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A Study of Acute Inflammatory Markers and Serum Lactate Dehydrogenase among Snake Bite Patient in a Tertiary Care Hospital

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Abstract: ***Background and Objectives: Most of the snake bites occur in developing countries with temperate and tropical climates in which populations subsist on agriculture and fishing. Snake bite, either hemotoxic, neurotoxic, cytotoxic or a combination of these are considered as a grave medical emergency[1]. Snake venom is believed to act as an acute phase reactants &releasing inflammatory mediators such as IL-6 and 8. IL-6 is believed to act on the liver increasing the production of acute phase reactants[2]. The phospholipase an important component of snake venom is thought to produce haemolysis. Serum LDH levels have been found to correlate well with the severity of envenomation. To study the role and analyse the relationship between acute inflammatory markers and serum LDH in cases of snake bite envenomation and helpful in predicting the early prognosis in snake bite patient. Methods: 50 patients with history of snake bite who were admitted in SSIMS&RC Devanagere, during the period September-2015 to September-2017, with clinical evidence of snake bite after taking into account of inclusion and exclusion criteria's. All the patients worked up for routine and specific laboratory investigations. Observation And Results: Most of our patients were presented with features suggestive of hemotoxic envenomation. Elevated acute inflammatory markers was seen in patients with severe grade of envenomation in which required more than 30 vials of ASV. A statistically significant correlation was found between acute inflammatory markers and Serum LDH (p value 0.001) with the grade of envenomation and outcome of the snake bite victims. Conclusion: Hemotoxic snake bites with features compatible with moderate envenomation were found most commonly in our study population. Acute inflammatory markers and Serum LDH levels help to differentiate between patients with severe envenomation and other grades of envenomation. The above markers also helps in predicting the early prognosis and outcome in the snake bite victims.***

Keywords: Serum CRP; Ferritin; Serum LDH; Fibrinogen, ESR

1. Introduction

Snakebite is a common medical emergency and an occupational hazard in most parts of India, with farming as a major source of employment.

Early in 2009,snake bite was finally included in the WHO's list of neglected tropical diseases confirming the experience in many parts of this region that snakebite is a common occupational hazard of farmers , plantation workers and others, resulting in thousands of deaths each year and many cases of chronic physical handicap.

Snake bite, either hemotoxic, neurotoxic, myotoxic or a combination of these are considered as a grave medical emergency which require immediate identification and treatment. The skill and expertise of clinicians in identifying snake bite, administering appropriate dose of anti-snake venom and managing complications of snake bite are important in the survival of victims. India do not have a snake bite registry, but around 81,000 snake envenomation's and 11,000 deaths from snake bites are reported annually[1]. The prohibitive cost of treatment and non-availability of adequate anti-snake venom at primary health care centers make this a major cause for mortality among underprivileged. For this reason India is known as land of exotic Snakebites.

Detecting the grade of envenomation at presentation is difficult and novel markers serve as a good guide. Snake venom is believed to act as an acute phase reactants and interact with target cells like macrophages releasing inflammatory mediators such as IL(Interleukin)-6 and 8. IL-6 is believed to act on the liver increasing the production of acute phase reactants like c-reactive protein, ESR, serum amyloid, haptoglobin, etc[2].The phospholipase an important component of snake venom is thought to produce hemolysis, a common manifestation of snake bite envenomation. Serum lactate dehydrogenase (LDH) levels have been found to correlate well with the degree of hemotoxicity of snake venom as well as severity of snake bite envenomation[3].

Most of snakebite patients in this part of the country present with hemotoxic manifestations. In a study done by Kandasamy .S[4] there was a statistically significant increase in the S. LDH values in the 30 snake bite patients at the time of admission and 24 hours later as compared to the control group of 30. In a similar study done in Maharashtra S.LDH values showed significant rise in the envenomed group as compared to the control group. Early rise in serum LDH levels within 48 hours of bite correlated with the degree of hemotoxicity of the bite. This was seen in a prospective study from Brazil that included children with moderate to severe snake bite envenomation. While a few studies have been done demonstrating the role of serum LDH as a marker of hemolysis and CRP and even ESR of acute inflammatory response, there have been no significant studies done showing a correlation between hemotoxicity and serum CRP or LDH in snakebite[5]. Hence in this study we aim to analyze the relationship between Serum CRP, LDH, and hematological profile and to ascertain their utility as marker of hemotoxicity in snakebite victims.

