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Evaluation of optimum dose of anti-snake venom required and its outcome based on severity of envenomation in snakebite case

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ABSTRACT

Background: Snakebite is an important occupational hazard in India as it is always been a land of poisonous snakes. The isssue which the physician confronts while treating a snake bite patient is assesment of degree of envenomation and requirement of ASV dose. **Aims and Objectives:** This study was taken to evaluate the optimum dose of anti-snake venom (ASV) required based on the severity of envenomation. **Materials and Methods:** Patients with a history of snakebite brought to the Department of General Medicine, Hassan, were included in this study. The study was conducted during the period from December 2014 to June 2016. The sample size of 80 patients was included in the study after fulfilling the inclusion criteria. **Results:** A total of 80 patients were included in the study. The majority of the victims were males (70%), age between 21 and 40 years (47.5%), and agriculture was the main occupation (67.3%). 51.25% did not identify the snake. The most poisonous were viper and cobra types which were 36.5% and 12.5%, respectively. A delay in lag time of 8.99±8.2 h was observed in severe envenomation. Overall, 51 cases (63.75%) had cellulitis, and 3 (3.75%) in the severe group required fasciotomy. Twenty percent had hematologic derangements. Ten percent of patients had developed renal failure and one required dialysis. 8.75% of patients developed respiratory failure and all required mechanical ventilation. The average dose of ASV vials used in mild, moderate, and severe envenomation was 9.04±3.51 vials, 18.5±5.27 vials, and 28.6±7.30 vials, respectively. The overall mortality rate was 5%. **Conclusions:** The optimum dose of ASV required in mild, moderate, and severe envenomation is 9.04±3.51 vials, 18.5±5.27 vials, and 28.6±7.30 vials, respectively to neutralize the circulating venom and lower the risk of development of serious complications.

Key words: Anti-snake venom; Lag time; Snakebite; ASV reactions

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INTRODUCTION

Snakebite is a major public health problem throughout the world, especially in tropical and sub-tropical countries such as India. In modern times, a serpent winding around the magic wound of the Greek god of medicine has found a place in the universal symbol of the medical profession.[1]

Over 2,000 species of snakes are known worldwide, of which around 400 are poisonous. In India, 256 species of snakes have been identified, and 52 are found to be poisonous; the most common include Russell's viper (*Daboia russelii*), Indian cobra (*Naja naja*), common krait (*Bungarus caeruleus*), and saw-scaled viper (*Echis carinatus*).[2] Based on the available evidence, the distribution of species varies with the epidemiology.

India had the highest number of envenomation (81,000/year) and the highest number of deaths (11,000/year) due to snakebites in the world.[3] In India, Tamil Nadu, West Bengal, Maharashtra, Uttar Pradesh, and Kerala are found to have the highest incidence of snakebites.[4]

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The actual incidence of snakebite may be higher than what is estimated, as the majority of cases go unreported. Only cases of severe envenomation reach the health-care center. Epidemiological studies have confirmed that snakebite in the tropics is more common in rural and among farmers, plantation workers, herders, and hunters.[5]

Snake envenomation is a serious medical crisis varying from local tissue damage to the involvement of almost all vital organs of the body. Clinico-toxicologically, the nature of snake envenomation is categorized into hemotoxic, neurotoxic, and myotoxic syndromes.[6]

Management of poisonous snakebites includes administration of anti-snake venom (ASV), local wound management, and other supportive measures based on the toxicity of envenomation.

Polyvalent ASV forms the cornerstone therapy, very expensive, and availability of which is scarce, especially in high-risk areas.[7] Although the use of ASV has been in existence for many years, there is no universally accepted standard treatment regimen regarding the optimum dose of ASV, its frequency, and duration of therapy.[8]

Few studies have been done so far to address the dosage requirement in snakebites based on the severity of envenomation: Mild, moderate, and severe, instead, they have formulated a generalized protocol. Hence, this study was taken up to evaluate the optimum dose of ASV required for the treatment of poisonous snakebite cases based on the severity of envenomation.

