. Nerve conduction study in 12 cases shows normal in 4 patients, axonal neuropathy in 4, motor sensory axonal neuropathy in 3, carpal tunnel syndrome in 1.

66.7% of snakebite patients showed peripheral neuropathy on nerve conduction studies. Neuropathy was localized to the bitten limb, supporting a direct neurotoxic effect of the venom.

The most common type was axonal neuropathy, particularly involving common peroneal and ulnar nerves. EMG signals showed normal pattern in 12 cases (Out of 12 cases).

Table 1: Demography.

Gender	Frequency (%)		
Male	37 (74)		
Female	13 (26)		
Age (in years)	**Males**	**Females**	**Total**
15-19	1 (2)	0 (0)	1 (2)
20-29	9 (18)	6 (12)	15 (30)
30-39	12 (24)	6 (12)	18 (36)
40-49	7 (14)	1 (2)	8 (16)
50-59	5 (10)	0 (0)	5 (10)
>60	3 (6)	0 (0)	3 (6)
Total	37 (74)	13 (26)	50
Types of snakes			
Russell's viper	30 (60)		
Saw-scaled viper	14 (28)		
Unidentified snakes	6 (12)		

Table 2: Clinical manifestations.

Clinical manifestation		Frequency	%
Local myalgia		48	96
Generalised myalgia		40	80
Localised muscle tenderness		45	90
Generalised muscle tenderness		40	80
Neurological		12	24
Fang marks		50	100
Swelling	Confined to bitten part	40	80
	Confined to half of limb	10	20
	Confined to whole limb	0	0
	Extending beyond limb	0	0
Bleeding from bitten site		11	22
Local necrosis		9	18

Table 3: Serum CPK V/S post bite admission time in 50 patients.

	Serum CPK					
	Normal (<200 U/l)		High (>200 U/l)		Total	
Post bite admission time	Frequency (%)	CPK Mean and SD	Frequency	CPK Mean and SD	Total frequency	Total Mean and SD
0-6 hours	5 (10)	174.4±15.22	23 (46)	437.14±259.66	28 (56)	305.77±137.44
6-12 hours	2 (4)	185±7.07	7 (14)	420.29±174.74	9 (18)	302.6±90.9
12-24 hours	3 (6)	134±73.63	10 (20)	326.73±48.56	13 (26)	230.36±61.09
Total	10 (20)	404.06±48.83	40 (80)	394.72±160.98	50 (100)	279.57±96.47

One Way Annova Test, p value–0.148.

Table 4: Serum CPK V/S local necrosis.

Local necrosis	Serum CPK (U/l)
Absent (82%)	312.02±137.05
Present (18%)	555.78±353.51
Total	355.90±211.39

Mann-Whitney U test, p value=0.007.

Table 5: Serum CPK V/S local muscle tenderness in 50 patients.

Serum CPK (U/l)			
L. muscle tenderness	<12 hours	12-24 hours	>24 hours
Present	381.0±242.6	372.5±247.1	464.7±293.7
Absent	314.9±143.8	328.7±136.6	299.8±125.4
P value (Mann-Whitney U test)	0.59	0.91	0.08

Table 6: Serum CPK with AKI among post snakebite patients.

AKI stage	Frequency	Haemodialysis	Mean creatinine (mg/dl)	Mean CPK (U/l)
No AKI	27 (54%)	0	1.05±0.24	301.31±144.73
AKI Stage 1 and 2	19 (38%)	0	1.66±0.48	355.9±211.39
AKI Stage 3	4 (8%)	4 (100%)	4.0±1.97	459.9±324.22
Kruskal–Wallis test P value			0.0001	0.5391

Table 7: Nerve conduction study in 12 patients.

Nerve conduction study	Frequency	%
Normal	4	33.3
Axonal neuropathy	4	33.3
Motor sensory axonal neuropathy	3	25
Carpal tunnel syndrome	1	8.3
Total	12	100

Table 8: Nerve conduction study v/s site of bite and swelling in 12 patients.

Cases	Nerve conduction study	Site of bite	Swelling confined to bitten part	Swelling confined to ½ of limb	Swelling confined to whole limb	Swelling extending beyond limb
1	Right CPN axonal neuropathy	Rt foot	Yes	No	No	No
2	Normal	Lt foot	Yes	No	No	No
3	Left ulnar motor sensory axonal neuropathy	Lt hand	Yes	No	No	No
4	Bilateral carpal tunnel syndrome	Rt hand	No	Yes	No	No

Continued.

Cases	Nerve conduction study	Site of bite	Swelling confined to bitten part	Swelling confined to ½ of limb	Swelling confined to whole limb	Swelling extending beyond limb
5	Left ulnar motor sensory axonal neuropathy	Lt little finger	No	Yes	No	No
6	Left CPN axonal neuropathy	Lt foot	Yes	No	No	No
7	Normal	Rt foot	Yes	No	No	No
8	Left CPN axonal neuropathy	Lt foot	No	Yes	No	No
9	Normal	Rt foot	Yes	No	No	No
10	Right ulnar motor sensory axonal neuropathy	Rt little finger	No	Yes	No	No
11	Right CPN axonal neuropathy	Rt foot	No	Yes	No	No
12	Normal	Rt foot	Yes	No	No	No

Table 9: Electromyography test in 12 patients.

EMG	Normal	%	Abnormal	%
Amplitude	12	100	0	0
Duration	12	100	0	0
MUAP	12	100	0	0
Recruitment	12	100	0	0

DISCUSSION

This prospective study was conducted to evaluate the myotoxic effects in hemotoxic snake bite patients and to evaluate the effect of myotoxicity over the acute renal failure during a period from January 2017 to December 2018 in the Department of Medicine, SCB Medical College, Cuttack.

