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RESEARCH ARTICLE

Clinical and Laboratory Predictors of Mortality Following Snake Bite Envenomation in Children in Central India: A Retrospective Observational Study

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Abstract

Background: About half of global deaths following snake envenomation occur in India and proportionally highest mortality at ages 5-14 years. Very few studies have evaluated clinical and laboratory predictors of mortality in children.

Objective: Evaluation of clinical and laboratory parameter associated with mortality of snake envenomation in children

Design: Retrospective observational cohort study.

Material and Methods: Medical record files of children of snake envenomation, between the periods of Jan 2011 to February 2016 were recovered from Medical Record and Statistics Section of institute. Files were analyzed for demographic data; variables included site of bite, time of bite, type of primary treatment and treatment provider, and type of snake envenomation, laboratory investigation and outcome.

Result: Of 46 children studied 37 (80.43%) were > 5 years and male to female ratio is 1.4:1. Lower limb was commonest site of bite in night time and mostly in monsoon. Local edema and vomiting was commonest presentation. Most 26(56.53%) had predominantly vasculotoxic envenomation while 14(30.43%) predominantly neurotoxic and 6(13.04%) mixed envenomation. 9 children died giving case fatality rate 19.56%. On univariate analyses following variables were found to be significantly associated mortality: age more than 5 years ($p=0.03$), diplopia ($p=0.001$), ptosis ($p<0.001$), altered consciousness ($p<0.001$), cellulitis (0.001), respiratory failure ($p=0.001$), hypotension ($p=0.04$) requiring inotropic support, and prolonged prothrombin time ($p=0.02$). None of the variables were significant on multivariate analysis.

Conclusion: Age >5 years, diplopia, ptosis, altered consciousness, cellulitis, respiratory failure, hypotension requiring inotropic support, and prolonged prothrombin time were the factors that increases the mortality of envenomed children. These prognostic variables can help pediatrician predict outcomes, may influence treatment decision and may reduce in-hospital mortality following snake envenomation.

Keywords: Envenomation; Central India; Predictors; Snake Bite; Risk Factors

Introduction

Venomous snakes are mysterious reptiles found all over world except the polar and high mountain areas [1]. Snake bite envenomation is an acute life threatening public health problem in many tropical and subtropical countries. Mortality after snake bite is preventable if the victim receives timely treatment. Snake bite was re-added in the list of neglected tropical disease by World Health Organization in the year 2017 [2]. The real burden of snake bite envenomation is underestimated due to inadequate datasets and most victims succumb themselves to self –cure at home using traditional treatment. The highest number of envenoming were reported in South Asia, South-east Asia and Sub-Saharan Africa where more than 100000 envenoming incidents occur annually [3,4]. Globally, every year, around 1.8- 2.7 million people develop serious clinical illnesses after snake bites, and greater than 95000 die and 300000 survive with permanent disability or disfigurement [5]. About half of global death occurs in India of which are due to 250000 incidents of snake bite, and proportionally highest mortality occurred at ages 5-14 years. However, India is not home for the largest number of venomous snakes in the world, nor is there a shortage of antisnake venom in the country [6]. A National Snakebite Treatment Protocol has been developed, and approved by Directorate General of Health Services, Government of India (August 2007) for uniform implementation throughout the country [7].

Several studies have evaluated the demographic characteristic, clinical profile and outcome of snake envenomation in children, and most of the studies in adults have evaluated clinical and laboratory predictors of mortality in adult but there are very few studies in pediatric population [8-18]. Therefore, we undertook this study with the objective of evaluation of clinical and laboratory parameters associated with mortality in children with snake envenomation. Such information would help in identifying children who need urgent referral from the primary care level and deciding the extent of support required in children admitted with snake envenomation in referral centre.

