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Indian Journal of Medical Sciences



Original Article Predictors of complications in venomous snakebites

Kedareshwar P. S. Narvencar¹, T. T. Favas¹, Amit Dias²

Departments of ¹Medicine, ²Preventive and Social Medicine, Goa Medical College, Bambolim, Goa, India.

ABSTRACT

Objectives: Factors responsible for causing complications in venomous snakebites are unknown. The present study was planned to identify such factors.

Material and Methods: This was a prospective and observational study. All patients presenting to the emergency department between April 2016 and August 2017 with venomous snakebites and meeting inclusion/exclusion criteria were enrolled. Patients were divided into two groups based on the presence/absence of complications. Risk factors associated with complications were analyzed.

Results: Out of 236 patients screened, 156 were eligible. Mean age was 39.5 ± 15.6 ; majority (n = 122, 78.2%) were in the age group of 20–59 years; 119 (76.3%) were males. Eighty-eight patients (56.4%) developed complications, of which, cellulitis/compartment syndrome (n = 54, 34.6%) was most common, followed by acute kidney injury (n = 18, 11.5%), coagulopathy/disseminated intravascular coagulation (n = 17, 10.9%), neuroparalysis needing ventilator (n = 12, 7.7%), shock (n = 8, 5.1%), acute respiratory distress syndrome (three patients, 1.9%), and sepsis (one patient, 0.6%). The mortality rate was 1.92%. On univariate analysis, low hemoglobin, elevated neutrophil count, lower lymphocyte count, serum creatinine, initial/total dose of anti-snake venom, and prolonged hospital stay had a statistically significant association with complications. On multivariate analysis, elevated neutrophil count (OR 1.084; 95% CI 0.997, 1.179) and prolonged hospital stay (OR 1.975; 95% CI 1.393, 2.800) were associated with complications. Bite-to-needle time was associated with mortality.

Conclusion: The nature of complications depends on composition of venom, and thus varies with geographical region. The Association of neutrophil and lymphocyte counts points to an inflammatory hypothesis. The Association of bite-to-needle time with mortality highlights the early use of antivenom. Awareness of risk factors may guide in predicting complications.

Keywords: Venomous snakebites, Complications, Neutrophil count, Lymphocyte count, Bite-to-needle time.

INTRODUCTION

Snake envenomation is a major cause of morbidity and mortality in most parts of the world including India.^[1,2] The annual incidence of morbidity and mortality due to snakebites in India is estimated to be 1.4-68 per lakh and 1.1-2.4 per lakh population, respectively.^[3,4] Although a large number of patients develop complications, the risk factors responsible for the same are not exactly known. A few studies have documented that complications are directly proportional to the duration of venom in blood before its neutralization by anti-snake venom,[5-8] thus suggesting that delay in the administration of antivenom may be a risk factor for complications. It is still debatable whether a high dose of antivenom is beneficial in preventing complications.^[9-12] Other factors which contribute to the development of complications need to be identified. The present study was, therefore, undertaken to identify predictors of complications in patients with venomous snakebites.

MATERIAL AND METHODS

This was a prospective and observational study carried out over 1 year and 5 months from April 2016 to August 2017, at the department of medicine of a tertiary care teaching hospital in the state of Goa. The study was conducted following the declaration of Helsinki and ICMR's ethical guidelines for biomedical research on human participants (2006), after obtaining approval from the Institutional Ethics Committee.

The detailed protocol of the study has been mentioned in our earlier paper.^[13] In short, all patients presenting to the emergency department of our institution with venomous snakebite and consenting to be a part of the study were screened. Patients without objective signs or symptoms of envenomation (either systemic or local), those with preexisting systemic illness (hepatic, renal, cardiac, neoplastic, etc.), children below the age of 12 years, and those patients who declined consent or left the hospital against

*Corresponding author: Dr. Kedareshwar P. S. Narvencar, Department of Medicine, Goa Medical College, Bambolim, Goa, India. kedarnarvenkar@yahoo.com Received: 08 July 2021 Accepted: 18 July 2022 Published: 22 August 2022 DOI: 10.25259/IJMS_328_2021

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medical advice were excluded from the study. Detailed history, examination, and laboratory workup were done on all patients. Patients were treated as per standard practice, following the national snakebite management protocol. Patients were observed from the time of admission up to discharge from the hospital or until the death of the patient.

