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Clinical Profile and Outcome of Children with Snake Envenomation

Rehna Nabeel, MD; Jhuma Sankar, MD; Leena Priyambada, MD; S Mahadevan, MD

Abstract

Background: Few studies have evaluated the demographic characteristics, clinical profile and outcome of children with snake envenomation prospectively.

Objectives: To evaluate the clinical profile and outcomes of critically ill children with snake envenomation

Methods: This prospective observational study was conducted over a 2 year period from November 2007 to January 2010 in a Pediatric intensive care unit of a tertiary care teaching hospital. Children less than or equal to 12 years of age admitted to our hospital with a definitive history of snake bite were enrolled in the study. Children were treated as per the World Health Organization guidelines on the management of snake bite in children (2005).

Results: Out of 67 children studied, 70% (n=47) were males. The presenting features were hemotoxic in 42 (62.7%), neurotoxic in 12 (18%), and only local symptoms in 13 (19.4%) children; bleeding from the site of bite and mucosa was the commonest manifestation. Use of pre-hospital first aid measures such as tourniquet and/or native treatment was found in 25% and 12% of the children respectively. While all children with hemotoxic and neurotoxic features received anti-snake venom, only nine with exclusive local symptoms required it. Ventilation, inotropes, blood products and dialysis were required in 14 (21%), 7 (10%), 11 (16%) and 11 (16%) patients respectively.

Of the 67 children, 10(15%) died and 3 (4.5%) had major disability in the form of necrosis and/or skin graft. The commonest causes of death were acute kidney injury and disseminated intravascular coagulation (4 and 3 respectively).

Conclusion: Majority of children had features of hematotoxic envenomation. One fifth of the study population had poor outcomes in the form of death and/or major disability.

Key words: Snake envenomation; Snake antivenom; Hematotoxic; Neurotoxic; Snake bite; Whole blood clotting time.

INTRODUCTION

Fear of snakes is an innate human emotion from time immemorial. Globally 421,000 envenomings and 20,000 deaths occur each year due to snakebite. These figures may be as high as 1,841,000 envenomings and 94,000 deaths. The highest burden exists in South Asia, Southeast Asia, and sub-Saharan Africa where approximately >100000 envenoming's occur annually [1]. However, despite all the fear and the high burden of mortality and morbidity associated with this disease it is often a neglected specialty of medicine. In order to increase awareness of this condition among researchers and policy makers snake bite was finally included in the World Health Organization's list of neglected tropical diseases [2].

Among the South East Asian countries India has emerged as the country with the highest mortality due to this deadly disease. In the first ever community based survey of snake bite deaths in India based on the verbal autopsy method, Mohapatra et al estimated that a total of 567 deaths (0.47%) could be assigned to snake bites [3]. Deaths mostly occurred in rural areas

Author's Affiliations: Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry

Reprints Requests: Dr. S Mahadevan, Professor, Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.

E-mail: smaha1232@rediffmail.com

(97%) during the monsoon months (June-September) and affected the males (59%). The overall age standardized rate was 4.1/100000 (99% CI: 3.6-4.5) with highest incidence in Andhra Pradesh (6.2/100000 population per year). Of the thirteen states with the highest incidence of snake bites Andhra Pradesh, Uttar Pradesh and Orissa are the worst affected [3]. Annually 459000 deaths (99%CI: 40900-50900) could be attributed to snake bites in our country and more than one quarter of these deaths occurred in children aged 5-14 years of age. Therefore, it is only apt that snake bite be considered a national medical emergency in general and in the pediatric age group in particular in the Indian subcontinent [4].

Several studies, mostly retrospective, have evaluated the demographic characteristics, clinical profile and outcome in both adults and children [5-9] with snake envenomation. There are only 2 prospective studies in children with snake bite till date from the Indian sub-continent published almost 2 decades ago. Several important changes have taken place in the country from the time of their publication. For example with rapid urbanization, improvement in health care facilities and the development of World Health Organization guidelines (2005) [10] snake antivenom has been made freely available even at the level of primary health centers. This could have had a positive impact on the critical outcomes of children with snake envenomation. We therefore undertook this study with the objective of evaluating the clinical profile and incidence of poor outcomes in children with snake envenomation.