This study presents a detailed evaluation of the clinical and biochemical profiles of patients admitted with venomous snakebite, with a particular focus on the relationship between myotoxicity and neuropathy in hemotoxic snakebite. The demographic data indicate a predominance of male victims (74%), most of whom belonged to the economically active age group (20–39 years), consistent with other regional studies that associate snakebite risk with outdoor occupational activity. Russell's viper was identified as the most common species responsible for envenomation (60%), followed by the saw-scaled viper (28%) (Table 1).

The male predominance has also been reported in several other studies such as Monteiro et al where the ratio was 1.38:1 and by Kulkarni et al where the ratio was 2.17:1. Subash and Vijay et al in their study showed that 75% of patients were below 49 years of age and the mean age was 38.11 years.[7] This correlates with other studies done by Suchithra et al, Monteiro et al and Sharma et al.[8,9] These findings are congruent with the known geographic distribution and medical importance of these snakes in endemic areas. Clinically, fang marks and localized swelling were present in all patients, reaffirming their diagnostic value. Myotoxic effects were significant, as evidenced by the high frequency of local myalgia (96%), generalized myalgia (80%) and both local (90%) and generalized muscle tenderness (80%) (Table 2). Neurological symptoms were documented in 24% of patients and hematologic complications such as bleeding from the bite site occurred in 22%, indicative of the hemotoxic effects of viper envenomation. Local necrosis was noted in 18% of patients, underscoring the potential for significant tissue damage.

Serum CPK levels, a biomarker of muscle injury, were elevated (>200 U/l) in 80% of the study cohort. The highest frequency of elevated CPK was observed in patients presenting within six hours post-bite (46%), followed by those admitted at 12–24 hours (20%) and 6–12 hours (14%) (Table 3). In other study by Silva et al in 2016 there was raised CPK in 178 out of 190 cases who had been treated with ASV within 6 hours and gradually decreasing.[2] Despite this trend, the difference did not reach statistical significance (p=0.148), suggesting that while early rises in CPK are common, admission timing alone does not reliably predict CPK elevation. Importantly, a significant correlation was observed between elevated CPK levels and the presence of local necrosis (p=0.007), with a notably higher mean CPK in patients exhibiting necrosis (555.78±353.51 U/l) compared to those without (312.02±137.05 U/l) (Table 4).

This suggests that CPK could serve as a useful adjunctive marker for predicting tissue damage severity in snakebite victims. Analysis of CPK levels in relation to local muscle tenderness revealed a trend toward higher values in patients with ongoing tenderness; however, these findings were not statistically significant (p>0.05 across all intervals) (Table 5). This implies that although CPK may reflect myotoxicity, it may not directly correlate with the

persistence of clinical muscle symptoms. Renal impairment was observed in 46% of patients, with 8% progressing to stage 3 acute kidney injury (AKI) requiring haemodialysis. A statistically significant association was noted between serum creatinine levels and AKI severity (p=0.0001), but no significant correlation was found between serum CPK and AKI stages (p=0.5391) (Table 6). These results suggest that while rhabdomyolysis may contribute to renal stress, CPK levels alone are insufficient as a predictor of renal failure in this context. Snake bite is the 2nd most cause of acute cortical necrosis.[10] Neurological assessment via nerve conduction studies in 12 patients revealed abnormalities in two-thirds of cases, including axonal neuropathy and motor-sensory deficits, all localized to the bitten limb (Table 7 and 8). Interestingly, electromyography (EMG) studies were normal in all cases, indicating that muscle fibre integrity remained intact despite peripheral nerve involvement. These findings point to a selective neurotoxic effect of envenomation, sparing direct myocyte damage detectable by EMG (Table 9).

In summary, the study highlights the multi-systemic impact of viper envenomation, the utility of CPK as a marker for local tissue damage particularly necrosis and the complexity of correlating biochemical markers with clinical outcomes. These findings underscore the importance of early identification, continuous monitoring and supportive care in managing snakebite victims. The study's limitations include a small sample size of 50 patients, which may not be representative of the larger population and a single-center design, which may not reflect experiences of other centers or regions. The study's findings may not be generalizable to other populations with different demographics or snake species. The study also relied on clinical diagnosis and laboratory tests, which may not always accurately reflect the severity of envenoming or myotoxicity. These limitations highlight the need for further research to validate the study's findings and improve understanding of hemotoxic snakebite and myotoxicity.

CONCLUSION

This study underscores the clinical and biochemical complexities of viperid snakebite envenomation. The predominance of Russell's viper as the offending species and the high incidence of local and systemic manifestations highlight the urgent need for timely intervention. Serum CPK levels were significantly associated with local necrosis, suggesting their potential utility as a biomarker for predicting tissue injury severity. However, CPK values did not correlate significantly with the time since bite, persistence of muscle tenderness or progression to acute kidney injury. Neurological assessments revealed localized nerve conduction abnormalities without evidence of muscle fibre degeneration on electromyography, indicating a selective peripheral neurotoxic effect. Despite the limitations of CPK as a standalone prognostic tool, its role in identifying patients at risk for local tissue complications warrants further investigation.

Overall, this study emphasizes the need for comprehensive clinical evaluation, targeted biochemical monitoring and early supportive management to mitigate morbidity associated with snake envenomation. Further large-scale, multicentric studies are recommended to validate these findings and refine the use of serum CPK in clinical decision-making.

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