For this paper, the study population was divided into two groups, those without any evidence of complications (termed an uncomplicated group) and those with evidence of complications (complicated group). The complicated group was further subdivided based on the nature of the complications. Complications were defined as under:

- i. Cellulitis: Local swelling involving more than half of the bitten limb, a rapid extension of swelling, or development of enlarged tender lymph node/s draining the bitten limb
- ii. Neurotoxicity: Neuroparalysis needing ventilatory support
- iii. Acute kidney injury: Acute rise in serum creatinine to >1.5 mg/dl, the percentage increase in serum creatinine of \geq 50%, or urine output of <0.5 ml/kg/h for 6 h
- iv. Hemostatic abnormalities/coagulopathy: Spontaneous systemic bleeding, thrombocytopenia (platelet count <1.0 lakh/mm³), prothrombin time (PT) prolongation >3 s above control, International Normalized Ratio >1.5, aPTT >10 s above control value, evidence of disseminated intravascular coagulation (DIC), or primary fibrinolysis
- v. Muscular: Necrosis of muscle or rhabdomyolysis
- vi. Shock: Hypotension (systolic blood pressure <90 mm Hg, diastolic BP <40 mm Hg, or Mean Arterial Pressure <60 mm Hg) not responding to fluid resuscitation or needing inotropic support
- vii. Cardiovascular abnormalities: Shock (MAP <60) and cardiac arrhythmia
- viii. Acute respiratory distress syndrome (ARDS): Clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure.
- ix. Sepsis.

Statistical methods

Data were captured in a predetermined pro forma and entered into a Microsoft Excel spreadsheet. Data are expressed as number (%) or mean \pm SD as appropriate. Statistical analysis was done using Statistical software SPSS for Windows, version 23.0. The categorical data were analyzed using the Chi-square test and continuous variables were analyzed using *t*-test for independent samples. Univariate analysis was done to find the factors associated with complications as well as mortality. Logistic regression analysis, both bivariate and multivariable, was carried out to find association of the factors with complications. The results were reported as Odds Ratio (95% CI). P < 0.05 was considered statistically significant.

RESULTS

Two hundred and thirty-six patients were screened, of which 156 patients met the inclusion criteria, and thus were recruited for the study. One hundred and nineteen patients (76.3%) were males. Hemotoxic features were seen in 120 patients (76.9%), 7 patients (4.5%) presented with neurotoxicity while 111 (71.2%) had local reaction either alone (n = 29) or with hemotoxicity (n = 82).

Eighty-eight patients (56.4%) developed complications [Table 1]. The most common complication was cellulitis and compartment syndrome (n = 54, 34.6%) followed by acute kidney injury (n = 18, 11.5%), coagulopathy/DIC (17 patients, 10.9%), neuroparalysis needing ventilator (12 patients, 7.7%), and shock (n = 8, 5.1%). ARDS and sepsis were seen in 3 patients (1.9%) and 1 patient (0.6%), respectively. Out of 156 patients recruited, three patients expired giving a mortality rate of 1.92%.

Predictors of complications in snakebites

As shown in [Table 2], low hemoglobin level, elevated neutrophil count, lower lymphocyte count, serum creatinine, an initial dose of anti-snake venom, a total dose of anti-snake venom, and prolonged duration of hospital stay were found to have a statistically significant association with complications on univariate analysis. On multivariate analysis, elevated neutrophil count (OR 1.084; 95% CI 0.997, 1.179) and the duration of hospital stay (OR 1.975; 95% CI 1.393, 2.800) were strongly associated with complications. Although high serum creatinine showed an association with the risk of complications (OR 1.929; 95% CI 0.445, 8.372) on multivariate analysis, it did not meet statistical significance.