Material and Method

This cohort of snake bite cases were retrospectively studied at one of the largest tertiary care & referral hospital that provide care to underprivileged, socioeconomically deprived population of central India from Jan 2011 to December 2016. As required by the government of Maharashtra, all snake bites were classified as medico-legal cases, and their records were kept separately in medical record section. After retrieving the registration number, the medical records were obtained from the medical case files from the Medical Record Section and Statistical Service of the institute. After approval from Institutional Ethics Committee, data were collected on pre-designed Proforma for this study. We reviewed all the relevant data needed for our analysis. Besides demographic data, the analyzed variables included site of bite, time of bite, type of primary treatment and treatment provider, type of snake poison, whether cases had been directly admitted to this hospital or referred from other health centers, time interval between snake bite and hospitalization, common symptoms suggestive of hematotoxicity, myotoxicity and neurotoxicity, local symptoms including fang marks, condition of wound and initiation of treatment.

Cases where the patients were discharged against medical advised were excluded. Cases of unknown bites in the absence of fang marks or any other symptoms not suggestive of venomous snake bites were also excluded.

Detailed systemic and local examinations findings were recorded in all patients. Routine and specific investigations were done, these includes complete hemogram, platelet count, peripheral smear, renal function test, liver function test, urine examination (protein, blood, hemoglobin, myoglobulin), bleeding time, clotting time. Specific investigation includes serum electrolytes, prothrombin time, activated prothrombin time and electrocardiogram in some patients.

All patients were treated as per protocol [7]. Neostigmine along with atropine was administered to patients with neuroparalysis till reversal of neurotoxic manifestation. All patients were studied for complication during hospital stay. Blood/platelet transfusion, ventilatory support and dialysis were carried out as and when indicated. Patients developing severe cellulitis received appropriate antibiotics and anti-inflammatory agents.

Statistical Analysis

The data was entered into Microsoft excel sheet and analysis was done by using software STATA version 14. Quantitative data were presented as mean ± SD while, qualitative data were expressed in frequency and percentages. Continuous variables were compared between survival and non-survival by performing independent "t" test for normalized data and Mann-Whitney test for non-normalized data. Categorical variables were compared by Chi-squre test. For small numbers Fischer Exact test was used wherever applicable. Multiple logistic regressions were performed to identify significant risk factors of mortality. Adjusted odds ratio and 95% confidence interval were calculated. A P value of less than 0.05 was considered as statistically significance.

Result

Demographic Characteristic

Eighty patients of snake bites were admitted, of which 34 did not show any signs of envenomation and were excluded from the study. Forty six patients had signs of envenomation and were included in study. Thirty seven (80.43%) patients were more than 5 years of age with mean age 7.52 ± 0.70 years. The male to female ratio was 1.4:1.Most of them (67.40%) were from rural areas and lower socioeconomic class where toilet facilities was not available and had faced electric load shedding at night time and so most of bites were 31(65.40%) in night time & lower limb was the commonest site of bite (Table 1). Maximum number of patients were admitted in monsoon 29(63.04%), followed by summer 8 (17.39%), post monsoon 5 (10.87%) and winter.

Most of the children received primary treatment from Medical personnel but 6.52% from village health healer and only 36.96% received ASV, tourniquet application 2.17% as a primary treatment. 52.17% children received primary treatment within 1 hour and were admitted in institute within 6 hours of bite.

Variable	With envenomation (n=46), %
Age (years) (mean ± SD)	7.52 ± 0.70
Male gender	27(58.70)
Time of bite (night)	30(65.21)
Residence (Rural)	31(67.40)