METHODS

We conducted this prospective observational study over a 2-year period from November 2007 to January 2010. We enrolled all children aged d"12 years with a definite history of snakebite. We excluded children with previously diagnosed chronic renal disease, congenital heart disease or any other chronic illness. The study protocol was cleared by the Institutional Ethics Committee and written informed consent was obtained from one of the parents.

Outcome variables and their measurement

The primary outcome variables were (a) the clinical profile of children with snake envenomation and b) incidence of poor outcome, defined as death or major disability such as need for amputation, skin graft, or motor weakness.

We prospectively collected information regarding the age, gender, pre-hospital factors, hospital course, details of SAV administration and clinical outcomes in a prestructured proforma.

Management of children with envenomation

We followed a uniform protocol for management of children with snake envenomation throughout the study period as per the 'WHO guidelines for management of snake bites in the South East Asian region' [10] and its Indian adaptation the 'National Snake bite protocols 2007' [11]. Accordingly, the diagnosis of snake envenomation was based on one or more of the following features - history of snake bite, presence of fang marks, presence of local manifestations such as pain and swelling at the site of bite or systemic manifestations such as spontaneous bleeding or features of neurotoxicity and/or if the dead snake was brought in for identification. The dead snakes when brought in were sent to the forensic lab for identification of the species. Once the diagnosis was confirmed, all children requiring SAV administration were shifted to the intensive care unit (ICU) for continuous monitoring.

Snake antivenom

Definitive therapy in the form of polyvalent snake antivenom (SAV) serum (manufactured by Serum Institute of India, Pune) which contains antiserum against *Naja Naja, Bungarus. Caerulus, Vipera. Russeli and Echis Carinatus* was administered as per the recommendations of the protocol [10]. The initial dose of SAV administered was 8-10 vials for hematotoxic as well as neurotoxic bites as per the recommendations of the protocol. This was administered by the infusion technique by diluting the required amount in 5ml/kg of isotonic fluid (dextrose normal saline) and administered over 1 hour. The resident on duty monitored the patients continuously during this period to watch for any adverse reactions. In case of a reaction the infusion was stopped and the patient administered intramuscular epinephrine, chlorpheniramine and hydrocortisone as per the recommendations of the protocol. The SAV was restarted once the patients' allergic symptoms abated [10, 15].

Subsequent doses of SAV in hematotoxic bites were administered based on the WBCT which was performed every 6 hours to determine the need for additional SAV. In patients with on-going bleeding repeat doses were administered within 1-2 hours of the initial dose. In cases of neurotoxic bites further doses were repeated based on progression of symptoms such as ophthalmoplegia, respiratory paralysis and/or quadriparesis after 1-2 hours of the initial dose. Once complete flaccid paralysis had set in no further doses of SAV were administered. These patients were then managed with only supportive care of the airway and ventilation. Atropine neostigmine test was performed in all cases of suspected neurotoxic bites. Those children who responded to this test were given repeat doses as per the doses recommended in the protocol till their symptoms improved completely. In cases where the snake was identified as a krait, no further doses were repeated if the children did not respond to the first dose [10, 15].

Enrolled children were managed with intravenous fluids, inotropes, antibiotics and blood products, and mechanical ventilation and dialysis as and when necessary. All children were administered tetanus toxoid vaccine depending on their recent immunization status. The children were shifted out of the ICU once they did not require intensive and continuous monitoring. Subsequently, they were discharged from the hospital as per the discretion of the treating physician.

Statistical analysis

Data was collected using a predesigned performa and entered in EpiInfo™ version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA). Statistical analysis was done using *Stata 9.1* (StataCorp, College Station, TX). Data were presented as mean (SD), number (%) or median (IQR) as appropriate. Categorical variables were compared between the groups using Chi-square /Fisher's exact test. Continuous variables were compared between the groups using either independent Student's t-test or Wilcoxon rank-sum test (based on the distribution of the data).