2. Grading of Envenomation

No Envenomation	
Local Menifestation	Mild Pain
Systemic Menifestation	None
Laboratory Findings	None
Mild Envenomation	
Local Menifestation	Swelling, eythema or echymosis confined to the site of bite
Systemic Menifestation	None
Laboratory Findings	None
Moderate Envenomation	
Local Menifestation	Progression of Swelling, eythema or echymosis beyond the site of bite
Systemic Menifestation	Non life threatening signs and symptoms. Perioral and peripheraal paresthesia, nausea, vomiting, diarrhea, ptosis, diplopia
Laboratory Findings	Mildly abnormal coagulation profile with no featuresof systemic bleeding. Mildly abnormal other laboratory tests.
Severe Envenomation	
Local Menifestation	Rapid swelling, eyrthemaechymosis involving the entire part or body
Systemic Menifestation	Hypotension, tachycardia, tachypnoea respiratory paralysis, seizures, fasciculation, altered mental status
Laboratory Findings	Systemic bleeding or markedly abnormal coagulation profile, unmeasurable INR, APTT and platelet count <20,000

Aims and Objectives

1) To study the role of acute inflammatory markers (serum CRP, fibrinogen, serum ferritin, ESR and serum albumin) and serum LDH in cases of snake bite envenomation.
2) To analyze the relationship between acute inflammatory markers, serum LDH and hematological profile in snake bite.
3) To study in predicting the early prognosis in snake bite patient with the help of above markers.

3. Materials and Methods

Source of Data

This is the cross sectional study conducted on 50 patients of SSIMS and RC for analysis the relationship between acute inflammatory markers, serum LDH and hematological profile inn patient presented themselves to emergency ward with symptoms, signs and definitive evidence of snake bite during the period September 2015 to September 2017.Patient are from the nearby rural areas area surrounding SSIMS and RC , Davangere. All patient was studied at the time of admission and during the course of hospital stay.

On patient presenting with history suggestive of snake bite, the following laboratory tests which will be included Hemoglobin, TC, DC ,ESR, platelet count, PCV, peripheral smear, urine routine and microanalysis, serum CRP ,LDH and albumin , aPTT , PT, INR . In these investigations serum LDH repeated after 24 hours thereafter.

Bleeding time, clotting time and a 20 minute whole blood clotting test will be repeated 6th hourly for first 24hrs of the hospital admission.

Dry bites will be defined as patient with a history snake bite but without symptoms or signs of local or systemic systemic envenomation or lab abnormalities even after 24hrs of .observation in the hospital.

Study design

Cross sectional study.

Sample size

A sample size of 50 was selected for the study using purposive sampling technique based on inclusion and exclusion criteria.

Inclusion Criteria

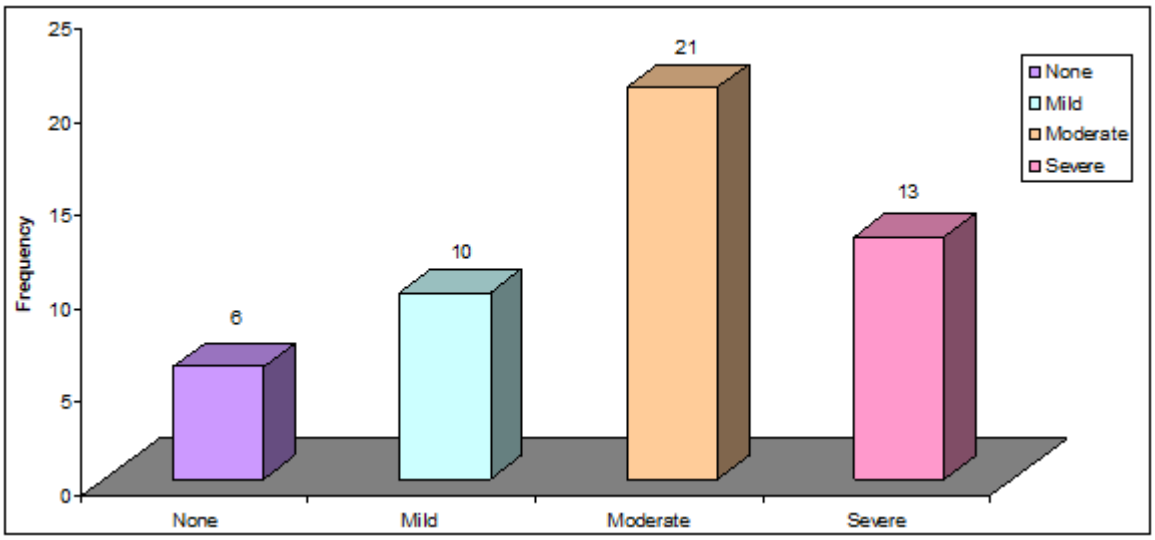
1) Patients with alleged history of snakebite in individual age more than or equal to 18yrs.
2) Patients with a history of unknown bite but with symptoms and signs compatible with snake bite envenomation.