Variable	With envenomation (n=46), %
Socioeconomic status	
Middle	14(30.43)
Lower	32(69.57)
Toilet facility (yes)	36(78.26)
Electric load shedding (yes)	24 (52.17)
Site of bite	
Upper limb	17(36.96)
Lower limb	29(63.04)
Primary treatment provider	
Medical person	34(73.91)
Paramedical staff	9(19.56)
Village health healer	3(06.52)
Type of primary treatment	
Tourniquet application	1(2.17)
ASV	17(36.96)
Tetanus Toxoid	41(89.13)
Primary treatment <1hr of bite	24(52.17)
Primary treatment >1hr of bite	22(47.83)
Admission <6Hrs of bite	25(54.35)
Admission >6Hrs of bite	21(45.65)
Sign and symptoms at admission	
Local edema	30(65.20)
Local pain	20(43.48)
Vomiting	30(65.21)
Diplopia	7(15.22)
Altered consciousness	10 (27.74)
Ptosis	5(10.87)
Cellulitis	22(47.83)
Hypotension	6(13.04)
Respiratory paralysis	4(8.70)
Acute renal failure	5(10.87)
Type of envenomation	
Predominantly vasculotoxic	26 (56.53)
Predominantly neurotoxic	14(30.43)
Mixed	6(13.04)
Investigation	
Admission Hb% (mean ± SD)	10.97 ± 2.68
INR (mean ± SD)	1.15 ± 0.06
Creatinine (mg/dl) (mean ± SD)	0.79 ± 0.21
PT (sec) (mean ± SD)	14.22 ± 0.70
PTTK (sec) (mean ± SD)	26.03 ± 3.53
Outcome	
Discharge	37(80.43)
Death	9(19.57)
Hospital stay	
Length of stay (days)	1-31
Mean stay (days) (mean ± SD)	11 ± 5.65

Table 1: Baseline characteristics, clinical, laboratory features, treatment and outcome of children with snake envenomation

Clinical Presentation and Complications

Local edema and vomiting was the commonest presentation followed by local pain in 43.48% in vasculotoxic and neurotoxic bite but altered consciousness (27.74%), diplopia (15.22%), and ptosis (10.87%) in neurotoxic bite. Cellulitis was the most common complication. Hypotension and acute renal failure was observed in vasculotoxic envenomation and respiratory failure in neurotoxic bite.

Outcome

Of the 46 children, 9(19.56%) died. Out of 9 children who died, four had predominantly vasculotoxic envenomation and died of acute renal failure and refractory shock. Three children with predominantly neurotoxic envenomation died due to raised intracranial pressure and respiratory paralysis. Two children of mixed presentation who died due to disseminated intravascular coagulopathy and refractory shock.

Risk Factor for Poor Outcome:

On univariate analysis, the following variables were found to be significantly associated with mortality: age more than 5 years, diplopia, altered consciousness, ptosis, cellulitis, hypotension, and respiratory failure and prothrombin time (Table 2). On multivariate logistic regression of all variables included in the univariate analysis, we did found any risk independent risk factors significantly associated with mortality (Table 3). Other variables were dropped because of co-linearity.

Variables	Non-survival (n=9)	Survival (n=37)	P Value
Age (mean ± SD)	6 ± 3.42	7.89 ± 1.41	0.01
Age ≥5years	5(55.55)	32(86.49)	0.03
Male gender	7(77.78)	20(54.05)	0.39
Primary Treatment provider			
Medical person	7(77.78)	27(72.97)	1.00
Paramedical staff	1(11.11)	8(21.62)	0.80
Village Health Healer	1(11.11)	2(5.41)	1.00
Type of primary treatment			
Tourniquet application	1(11.11)	00	
ASV	5(55.55)	12(32.43)	0.19
Tetanus Toxoid	7(77.78)	34(91.89)	0.19
Primary treatment <1hr of bite	3(33.33)	21(56.76)	0.20
Primary treatment >1hr of bite	6(66.67)	16(43.24)	0.20
Admission <6Hrs of bite	6(66.67)	19(51.35)	0.40
Admission >6Hrs of bite	3 (33.33)	18(48.65)	0.40
Local edema	7(77.78)	28(75.67)	0.89
Vomiting	6(66.67)	20(54.05)	0.49
Diplopia	7(77.78)	8(21.62)	0.001
Altered consciousness	9(100)	12(32.43)	<0.001
Ptosis	9(100)	12(32.43)	<0.001
Cellulitis	2(22.22)	29(78.38)	0.001
Hypotension	3(33.33)	3(8.10)	0.04
Respiratory failure	8(88.89)	11(29.73)	0.001
Acute renal failure	3(33.33)	5(13.51)	0.15
Type of envenomation			
Predominantly vasculotoxic	4(44.44)	22(59.46)	0.41
Predominantly neurotoxic	3(33.33)	11(29.73)	0.83