RESULTS

Baseline characteristics and type of envenomation

Sixty seven children were eligible for enrolment during the study period. The baseline characteristics of the study population are described in *Table 1*. The mean age of the study subjects was 7.1 years, ranging from 1 to 12 years with majority of them 47 (70.2%) being males. Majority of the children were in the age group of 0-5 years (n=26; 39%) while 30% (n=20) and 31% (n= 21) belonged to the 5-10 years and > 10 years category respectively. The male female ratio was 2.4: 1 in the study group.

All except one were from rural areas (99%). Most of the bites, 37.3% (n=25) occurred while the child was sleeping and during the night, (n=44, 66%). Except for one, all were sleeping on the floor. Twenty two (32.8%) cases were bitten while they were playing and 15 (22.4%) cases while they were walking outside. Most common site of bite was below ankle in more than half the children (n=36) followed by below elbow in 34% (n=23) of children. Fang marks were present in majority (n=57; 85%) of the cases. Snake colour could be identified in only 31 (46.3%) cases and most of them were black coloured (83.9%). Species identification was done in only 22 (32.8%) cases and most of these (77%) were vipers. Only 3 cobras and 2 kraits were identified.

Table 1 : Baseline characteristics, clinical features, laboratory manifestations and type of envenomation

Variable	N=67
Age in years	7.5(5, 11)
Sex (Male: Female)	47:20
Presence of fang marks	57(85.1)
Type of envenomation	
Hemotoxic	43(64.2)
Neurotoxic	13(19.4)
Only local symptoms	11(16.4)
Patients receiving native treatment before hospitalization	8(11.9)
Tourniquet applied in	26(38.8)
No of patients visiting PHC prior to hospitalization	40(59.7)
No of patients receiving SAV at PHC	40(100)
No of vials received at PHC	3.5(1,8)
Time taken to reach any health facility(hrs)	5 (4, 9)
Time elapsed between admission at primary health center and referral	7(4, 11)
Signs and symptoms at admission	
Local swelling	60 (89.6)
Local lymphadenopathy	34(50.8)
Bleeding manifestations (local/systemic)	36(54)
Respiratory failure/ distress	13(19)
Ptosis	13(19)
Capillary leakage/shock	7(10)
Investigations	
Abnormal 20-min whole blood clotting time test at admission	30(44.8)
Abnormal 20-min whole blood clotting time test abnormality at 24 hrs	6(20)
Hemoglobin <8gm/dl	11(16.4)
D-dimers +	6(8.9)
Abnormal renal function tests	11(16.4)
Potassium levels (>5)	5(7.4)

PHC, Primary Health Centre; SAV, Snake Antivenom;

Data is expressed as n (%), median (IQR) or mean (SD) as appropriate

Native treatment was given to 8 (11.9%) cases. Of the 8 cases, half of the cases had cut over the bite area. The other native treatment included oral powder ingestion, balm application, lime application, ingestion of pig oil and squeezing. Tourniquet was applied in 26 (38.8%) cases. None in our study group had immobilized their bitten part. Majority had walked less than one kilometer to reach home or hospital (n=65; 97%).Only 2 cases had walked more than a kilometer. Majority reached hospital whether PHC or JIPMER in 1to 6 hours (n=36; 53%). About 21(31.3%) patients had reached hospital within 1 hour as against 10 (14.9%) cases who reached hospital only after 6 hours. Of the 67 cases, 63% were hemotoxic bites (n=42). Rest were divided almost equally among those with neurotoxic envenomation (n=12; 18%) and local envenomation (n=13; 19%).

Manifestations of envenomation

Vomiting (14.9%) and abdominal pain (5.9%) were the most common systemic manifestations. Limb swelling was present in 59 (89.9%) cases and 34 (50.8%) cases had local lymphadenopathy. Of the 42 hematotoxic bites, bleeding from the bite site was seen in 28 (66.7%) cases, mucosal bleeds were present in 10 (23.8%) cases and hematuria in 4(9%) children. Of the 12 neurotoxic bites, ptosis and respiratory paralysis were the predominant manifestations in majority of the cases (n=8, 66.7%). Other clinical features of neurotoxic bites included dysphagia in 3 cases, seizures in 2 cases and diplopia and slurring of the speech in one case

Treatment details

Sixty-three children received SAV either from JIPMER or PHC. It was not given in 4 children who had only local symptoms as it was not satisfying the WHO criteria for SAV administration (*Table 2*). 26 (41%) children received SAV within 1 to 6 hours of bite. The median dose for non-survivors was 15 vials as compared to 10 vials for survivors (p=0.03). Seventeen children (27%) had local/systemic reactions to SAV, the most common reaction being hypotension (n=6). Hemotoxic bites required more number of SAV vials 11.5 (10, 29) than neurotoxic bites, 19 (10, 30). Ventilation, inotropes, blood products and dialysis were required in 14(21%), 7(10%), 11(16%) and 11(16%) patients respectively.