Exclusion Criteria

1) Cases other than snake bite
2) Patients with history of bleeding disorders
3) Patients who received ASV before arriving to the hospital.
4) Patient with a history of vasculitis
5) Patient with a history of acute or chronic liver disease
6) Patient with history of malignancy
7) Patient with history of acute myocardial infarction

4. Results and Observation

This study was done in patients admitted to SSIMS and RC, Davangere. A total of 50 patients with history of snake bite or evidence of envenomation admitted to our hospital were studied and followed up for next 24 hours. The data in the form of investigations and profile of the patient is presented below.



Graph 1: Grade of envenomation

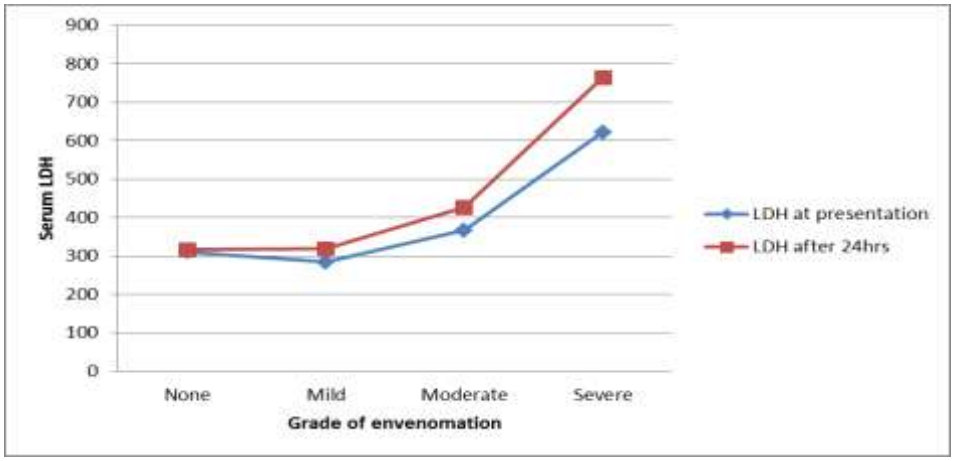
In our study about 21 patients i.e 42% presented with features compatible with moderate grade of envenomation which was the highest among 50 patients , while 13 people i.e, 26% showed severe degree of envenomation.

Distribution of cases based on grade of envenomation and its comparison with acute inflammatory markers and serum LDH

Table 1: Grade of Envenomation and its comparison with acute inflammatory markers and serum LDH:

	Grade Of Envenomation*				F	P Value
	None	Mild	Moderate	Severe		
CRP	2.08 ± 1.0	2.66 ± 1.1	4.85 ± 1.7	11.52 ± 5.6	20.818	<0.001
Fibrinogen	228 ± 71.7	257.8 ± 62.3	292.52 ± 99.9	409.3± 152.3	5.745	0.002
ESR	10.5 ± 1.7	13.7 ± 3.5	21.73 ± 6.2	28.07 ± 8.5	15.626	<0.001
Ferritin	126 ± 90.8	156.8 ± 76.3	221 ± 88.1	296.1± 100.3	6.954	0.001
LDH at presentation	310.3± 68.9	283.8±55.4	365.8± 101.4	621.2±248.7	12.882	<0.001
LDH after 24hrs	316±68.7	317.5± 63	426.09±128	763.9±314.6	14.925	<0.001
Sr Albumin	4.46± 0.3	4.3 ±0.4	3.88± 0.49	3.34 ±0.44	12.523	<0.001