Prognostic indicators of death in snakebites

Bite to needle time was significantly associated with survival (P < 0.001). Other parameters which were associated with complications did not show a statistical correlation with mortality [Table 3].

Factors associated with individual complications

We attempted to identify factors, which could be associated with individual complications. Lower hemoglobin level was associated with cellulitis/compartmental syndrome, acute kidney injury, and ARDS; elevated neutrophil count and lower lymphocyte count were associated with cellulitis/ compartmental syndrome, shock, and acute kidney injury.

Table 1: Percentage distribution of the sample according to complications.							
Complications	Number of patients (n)	Percentage out of total patients	Percentage out of all complications				
Total Complications	88	56.4	100.0				
Cellulitis/compartment syndrome/gangrene	54	34.6	61.6				
Coagulopathy/DIC	17	10.9	19.3				
Shock	8	5.1	9				
Acute kidney injury	18	11.5	20.4				
Neuroparalysis	12	7.7	13.6				
ARDS	3	1.9	3.4				
Cardiotoxicity/arrhythmias	0	0.0	0				
Sepsis	1	0.6	1.1				
Muscle necrosis/rhabdomyolysis	0	0.0	0				
Ventilator associated pneumonia	1	0.6	1.1				
Death	3	1.9	3.4				
ARDS: Acute respiratory distress syndrome, DIC: Dissemi	nated intravascular coagulation						

While prolonged bite to needle time was not associated with overall risk of complications, it was found to be associated with risk of cellulitis/compartmental syndrome, coagulopathy/DIC, and ARDS. Neuroparalysis was found to be strongly associated with initial dose and total dose of antisnake venom, and prolonged duration of hospital stay.

DISCUSSION

The World Health Organization has recently declared snakebite as a neglected tropical disease and is developing a road map for a reduction in mortality and morbidity due to it.^[1] Identification of predictors of complications will help in initiating steps in this direction. The present study, therefore, assumes significance. This is the first study conducted in the state of Goa on risk factors associated with complications in victims of venomous snakebites. A previous study conducted in Goa^[6] to find a correlation between the timing of ASV administration and complications was limited by smaller sample size and did not look at other risk factors.

More than 56% of patients enrolled in this study had complications. Such a higher rate of complications is probably due to a referral bias, our center being a tertiary care referral medical institute.

The nature of complications, which are likely to develop in any snakebite case in a particular area, will depend on the composition of snake venom and the species of snake prevalent in that particular region. The most common species prevalent in our region is Russell's viper, which causes hemotoxic and cytotoxic features, thus explaining the higher incidence of coagulopathy and local complications such as cellulitis and compartmental syndrome seen in the present study. Lesser incidence of neurotoxicity is due to lesser cases of neurotoxic bites seen in this study. Complications such as shock, ARDS, and sepsis were seen only rarely. This pattern of complications is similar to that seen in other studies^[10,14-18] conducted in other parts of the country, where viperine bites are common.

Acute kidney injury is known to be strongly associated with coagulopathy and is a common complication in viperine bites.^[19] While both coagulopathy, as well as acute kidney injury, were common complications in our study, we could not establish an association between the two.

Interestingly, unlike other studies,^[14,19] gangrene of the extremities was not seen in our study, even though the local reaction was the most common complication. This could again be due to the difference in composition of snake venom or due to prompt and adequate local care given to patients with cellulitis.

Predictors of complications

As seen in the results, low hemoglobin level, elevated neutrophil count, lower lymphocyte count, serum creatinine, an initial dose of anti-snake venom, a total dose of antisnake venom, and prolonged duration of hospital stay showed a statistically significant association with overall risk of complications on univariate analysis, of which elevated neutrophil count and the duration of hospital stay showed a strong association with complications on multivariate analysis.