Outcome

Of the 67 children, 10 (15%) died and 3 (4.5%) had major disabilities like skin necrosis *(Figure 1)*. Of the 10 children who died, 9 had features of hematotoxic envenomation of which 4 and 3 children died of either acute kidney injury or disseminated intravascular coagulation respectively. The remaining two children with hematotoxic envenomation died of refractory shock. The only child who died following neurotoxic envenomation presented with respiratory failure, and had seizures followed by cardiac arrest within one hour of admission. All the three children with major disabilities had cobra bites with features of neurotoxic

Table 2 : Treatment details and outcome of patients with envenomation

Parameters	N=67
SAV administered	
Hemotoxic	43/43(100)
Neurotoxic	12/13(92)
Only local symptoms	8/11(72.7)
Time to initial SAV administration	
<1 hr	22(34.9)
1-6 hours	25(39.6)
>6hours	16(23.5)
Dose of SAV administered	11(8,18)
Hemotoxic	11(8,15)
Neurotoxic	17(6.4)
Local symptoms	9(3.5,16.5)
Children with SAV reaction	17(25.4)
Atropine-Neostigmine administered	7/13(53.8)*
Mechanically ventilated	14(20.9)
Inotropic support	7(10.6)
Dialysis(peritoneal/hemodialysis)	11(16.4)
Blood products	11(16.4)
Duration of hospital stay	5(3,10)
Outcome	
Discharge	54(80.6)
Death	10(14.9)
Disability (skin grafting/prostheses)	3(4.5)

Figure 1 : Local tissue necrosis secondary to Cobra bite

envenomation. They required skin graft for necrosis following compartment syndrome.

DISCUSSION

Snake bite remains a public health problem in most developing countries though the precise numbers may be an underestimate. Snake bite has always been an intractable problem and still continues to exact a tremendous toll in human suffering and mortality in India. The epidemiological features of snake bite vary from region to region.

In this prospective observational study, sixty seven patients with snake bite were included. The epidemiological profile, clinical features, treatment and outcome was studied. Majority were males. It may be that boys are more playful and tend be outside rather than girls and that is the reason for having a male preponderance. Similar observations have been made by Kulkarni et al [7] and Hon et al [13] in which males were 68.4% and 86% respectively.

The children were almost equally distributed in the age groups-0-5 years, 5-10 years and > 10 years with slight preponderance in 0-5 years' group. This was somewhat different from that reported by Kulkarni et al [7] who found majority of the cases in the age group of 11-15 years. Younger children are usually kept closer to their mothers and sleep on the beds as compared to older children who may sleep outside with their fathers in villages. However, in our study most of the children were sleeping on the floor and most of the bites were in the night. This may probably explain the preponderance of under-fives. There was no difference between non survivors and survivors with regard to age and sex distribution.

Venomous snakes are distributed through out warm continents. Only in 23 (34.3%) of the 67 cases we were able to accurately identify the species of snake. Vipers are the most abundant snake species in South India and therefore it was not surprising that of the 23 identified species, 17 (74.9%) were vipers.

The pre- hospital treatment found in our study included native treatment, application of tourniquet and immobilization. Despite national guidelines on snake bite management and do's and don'ts of snake bite laid down clearly by the policy makers and supported by literature the practice of applying tourniquet and giving local treatment has not changed. Most of the first aid like tourniquet, cutting etc currently carried out is ineffective and dangerous [13].