Variables	Non-survival (n=9)	Survival (n=37)	P Value
Mixed	2(22.22)	4(11.76)	0.36
Investigation			
Admission Hb%	10.96 ± 1.10	10.68 ± 2.82	0.77
INR	1.2 ± 0.07	1.2 ± 0.07	1.00
PT (sec)	15.56 ± 2.37	14.68 ± 0.1	0.02
PTTK(sec)	26.22 ± 1.68	26.69 ± 2.82	0.63
Creatinine(mg/dl)	0.95 ± 0.5	0.8 ± 0.14	0.11
Length of stay(days)	1-15	1-31	
Mean stay (days)	4.43 ± 4.43	5.86 ± 5.13	0.12

ASV: Anti Snake Venom; INR: International Normalized Ratio; PT: Prothrombin time; PTTK: Partially Activated Prothrombin Time

Table 2: Univariate logistic regression of factors affecting outcome in children with systemic envenomation

Variables	Non-survival	Survival	Adjusted OR (95% CI)	P value
Age >5 years	5(55.55)	32(86.49)	0.35(0.01-7.11)	0.497
Diplopia	7(77.78)	8(21.62)	2.45(6.12-47.83)	0.553
Hypotension	3(33.33)	03(8.10)	164.58(0.05-119.07)	0.307
Cellulitis	2(22.22)	29(78.38)	0.049(0.00-165.72)	0.468
Prothrombin Time (Sec)	15.56 ± 2.37	14.68 ± 0.1	0.59(0.28-1.23)	0.161

Table 3: Multiple logistic regressions of factors for predictors associated with outcome with snake envenomation.

Discussion

Snake envenomation is an important global public health problem in rural tropics except for a few islands, high altitude and frozen environment [1,3]. In India, of the 216 species of snakes found; 52 species are reported to be poisonous and constitutes about 5% of all injury deaths and nearly 0.5% of all deaths [6]. The snake bite mortality is more than 30 folds higher than reported because of underreporting due to most deaths occurring outside health facilities treated by traditional village health healers, lack of transport facilities, electric load shedding in night times, lack of toilet facilities, religious customs. Children are more prone for severe envenomation and mortality due to larger body surface area, smaller extracellular fluid volume, and less protein to bind the circulating venom [19]. Most of the studies in central India evaluated predictors of outcome following snake envenomation in adult but to best of our knowledge ours is the first study evaluating clinical and laboratory predictors of mortality in snake envenomation.

In present study, most of the children were from rural areas of lower socioeconomic class and lower limb was the commonest site of bite. The clinical profile of enrolled children including clinical features, type of envenomation was comparable to previously reported studies in children from India [8,9,18]. The mortality rate in our study was 19.56% which was higher than reported by Sharma, *et al.* from North India (13.3%), Sankar, *et al.* (13%) and Jayakrishnan, *et al.* (10.3%) from South India. Chaudhari, *et al.* reported higher (22.3%) mortality from same institute on adult population. Such a high mortality might be due to rural population facing electric load shedding problem and lack of transport facility in night times, receiving primary treatment from village health healer, delayed reach to hospital and poor knowledge about, and experience in management of snake bite at primary health centers [20]. Similar observations were also reported by Bawaskar, *et al.* [21].

On analyzing the determinants of poor outcome, we found that the age more than 5 years was significantly associated with mortality in contrast to Sankar, *et al.* who reported that younger age group had higher mortality. This might be due to the fact that in our cohort most of the children were more than 5 years age group. Our finding are in concordance with Krishnamurty, *et al.* who observed acute kidney injury was more common in children of more than 5 years age group children in Russell's viper envenomation [22]. Other factors like gender, nocturnal bite, site of bite, primary treatment provider, time from bite to primary treatment and hospitalization did not found statistically significant association with mortality. Various authors reported significant higher mortality in patient with male gender, nocturnal bite, home to hospital distance, bite to hospital time, bite to injection time, rural population, walking for more than 1km after bite in children and adult population [13-16,20,23,24].