Objectives

1. To study the sociodemographic profile of snakebite
2. To evaluate the effective dose of ASV required based on the severity of envenomation
3. To monitor the adverse effects of ASV.

MATERIALS AND METHODS

A prospective observational study was conducted in Sri Chamarajendra Hospital, Department of General Medicine, HIMS, and patients with a history of snakebite brought to the Department of General Medicine, Hassan, were included in this study. The study was conducted during the period from December 2014 to June 2016. The sample size of 80 patients was included in the study after fulfilling the inclusion criteria.

Inclusion criteria

- Patients aged >13 years were admitted with clinical features of snake envenomation
- Cases presenting within 24 h of snakebite.

Exclusion criteria

- Patients previously diagnosed with bleeding/coagulation disorder
- Pre-existing neurological illness
- Patients who had received ASV before arriving at the hospital.

The study was conducted after taking the ethical committee clearance. After obtaining the written informed consent from the patients, the sociodemographic details, the interval between the time of the bite and ASV administration, general physical examination, and local examination were carried out.

Laboratory investigations such as complete blood count, renal function test, and urine analysis were done. Based on these parameters, patients were grouped into mild, moderate, and severe categories (Table 1).

All cases of snakebite were given 0.5 ml of tetanus toxoid IM, intradermal sensitivity testing was done to rule out hypersensitivity reactions, and polyvalent ASV IV was started. During the follow-up period, BT, CT, blood urea, and serum creatinine were done, and the total dose of ASV vials used in each patient and any adverse reaction that occurred due to ASV use were collected and documented until discharge or death.

Other supportive measures such as:

- Antibiotics – Ceftriaxone (1 g) IV two times a day for 5–7 days
- Surgical intervention for cellulitis – Fasciotomy
- Neuroparalysis/respiratory distress – Ventilatory support and neostigmine (0.5–1 mg), atropine (0.6 mg)
- Shock – Fresh frozen plasma/blood, inotropic support
- Acute renal failure – Dialysis
- ASV reactions – injection CPM (10 mg) IV, injection hydrocortisone (200 mg) IV, and injection adrenaline 1:1000 I M, given when indicated.

Statistical analysis

Results on continuous measurements are presented as mean±SD (min-max) and results on categorical measurements are presented in numbers (%). Significance is assessed at a 5% level of significance. Analysis of variance

Table 1: Categorization of patients based on severity of envenomation.[13]

Severity	Clinical manifestations
Mild	Local findings only (e.g., pain, local ecchymosis, non-progressive swelling)
Moderate	Swelling that is clearly progressing, systemic signs or symptoms, and/or laboratory abnormalities
Severe	Respiratory distress, neurological dysfunction, and/or cardiovascular instability/shock

has been used to find the significance of study parameters between the three groups of patients. The Chi-square test has been used to find the significance of the difference in study parameters on a categorical scale between the groups. Graphs were generated using Microsoft Office Excel.

RESULTS

A total of 80 snakebite patients presented to our hospital during the study period (December 2014–June 2016). They were analyzed as follows.

Sociodemographic characteristics

Among snakebite victims, age ranged between 13 and 70 years, and the majority (47.5%) of patients were in the age group of 21–40 years (Figure 1).

The male gender (70%) had a higher incidence of snakebite poisoning than female gender (30%) (Figure 2). The majority of the patients included in our study were farmers (43.75%) followed by plantation workers (31.25%), housewives (18.75%), and students (5%).

There were two peak seasons seen once in July to September (38/80, 47.5%) and the other in January to March (21/80, 26.25%) (Figure 3).

Definitive fang marks were seen in 28 cases (35%) and 52 cases (65%) fang marks were not obviously seen (Table 2).

Fifty-four (67.05%) patients were bitten on the lower limb, 25 (31.25%) on the upper limb, and the remaining one patient (1.25%) on the forehead (Table 3).