A low level of hemoglobin was also found to be an independent predictor for the development of cellulitis/ compartmental syndrome as well as acute kidney injury in a subgroup analysis of different complications and is similar to that reported in various other studies.^[20,21] Although an exact reason for this association could not be ascertained, hemoglobin level is a marker of nutritional status and overall well-being of the patient;^[22] thus, the lower level may predispose the patient to complications.

Table 2: Predictors of complications in snakebites.								
Parameters studied	Uncomplicated	Complicated	P-value	Multivariate analysis				
	(<i>n</i> =68)	(<i>n</i> =88)		Unadjusted OR (95%CI)	P-value			
Age (mean±SD)	39.82±15.889	39.28±15.443	0.831					
Sex								
Male, <i>n</i> (%)	54 (45.4)	65 (54.6)	0.419					
Female, <i>n</i> (%)	14 (37.8)	23 (62.2)						
Comorbid conditions								
Present, n (%)	10 (43.5)	13 (56.5)	0.991					
Absent, <i>n</i> (%)	58 (43.6)	75 (56.40)						
Occupation, <i>n</i> (%)								
Student/housewife/retired	49 (72.1)	59 (67.0)	0.470					
Professional	0(0.0)	1 (1.1)						
Technicians and associate professionals	1 (1.5)	0 (0)						
Clerical workers	0 (0)	2 (2.3)						
Sales workers and service	10 (14.7)	15 (17)						
Skilled agricultural	2 (2.9)	0 (0)						
Craft	0 (0)	1 (1.1)						
Plant and machine operators	3 (4.4)	4 (4.5)						
Elementary	3 (4.4)	6 (6.8)						
Type of snake identified n (%)								
Russell's viper	8 (11.8)	10 (11.4)	0.966					
Cobra	2 (2.9)	2 (2.3)						
Krait	2 (2.9)	2 (2.3)						
Not identified	56 (82.4)	74 (84.1)						
Bite-to-needle time <i>n</i> (%)								
1–6 h	53 (45.3)	64 (54.70)	0.131					
6–12 h	8 (38.10)	13 (61.90)						
12–24 h	1 (11.10)	8 (88.90)						
>24 h	0 (0)	2 (100.0)						
Laboratory parameters (mean±SD)								
НЬ	14.32±1.931	13.16±2.605	0.002*	0.902 (0.748, 1.087)	0.278			
Total count	12666.67±13186.55	12942.64±6791.051	0.867	1.084 (0.997, 1.179)	0.05*			
Neutrophil count	74.92±17.064	82.23±11.932	0.004^{*}	1.088 (0.975, 1.214)	0.130			
Lymphocyte count	16.5±11.65	12.24±9.152	0.016*	1.929 (0.445, 8.372)	0.380			
Neutrophil/lymph	9.15±8.711	11.59±9.819	0.113					
Platelet (lakhs)	2.36±0.694	2.2±0.963	0.231					
Serum creatinine	1.02 ±0.216	1.84 ± 2.406	0.002*					
Serum bilirubin total	1.1±0.709	1.36 ± 0.849	0.101					
Serum bilirubin dir.	0.27±0.45	0.33 ± 0.504	0.561					
SGOT	40.18±24.545	71.85±141.433	0.063					
SGPT	33.8±28.636	37.63±33.462	0.541					
ALP	85.92±40.036	80.61±34.887	0.47					
Initial dose of ASV (mean±SD)	8.74±4.287	10.58±6.355	0.041*	0.975 (0.854, 1.113)	0.709			
Total dose (mean±SD)	10.13±5.274	14.17±7.302	< 0.001*	1.104 (0.994, 1.227)	0.064			
Duration of hospital stay (mean±SD)	1.84±1.016	5.17±5.604	< 0.001*	1.975 (1.393, 2.800)	0.000*			
*Statistically significant								