- (*ANOVA Test)**:** Out of 13 cases with increased CRP, 11cases (84.6%) had severe grade of envenomation and 2 cases (15.4%) had moderate grade of envenomation.
- Out of 8 cases with increased fibrinogen level, 6 cases (75%) had severe grade of envenomation and 2 cases (25%) had moderate grade of envenomation.
- Out of 34 cases with increased ESR level, 11 cases (32.4%) had severe grade of envenomation and 19 cases (55.9%) had moderate grade of envenomation and 4 cases (11.8%) had mild grade of envenomation.
- Out of 24 cases with decreased albumin level, 12 cases (50%) had severe grade of envenomation and 10 cases (41.7%) had moderate grade of envenomation and 2 cases (8.3%) had mild grade of envenomation.
- Out of 34 cases with increased ferritin level, 9 cases (56.3%) had severe grade of envenomation and 6 cases (37.5%) had moderate grade of envenomation.
- Out of 11 cases with increased LDH level, 9 cases (81.8%) had severe grade of envenomation and 2 cases (18.2%) had moderate grade of envenomation.



Graph 2: Association of serum LDH and grade of envenomation.

Table 2: Relationship Between Acute Inflammatory Markers ,LDH And Hematological Profile In Snake Bite

Hematological Profile and Acute Inflammatory Markers		LDH Elevated		Total
		Increase	***normal***	
Hb	<13	26	0	26
		57.8%	0.0%	52.0%
	13-18	19	5	24
		42.2%	100.0%	48.0%
TC	4000-11000	22	4	26
		48.9%	80.0%	52.0%
	>11000	23	1	24
		51.1%	20.0%	48.0%
ESR	<13	9	3	12
		20.0%	60.0%	24.0%
	>13	36	2	38
		80.0%	40.0%	76.0%
PT	<10	1	0	1
		2.2%	0.0%	2.0%
	>10	36	4	40
		80.0%	80.0%	80.0%
	Prolonged	8	1	9
		17.8%	20.0%	18.0%
WBCT	<30	29	4	33
		64.4%	80.0%	66.0%
	Prolonged	16	1	17
		35.6%	20.0%	34.0%
SR ALBUMIN	<3.5	18	0	18
		40.0%	0.0%	36.0%
	3.5-5	27	5	32
		60.0%	100.0%	64.0%
Total		45	5	50
		100.0%	100.0%	100.0%

Outcome of the Patient and its Correlation with Acute Inflammatory Markers and Serum LDH:

Table 3: Acute Inflammatory Markers and Serum LDH and their correlation with outcome

	*Outcome **		*t*	*P Value*
	Improved	*Worsened*		
CRP	4.43 ± 3.1	12.11 ± 5.7	5.657	<0.001
Fibrinogen	281.92 ± 90.6	427.88 ± 178.6	3.595	0.001
ESR	18.59 ± 7.5	28.77 ± 8.5	3.569	0.001
Ferritin	197.87 ± 94.35	300.44 ± 113.8	2.847	0.006
LDH at presentation	347.02 ± 106.5	692.22 ± 251.4	6.631	<0.001
LDH after 24hrs	396.09 ± 136.9	856.77 ± 314.9	6.978	<0.001
Sr Albumin	4.06 ± 0.52	3.17 ± 0.27	4.898	<0.001

(*Independent t test)

In the above table, there is significant increase in mean of inflammatory markers among patients whose conditions worsened/deteriorate than those who are improved. And there is significant decrease in mean serum albumin among patients whose conditions worsened than those who are improved. Hence it can be said that the above inflammatory markers can be used to predict prognosis of snake bite patients.

Number of ASV Vials Used and its Comparision with Serum LDH:

Table 4: Requirement of ASV

ASV	*LDH Level*				*Total*	
	Elevated		*Normal*			
	Patients	*Percentage*	*Patients*	*Percentage*	*Patients*	*Percentage*
<10	12	80%	3	20%	15	100%
10-20	10	100%	0	0%	10	100%
20-30	11	92%	1	8%	12	100%
>30	11	100%	0	0%	11	100%
None	1	50%	1	50%	2	100%

In the above table showed most of the victims in our study required less than 10 vials of ASV. As the number of ASV vials increases level of serum LDH also elevated with was seen in 11 patients (who required > 30 ASV) showed elevation in the serum LDH.