In present study, 56.53% children were predominantly vasculotoxic, 30.43% predominantly neurotoxic and 13.04% combined

vasculotoxic and neurotoxic type of envenomation. Similar type of distribution of envenomation was recently reported by Jayakrishnan, *et al*. from South India. Though, local edema, local pain and vomiting were most common presentation but these were not significantly associated with mortality. Children who presented with neurotoxic envenomation like diplopia, ptosis and altered consciousness were significantly associated with mortality. Commonest neurotoxic snake is cobra in our area and most of the authors in central India reported higher mortality in cobra bite in compared to vasculotoxic in north India [13,20]. Sharma, *et al*. observed neurotoxic envenomation, children presented with diplopia, ptosis had higher complication and mortality in children, likewise Pore *et al*. Kalantri, *et al*. and Chaudhari, *et al.* reported similar observation in adult population.

Cellulitis and respiratory failure were observed in neurotoxic envenomation and acute renal failure, refractory shock and disseminated intravascular coagulation were observed in vasculotoxic and mixed envenomation. Mechanical ventilation, inotropic support, renal replacement therapy and fresh frozen plasma were used for appropriate management. Cellulitis, respiratory failure, hypotension were significant predictors of mortality on univariate analysis in our study but none were independent variables on multiple logistic regression model. Sharma, *et al.* observed respiratory failure and hypotension requiring inotropic support were strong predictors of mortality in children while capillary leak syndrome, bleeding tendency, decrease urine output, intracranial bleed, use of mechanical ventilation were the strong predictors of mortality in adult and children.

Haemostatic disturbance is well recognized as an indictor of mortality with high risk. Laboratory parameters like hemoglobin less than 10 gm%, polymorphonuclear leucocytosis on day 1, thrombocytopenia, prothrombin time, partially activated prothrombin time, INR, prolonged 20 minutes WBCT, serum creatinine and albuminuria were indicators of coagulation and renal failure and they are well recognized risk factors of mortality in literature. We found prothrombin time was significantly associated with higher mortality but not as an independent predictors of mortality.

In present study, mortality following snake envenomation depends upon multiple factors. On univariate analysis the risk factors found to be significantly associated with mortality were; age more than 5 years, diplopia, ptosis, altered consciousness, cellulitis, respiratory failure and hypotension requiring inotropic support, prolonged prothrombin time. Gender, primary treatment provider, type of primary treatment, duration of bite and primary treatment or hospitalization, local edema, vomiting and laboratory investigation like hemoglobin at admission, International Normalized Ratio, PTTK time and serum creatinine were not significantly associated. On multiple logistic regression models none of above factors was statistically significant might be due to small sample size. Duration of hospital stay was shorter with non-survival of children compared with survival but the difference was not significant.

Conclusion

Age more than 5 years, diplopia, ptosis, altered consciousness, cellulitis, respiratory failure, hypotension requiring inotropic support, and prolonged prothrombin time were the factors that increases the mortality of envenomed children. These prognostic variables can help the pediatrician to predict outcomes more accurately and parsimoniously, which may influence treatment decision and may reduce in-hospital mortality following snake envenomation. More research is needed on larger patients to validate these finding and to evaluate whether early identification of prognostic indicators and aggressive management can reduce the risk of death in children following snake envenomation, particularly in resource -limited setting.

Limitation

Major limitation of our study was the small sample size that may not have been sufficient to evaluate the association between all of the risk factors and mortality and retrospective in nature.

A multicentre study with about 1000 children would help to correctly identify the risk factors. Other important limitation was that, for logistic regression model, we could not identify independent predictors of mortality probably due to small sample size.

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