Only in 39 cases, species of snake were identified most common being Russell's viper in 29 cases (74.35%) followed by cobra in 10 cases (25.6%). For 41 cases, we were unable to identify the species, hence classified as "unknown" poisonous snakes (Table 4).

Hemotoxic envenomation was observed in 67 (83.75%) cases and the neurotoxic nature of envenomation was in 12 (15%) cases whereas only 1 (1.25%) case had both hemotoxic and neurotoxic manifestations (Table 5).

The proportion of patients with cellulitis was significantly higher in the moderate category compared to other groups. Sixteen cases developed coagulopathy; 6/20 (30%) cases of the severe group required blood transfusion (two patients required whole blood, two patients required whole blood and fresh frozen plasma, one patient whole blood packed red blood cell and FFP, and one patient packed cell and whole blood). Requirement of mechanical ventilation was required for respiratory failure in 5/20 (25%) cases of severe envenomation for a duration of 32.6±23.38 h and 2/38 (5.2%) cases of moderate envenomation for a duration of 22±5.65 h.

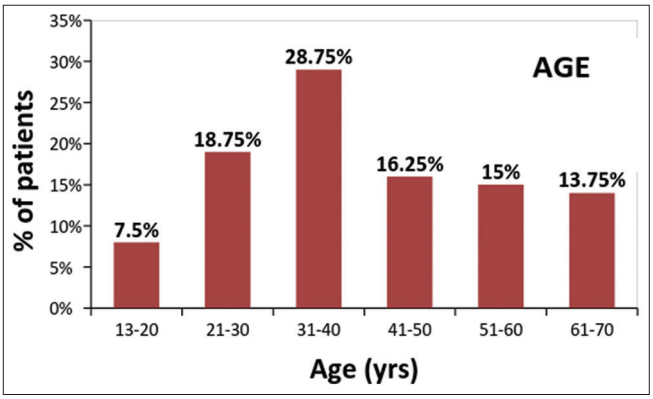

Figure 1: AGE-wise prevalance of snake bite

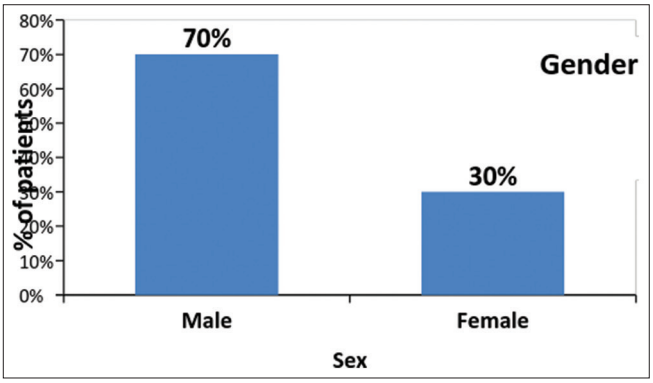

Figure 2: Sex incidence of snake bite

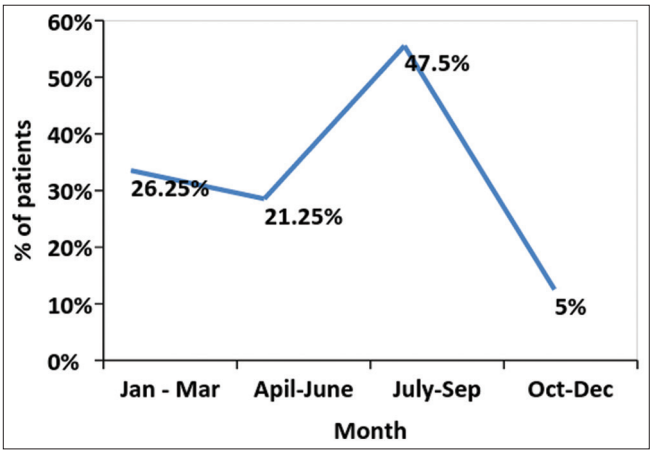

Figure 3: Seasonal incidence of snake bite

Acute renal failure was noticed in seven cases, of which 3/38 (7.8%) cases were of moderate envenomation and 5/20 (25%) cases with severe envenomation, dialysis was required only for one case of severe envenomation.