In our study, a higher neutrophil count and a lower lymphocyte count were significant predictors of the development of overall complications, as well as cellulitis/ compartment syndrome, acute kidney injury, and shock. This finding corroborates the inflammatory hypothesis. A higher neutrophil to lymphocyte ratio is a marker of inflammation and is associated with complications.^[23] Extensive tissue destruction and devitalization, which occur due to the action of proteolytic components of venom, activate inflammatory cascade, thus leading to elevated neutrophil count.^[24,25] The higher level of neutrophils, in turn, leads to heightened systemic inflammatory response syndrome ultimately resulting in various complications. The elevated neutrophil count may also be a consequence of local reaction. The

Table 3: Prognostic indicators of death in snake	ebites.		
Parameters studied	Survival group (<i>n</i> =153)	Non-survival group (<i>n</i> =3)	P-value
Age (mean±SD)	39.37±15.655	47.33±10.786	0.382
Sex			
Male <i>n</i> (%)	117 (76.50)	2 (66.70)	0.693
Female <i>n</i> (%)	36 (23.50)	1 (33.30)	
Comorbid conditions			
Present, n (%)	23 (100)	0 (0)	0.467
Absent, <i>n</i> (%)	130 (97.7)	3 (2.3)	
Occupation, <i>n</i> (%)			
Student/housewife/retired	106 (69.30)	2 (66.70)	0.779
Professional	1 (0.70)	0 (0.00)	
Technicians and associate professionals	1 (0.70)	0 (0.00)	
Clerical workers	2 (1.30)	0 (0.00)	
Sales workers and service	25 (16.30)	0 (0.00)	
Skilled agricultural	2 (1.30)	0 (0.00)	
Craft	1 (0.70)	0 (0.00)	
Plant and machine operators	7 (4.60)	0 (0.00)	
Elementary	8 (5.20)	1 (33.30)	
Type of snake, n (%)			
Russell's viper	18 (11.8)	0 (0)	0.894
Cobra	4 (2.6)	0 (0)	
Krait	4 (2.6)	0 (0)	
Not identified	127 (83.0)	3 (100.0)	
Bite-to-needle time, n (%)			
1–6 h	115 (78.8)	2 (66.7)	< 0.001*
6–12 h	21 (14.4)	0 (0)	
12–24 h	9 (6.2)	0 (0)	
>24 h	1 (0.70)	1 (33.30)	
Laboratory parameters (mean±SD)			
НЬ	13.73±2.279	10.33 ± 5.859	0.422
Total count	12780.73 ± 10083.34	14966.67±7352.777	0.71
Neutrophil count	78.98±14.892	84±5.292	0.562
Lymphocyte count	14.13 ± 10.562	11.67±5.859	0.689
Neutrophil/lymphocyte	10.55 ± 9.462	9.67±7.234	0.872
Platelet (lakhs)	2.27±0.849	2.33±1.528	0.895
Serum creatinine	1.46 ± 1.873	2.67±1.155	0.27
Serum bilirubin total	1.27 ± 0.816	1.33 ± 0.577	0.891
Serum bilirubin direct	0.31±0.485	0.33 ± 0.577	0.926
SGOT	59.15±116.086	123.67±104.711	0.343
SGPT	35.69±31.296	59±49.568	0.211
ALP	82.12±36.846	102 ± 38.184	0.451
Initial dose of ASV (mean±SD)	9.77±5.663	10 ± 0	0.944
Total dose (mean±SD)	12.33±6.789	16.67±5.774	0.274
Duration of hospital stay (mean±SD)	3.64 ± 4.432	7.67±9.866	0.553
*Statistically significant			

devitalized tissue at the bite site predisposes it to bacterial infection (the causative organisms being the oral flora of the biting snake),^[24] leading to a rise in neutrophil levels. However, the role of prophylactic antibiotics to prevent wound infection is debatable, as their use is not shown to improve outcomes.^[26] An association between total WBC count and compartmental syndrome has also been shown;^[27] however, the present study did not show any such

correlation. Similarly, the delta neutrophil index, a novel indicator of premature granulocytes, has also been shown to be a predictor of sepsis and coagulopathy in snake bites;^[28] however, we have not evaluated this index in our study.