Tourniquet was applied in 38.8% cases. It was the most commonly used first aid measure as previously studied by Bawaskar in Western Maharashtra, India [14]. Among 67 cases, tourniquet was applied in 38.8% of cases. Thirty percent of non-survivors and 40% of survivors had applied tourniquet the difference being statistically insignificant. Tourniquet increases the risk of ischemia and loss of the limb [15]. Most of our snake bite victims are from rural areas and unaware of the correct method of application. Since tourniquet is still used in more than one third of cases, it indicates that lay persons may not be aware that these practices are now not recommended in the treatment of snake bite.

Incision leads to uncontrolled bleeding, damages nerves, blood vessels or tendon and may introduce infection. Suction, chemicals and cryotherapy lead to necrosis of tissues. Suction devices increase envenomation as they inhibit natural oozing of venom from the wound and they have been shown to increase the local effects of necrosis [16]. Current recommendation in the protocol is to immobilize in the same way as a fractured limb. Pressure immobilization was initially recommended for neurotoxic elapid bites including sea snake but should not be used for viper bites because of the danger of increasing the local effects of the venom.

None of the children had practiced immobilization bandage over the bitten extremity. The message has to be propagated among public about the benefits of immobilisation. Spread of venom appears to be a result of compression of lymphatics and superficial veins, and reduction of lymph flow. Immobilization is thus a critical factor in determining outcome after envenomation as it prevents the transit of venom.

The manifestations of snake bite varied from local symptoms to systemic ones. Local reaction included swelling and lymphadenopathy. Viper venom usually produces more local effects because of the vasculotoxic effects. Our study had predominantly hematotoxic manifestations manifesting as hemostatic abnormalities in the form of abnormal WBCT test, bleeding from the bite site, mucosal bleeds and hematuria. Kulkarni et al showed similar findings in their study in which 55.9% cases had hemorrhagic syndromes[7]. The neuroparalytic features seen in descending order of frequency were ptosis, respiratory paralysis, dysphagia, seizures, diplopia and slurring of the speech. The incidence of ptosis correlated with studies done by Kularatne [17] and Seneviratne in Srilanka [18].

The main stay of snake bite treatment is SAV. Although the dose of antivenom is not fixed, the indications are well known [11, 15]. After the introduction of the National snake bite protocol, both risk and wastage of SAV are reduced to negligible levels consistent with optimal snake bite management *(unpublished data*). Of those who received SAV, majority received it within the first 6 hours whether in PHC or JIPMER. Studies have shown that if SAV is received late, more complications can arise [9]. The availability of treatment, particularly close to the scene of the bite, is a crucial factor in ensuring good outcome [19].

Although a mainstay of therapy the benefits and risks of SAV have to be weighed before administration and continuous bedside monitoring is quintessential to its administration. Despite strict monitoring and standby emergency resuscitation measures, deaths have been reported with the administration of this antidote.

SAV reactions were observed in one quarter of the cases. Various studies have reported the incidence of SAV reactions to be in the range of 14%- 17% [7, 20, 21]. Kulkarni et al [7] in his study had SAV reactions in 8 cases out of 479 cases where SAV was administered. The slightly higher incidence of SAV reaction in our study was probably due to different SAV preparations used in the study. Hypotension was the most common reaction observed in our study. One child expired as a consequence of hypotension following SAV administration.

Of the neurotoxic bites ventilation was required in 58% of the cases. Respiratory arrest is a common complication in neurotoxic bites as compared to hemotoxic bites where it may be a delayed complication secondary to shock or AKI. The mean duration of ventilation was 84 hours which was higher than that reported previously by Agarwal et al where the median duration of ventilation was only 17 hours [21]. As atropine neostigmine test was negative in all the cases done, it was attributed that they were krait bites and that may be the reason why the mean duration of ventilation was higher.

The mortality rate reported in previous studies from our country ranged from 3-5% [7,8]. In our study the mortality rate was 14.9% which was higher in comparison to these studies. We presume the differences in the severity of envenomation and the availability of resources to be the possible reasons for the higher mortality rate observed in our study. Being a referral hospital, children with severe envenomation are more likely to be referred to our center from a primary care facility. Three children in our study had major morbidities like skin necrosis requiring grafting, and paralysis of a limb.

CONCLUSION

To conclude hematotoxic envenomation is the commonest type of envenomation in children with snake bite in this part of the country. One fifth of the study population had poor outcomes in the form of death and/or major disability.

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