Table 2: Visibility of fang marks in snakebite victims

Fang marks	No. of cases (%)
Yes	28 (35%)
No	52 (65%)

Table 3: Location of snakebite

Site of bite	No. of cases (%)
Lower limb	54 (67.5%)
Upper limb	25 (31.25%)
Forehead	1 (1.25%)

Table 4: Type of snake species

Species	No. of species (%)
Viper	29 (36.25%)
Cobra	10 (12.9%)
Unknown	41 (51.25%)
Krait	0
Total	80

Table 5: Toxicity profile

Toxicity	No. of cases (%)
Hemotoxicity	67 (83.75%)
Neurotoxicity	12 (15%)
Both hemotoxicity and neurotoxicity	1 (1.25%)

The proportion of patients who developed complications such as coagulopathy, renal failure respiratory paralysis, and the need for supportive measures for treating them such as fasciotomy and ventilation was significantly ($P<0.05$) high in the severe category.

All the recovered cases had minimal complications, and hence, the dose of 9.04±3.51 ASV vials for mild, 18.5±5.27 vials for moderate, and 28.6±7.30 vials for severe category of envenomation is considered to be optimum. The above results are statistically significant ($P<0.05$).

Duration of hospital and requirement of ASV was significantly higher in the severe envenomation category. Overall mortality was 5% in the severe envenomation group. One of them was in shock at the presentation and went on to develop multi-organ dysfunction and the other deaths were due to respiratory failure (Table 6).

DISCUSSION

Our study was carried out in 80 cases of snakebite envenomation irrespective of snake species. Male preponderance was seen as similar to other studies.[9,10] The majority of them were farmers in the age group of 21–40 years.[11] This can be explained by the fact that earning members in the majority of families are males and their lifestyles involve farming and fieldwork. Hence, working outdoors and sleeping in the farmyard during harvesting are more common.

The peak of snakebite was seen during July–September which corresponds to monsoon season. A similar conclusion has been reached in studies conducted earlier.[12]

During this period, farmers are involved in agricultural activities and there is increased flooding of the habitats of the snakes for their prey. The breeding habits of frogs closely follow the monsoons and habitats of rodents and lies in close proximity to human dwellings during these seasons. The next common season of snakebite was January–March which is harvesting season.

Fang marks were visible only in 35% of cases and in 75% of cases, it was not obvious; a probable reason would be edema of bitten limb in which fang marks go unnoticed.

The majority of the bites were observed in the lower extremities, with feet being the most common site, followed by the upper limb and the least on other sites such as the forehead, similar findings are reported in other studies.[13] Probably, this may be due to more barefoot walkers in this region. Most cases of envenomation were seen due to viper snakebite (74.35%) followed by cobra bite (12.5%). This indicates that our study region, i.e., Hassan district of Karnataka state is more prevalent for viper snake species. Variations in the prevalence of different species of snake in different geographic regions may be due to various environmental/climatic conditions such as rainfall, altitude, vegetation, and abundance of preferred prey.[14,15]

The majority of the cases reached the hospital in <6 h. Possible reasons would be increased awareness about the treatment of snakebites and availability of transportation facilities, quick referral to the district hospital, since Hassan is equidistant to almost all taluk places. The lag time probably was long in the severe grade of envenomation, resulting in a more profound effect of snake venom and hence requiring large doses of ASV. A similar observation was seen in other studies.[16]

The rationale for the use of ASV is well-defined; doses required vary according to the severity of envenomation and the snake species associated.[17] In our study, patients could be managed with 9.04±3.51 vials in mild, 18.5±5.27 vials in moderate, and 28.6±7.30 vials in severe envenomation. A study conducted by Srimannarayana et al., showed that the average requirement of ASV was 12.8 vials in