Elevated serum creatinine had a statistically significant association with complications on univariate analysis in our study and had a higher odds of 1.929 (95% CI 0.445, 8.372) for developing complications. This is despite the fact that acute kidney injury was seen in only 11.5% of the total patients. This suggests the role of serum creatinine as a predictor of complications independent of acute kidney injury. A similar association has been shown in other studies as well.^[16,21]

Bite-to-needle time was an independent predictor of mortality as well as complications such as cellulitis/local reaction, coagulopathy, and ARDS in the present study. This confirms that a delay in treatment leads to complications as well as death. An earlier paper published by us^[6] also demonstrated a similar association of prolonged bite to needle time with complications. The Association of bite to needle time with mortality as well as complications (especially acute kidney injury) has also been shown in many other studies.[5,8,14-16,19,21,29] This finding suggests that circulating venom in plasma could be directly toxic to various organs, while the venom deposited at the bite site could continue to produce damage at the local site until it is neutralized by antisnake venom. Antisnake venom can only neutralize the free venom in the plasma before it gets bound to tissues. This highlights the importance of early treatment with antisnake venom. In developing countries like India, a considerable proportion of patients report late to the health-care facility due to various reasons such as accessibility, difficult terrain, lack of awareness, superstitions, and traditional healers, which, in turn, increases the risk of complications. It is, therefore, important to raise community awareness as well as to make antivenom easily available in all peripheral areas for immediate administration to patients on arrival, even before shifting them to higher centers for further management.

The Association between higher initial dose and total dose of antisnake venom as well as longer duration of hospital stay in a complicated group is self-explanatory. Although the exact amount of venom injected into the patient could not be estimated in the present study due to lack of facilities, a higher dose of antivenom needed for neutralization in a complicated group suggests the possibility of higher levels of snake venom injected in these patients. However, this needs to be proven. It is also likely that in complicated patients, physicians tend to give higher or repeated doses of antivenom, thus showing the correlation.

Mortality

Although the rate of complications was high in this study, the mortality rate was significantly lower at 1.92%. All three patients who died had coagulopathy, two patients in addition had an acute renal failure while one patient had ARDS along with coagulopathy. The mortality rate differs in studies reported from various parts of the Indian subcontinent such as Pore *et al.* (5.11%),^[8] Chaudhari *et al.* (22.3%),^[14] Monteiro *et al.* (6.5%),^[17] Harshavardhan *et al.* (22.3%),^[19] and David *et al.* (7.5%).^[29] The lower rate of death in the present study as

well as in many other studies from other parts of the world^[8,30] as well as the association of mortality with bite to needle time seen in the present study shows that mortality is avoidable even in complicated cases by early and prompt treatment.

CONCLUSION

The nature of complications that occur in snakebites depends on the composition of snake venom, thus varying in different geographical regions. Low hemoglobin count, elevated neutrophil count, low lymphocyte count, elevated serum creatinine levels, the dose of anti-snake venom, and duration of hospital stay are significantly associated with the development of complications on univariate analysis. These markers may be used for the prediction of complications in patients with venomous snakebites.

Although a bite to needle time is not associated with overall complications, it is associated with survival and local complications. Delay in the administration of antivenom increases the risk of death in the patient. Antivenom should, therefore, be administered as early as possible to the patient. Early transportation of the patient to a healthcare facility and easy availability of antivenom in peripheral areas will help reduce mortality in snakebites.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Narvencar KP, Favas TT, Dias A. Predictors of complications in venomous snakebites. Indian J Med Sci 2022;74:86-92.