5. Discussion

1) Snake bite is a common and a serious problem in a tropical country like India. Epidemics of snake bite have resulted from a sudden increase in snake population density. Purpose of this study is to study the acute inflammatory markers and serum LDH in snake bite patients in SSIMS and RC Davangere and their correlation with the outcome of the patient.
2) Inflammatory markers and serum LDH.
3) In our study when we compared grade of envenomation with the acute inflammatory markers (CRP, fibrinogen, ferritin, ESR and albumin) and serum LDH following observation was found:
   - In 84.6% of snake bite victims with elevated CRP level showed severe grade of envenomation which was statistically significant.
   - Serum fibrinogen level was also showed statistically significant i.e. 75% of the victims showed severe grade of envenomation with elevated fibrinogen level.
   - ESR which is acute inflammatory marker was also elevated in serum grade of envenomation in 32.4% which is statistically significant of p value less than 0.001.
   - Serum ferritin was elevated in 56.3% of the snake bite victims who had severe grade of envenomation with p value 0.001 which is statistically significant.
   - In 50% of the snake bite victims with decreased serum albumin level showed severe grade of envenomation with p value less than 0.001 which is statistically significant.
4) These above results were correlated with the study by Barraviera.B et al[5,6,7,8]where patient studied acute phase reactants in victims bitten by bothrops and crotalus snakes in Brazil, in which ophidic venom releases cytokines and other inflammatory mediators.
5) In our study hematological profile was also altered and it was compared with serum LDH and other acute inflammatory markers. As the haemoglobin drops which is a sign of hemolysis show significant increase serum LDH which was seen in 26 patients (57.8%) similar to reported by Saini et al (40%).
6) In the table no 24, there is significant increase in the mean of acute inflammatory markers which included CRP, fibrinogen, ferritin and ESR among patients whose conditions worsened/deteriorate than those who were

improved. And there is significant decrease in the mean serum albumin level among patients whose conditions worsened than those who were improved. A study[3] done in China, patient divide into mild, moderate and sever group based on the severity of envenomation. They were further divided to SIRS (systemic inflammatory response syndrome) and non –SIRS groups based on the complications. Serum CRP levels were elevated in the moderate to severe group and also in SIRS group which was used as predictive marker in the outcome of the victims.

7) Level of serum LDH at the time of presentation and after 24 hours also had significant correlation with outcome of the patient which was statistically significant with the p value of less than 0.001. Serum LDH which is a marker of hemolysis which is worst prognosis in the outcome of the victims were correlated. A study[4] done on Sholapur on 30 snake bites reorted elevated serum LDH in all the patients. The LDH levels correlated well to the severity of hemolysis compared to normal levels in the control group. A prospective study[5] from Brazil among children with moderate to severe snake bite envenomation showed early and persistent rise in serum LDH levels upto 48 hours which correlated well with degree of hemotoxicity of snake bite[9].
8) In our study group most of them required less than 10 vials of ASV after admission which was correlated with the study[10] done in Maharashtra by Pore SM, et al. 49% of the patients received less than 10 vials of ASV whereas 41% received 10-20 vials of ASV while only 10% received more than 30 vials. In a study done in Bangalore by Harshavardhana HS, et al[11].12 52% of the patients received more than 30 vials of ASV. The less dose of ASV administration in our study could be attributed to smaller number of patients with systemic envenomation. Also to be noted was that there was no common criteria between the 3 studies for the administration of ASV and it was purely at the discretion of the treating physician. An observation was made in our study that patients requiring more than 30 vials of Polyvalent ASV had elevated serum LDH(100%) values at the admission.

6. Conclusion

The present study can be concluded with the following observations:

- Incidence of snake bite was more common in adults who belonged to working class and this affects the economy of the concerned family.
- Hemotoxic snake bite with features compatible with moderate grade of envenomation is most common manifestation observed in significant amount in this geographic area.
- Hematological profile was also deranged in severe grade of envenomation which is cost effective in comparison with acute inflammatory markers.
- Statistically significant association was found between the acute inflammatory markers and serum LDH in the outcome of the snake bite victims.
- As the serum LDH level elevated requirement of total number ASV vials in the management of snake bite also increased.
- Hence the above acute inflammatory markers and serum LDH can be considered as the predictors in assessment of severity grading of envenomation, in the prognosis of the snake bite victim which in turn asses the outcome.

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