Table 6: Complications, treatment details, and outcomes of patients

	Mild (n=22)	Moderate (n=38)	Severe (n=20)	P value
Cellulitis	9 (17.6%)	26 (50.9%)	16 (31.37%)	0.0222
Fasciotomy	0	0	3 (15%)	0.0093
Coagulopathy	0	10 (26.31%)	6 (30%)	0.0083
Transfusion (FFP/packed cells/whole blood)	0	0	6 (30%)	0.00005
Whole blood	0	0	2 (10%)	
Whole blood/packed cell/FFP	0	0	1 (5%)	
Packed cell/whole blood	0	0	1 (5%)	
Whole blood/FFP	0	0	2 (10%)	
Respiratory paralysis	0	2 (5.2%)	5 (25%)	0.0095
Ventilatory support	0	2 (5.2%)	5 (25%)	0.0095
Renal failure	0	3 (7.8%)	5 (25%)	0.0022
Need for dialysis	0	0	1 (5%)	0.2189
Lag time (h)	3.31±1.35	4.25±5.02	8.99±8.2	0.002
Average number of ASV vials	9.04±3.51	18.5±5.27	28.6±7.30	<0.0001
Duration of hospital stay (mean±SD)	2.63±1.09	4.65±1.91	7.21±6.4	0.0003

P<0.05 statistically significant

mild, 17.9 vials in moderate, and 23.3 vials in severe envenomation.[17] In Murgan et al., study average ASV vials required was 8.57±0.98 in mild, 12.68±5.09 in moderate, and 20.78±4.18 in severe envenomation.[14]

Hegazy et al. reported that a dose of (21.06±10.89) ASV vials is required to manage severe envenomation cases with fewer complications compared to the low-dose group.[18]

In contradictory Cherian et al.,[19] studies have shown that the average number of ASV required is 5.22±1.86 in mild, 5±1.07 in moderate, and 8.78±3.63 in severe envenomation.

We also noticed that complications such as ARF (10%), respiratory paralysis (8.75%), and coagulopathy (20%) were less compared to Murgan et al. study which showed coagulopathy (62.20%), sepsis (15.85%), ARF (14.63%), and respiratory failure (19.5%).[14]

Cherian et al.,[19] study showed 12.9% cases of ARF and 12.9% cases of neuroparalysis.

Probable reasons for the higher requirement of antivenom therapy in the current study may be due to delay in lag time in the severe envenomation category and to lower the risk of development of late complications such as worsening of cellulitis, renal failure, and coagulation abnormalities.

In contrast to the present study, Gadwalkar et al. and Tariang et al., studies have shown that small doses had an equivalent effect as large doses with lesser complications than high dose group.[20] Overall mortality was 5% in the severe envenomation group. One of them was in shock at the presentation and went on to develop multi-organ dysfunction and the other deaths were due to respiratory failure.

Limitations of the study

Severity of symptoms might be affected by other preexisting medical conditions (diabetes, hypertension, ckd) before snake bite which is not collected in the current study.

CONCLUSION

- Incidence of snakebite is common in rural areas; taking precautionary measures such as wearing protective footwear, carrying a stick, and approaching debris cautiously are perhaps the most effective tools that might significantly bring down the occurrence of snakebite
- From this study, we conclude that the optimum dose of ASV required in mild, moderate, and severe envenomation is 9.04±3.51 vials, 18.5±5.27 vials, and 28.6±7.30 vials, respectively, to neutralize the circulating venom and to lower the risk of development of serious complications
- To adverse ASV reactions, mild adverse reactions such as chills, itching, rashes, and vomiting were observed in 22.5% of patients. Only one case developed anaphylactic shock which was treated satisfactorily.

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Authors Contribution:
KS- Study design, data acquisition, interpretation of the results, reviewed the literature and manuscript, and prepared the draft of the manuscript; **NGK and SGN-** Statistical analysis and editing of the manuscript.

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