ejpmr, 2018,5(5), 392-397

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

VENOMOUS SNAKEBITE- AN OUTCOME BASED ANALYSIS IN A TERTIARY CARE HOSPITAL

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Article Received on 08/03/2018 **Article Revised on 29/03/2018** **Article Accepted on 19/04/2018**

ABSTRACT

Background: Snake bite is the prime of all neglected tropical diseases wherein our health care systems have little success. The spectrum of manifestations range from minimal edema to full blown Multi Organ Dysfunction Syndrome[MODS] and death. The presentation varies according to the geographic location and the regional predominance of various species. Though there are voluminous data on the subject, few researchers have focused on the extrinsic factors leading to adverse outcome after a venomous bite. This study aimed to elucidate the modifiable extrinsic factors which are associated with adverse outcomes after a venomous bite. **Materials and Methods:** A retrospective study was conducted based on the electronic data base and case sheets of snakebite envenomed patients at Government Villupuram Medical College and Hospital. 200 cases of snakebite envenomation were included in the study. Only systemically envenomed adult patients were enrolled. The case records and electronic data base were systematically analysed and the modifiable extrinsic factors associated with adverse outcomes documented. The primary adverse outcomes were acute kidney injury requiring hemodialysis, respiratory failure with prolonged ventilator support, Multi Organ Dysfunction Syndrome[MODS], compartment syndrome and death. For each adverse outcome the associations were noted under 2 separate heads- Clinical findings and management issues. The data were compared with patients who had favorable outcome. The data were compared using a two-sided Wilcoxon rank sum test and the unpaired student's t-test. 'P' value <0.05 was considered as significant. **Results:** A total of 200 patients were included in the study. The male to female ratio was 1.9:1. 77%[154] of cases suffered hemotoxic envenomation , 19% neurotoxic and 4% was a mixture of both. The principle adverse outcome frequency was AKI 22(11%), respiratory failure with prolonged ventilator support 13(6.5%), MODS 8(4%), compartment syndrome 5(2.5%) and death 7(3.5%). AKI was significantly associated with hemotoxic envenomation(90.9%), dehydration(36.3%), shock(36.3%), hematuria(54.5%), delayed presentation[>6 hrs](40.9%) and high dosage of ASV [>20 vials]. Respiratory failure had significant relation with late presentation(76.9%), krait bite(61.5%) and aspiration pneumonitis(38.4%). The management issues showed that (92.3%) weaning protocol was not followed. MODS had a cause and effect correlation with hemotoxic envenomation100% and high dose ASV(87.5%). Finally the ultimate adverse outcome of death was associated with hemotoxic envenomation (85.7%), delayed presentation(71.4%), MODS (100%) and high dose ASV(75%). **Conclusion:** In our study we identified a few modifiable factors which are a significant cause for dismal outcome in snake bite. These include delayed presentation, occurrence of DIC, MODS, dehydration and usage of high dose ASV.

KEYWORDS: Snake bite, Mortality, Adverse outcomes, Modifiable factors.

INTRODUCTION

Snake bite is the prime of all neglected tropical diseases wherein our health care systems have little success. Snakes are ubiquitous, being found throughout most of the world, except in few frozen environments and high altitudes (Anuradhani Kasturiratne, et al., 2008).[1] It is estimated that worldwide, venomous snakes causes "5.4million bites about 2.5 envenomings and over 125,000 deaths annually", "more than 3 million bites per year resulting in more than 150,000 deaths".[2,3] Furthermore, the highest burden of snakebite envenomings and deaths occurs in Southeast Asia and sub-Saharan Africa.[3,4] India takes the brunt of the attack with the highest annual number of envenomation (81,000) and deaths (nearly 11,000).[1]

The spectrum of manifestations range from minimal edema to full blown Multi Organ Dysfunction Syndrome[MODS] and death. The presentation varies according to the geographic location and the regional predominance of various species. Though there are voluminous data on the subject, few researchers have

focused on the extrinsic factors leading to adverse outcome after a venomous bite. This study aimed to elucidate the modifiable extrinsic factors which are associated with adverse outcomes after a venomous bite.

MATERIALS AND METHODS

Study Design: A retrospective study was conducted based on the electronic data base and case sheets of snakebite envenomed patients.

Study Centre: Government Villupuram Medical College and Hospital, Department of Internal Medicine and Medical Records Department.

Sample Size: We collected the data of 200 envenomed patients who were admitted to our hospital between January 2015 and December 2017.

Methodology: 200 cases of snakebite envenomation were included in the study. Only systemically envenomed adult patients were enrolled. The inclusion and exclusion criteria are mentioned in Table 1.The case records and electronic data base were systematically analysed and the modifiable extrinsic factors associated with adverse outcomes documented. The primary adverse outcomes were[Case definitions as per Table 2]:

a) Acute kidney injury requiring hemodialysis.
b) Respiratory failure with prolonged ventilator support.
c) Multi Organ Dysfunction Syndrome[MODS]
d) Compartment syndrome.
e) Death.

All the critical issues relating to outcome like time to resuscitation, time to institution of Antisnake Venom Serum[ASV], dosage of ASV, intensive monitoring, supportive/surgical care, need for ventilator, Fresh Frozen Plasma[FFP] and hemodialysis were noted. For each adverse outcome the associations were noted under 2 separate heads- Clinical findings and management issues. The data were compared with patients who had favorable outcome, namely survival with or without minimal morbidity[Figure 1]. The findings were computed and periodically reviewed.

Data Analysis: Two-sided *P* values were calculated using the chi-square testor Fisher's exact test for (qualitative) dichotomous and ordinal variables. Continuous (quantitative) variables were compared using a two-sided Wilcoxon rank sum test and the unpaired student's t-test. 'P' value <0.05 was considered as significant. Statistical software SPSS version 2.0 was used.

RESULTS

A total of 200 patients were included in the study. The male to female ratio was 1.9:1. 77%[154] of cases suffered hemotoxic envenomation , 19% neurotoxic and 4% was a mixture of both. The principle adverse outcome frequency was:

a) Acute kidney injury requiring hemodialysis. 22(11%)
b) Respiratory failure with prolonged ventilator support. 13(6.5%)
c) Multi Organ Dysfunction Syndrome[MODS] 8(4%)
d) Compartment syndrome. 5(2.5%)
e) Death. 7(3.5%)

The significant associations pertaining to clinical and management issues were compared with favorable outcome group. They are summarized in Table 3. The patients who suffered severe AKI were significantly associated with hemotoxic envenomation(90.9%), dehydration(36.3%), shock(36.3%), hematuria(54.5%), delayed presentation[>6 hrs](40.9%). The management issues which figured prominently were high dosage of ASV [>20 vials], nephrotoxic drugs(18.1%),inadequate intravenous hydration(54.5%). The second major outcome was Respiratory failure requiring prolonged ventilator support which had significant relation with late presentation(76.9%), krait bite(61.5%) and aspiration pneumonitis(38.4%). The management issues showed that (92.3%) weaning protocol was not followed and in (46.1%) patients there was significant delay in initiation of ventilator support. The third main outcome assessed was MODS which had a cause and effect correlation with hemotoxic envenomation100%, Disseminated Intravascular Coagulation[DIC] (75%), AKI(100%),delayed presentation 100% and shock 100%. From management point of view, MODS was associated with high dose ASV(87.5%) and fresh frozen plasma transfusion(75%). Finally the ultimate adverse outcome of death was associated with hemotoxic envenomation(85.7%), delayed presentation(71.4%), MODS and shock(100%). Therapeutically, mortality was associated with high dose ASV(75%).

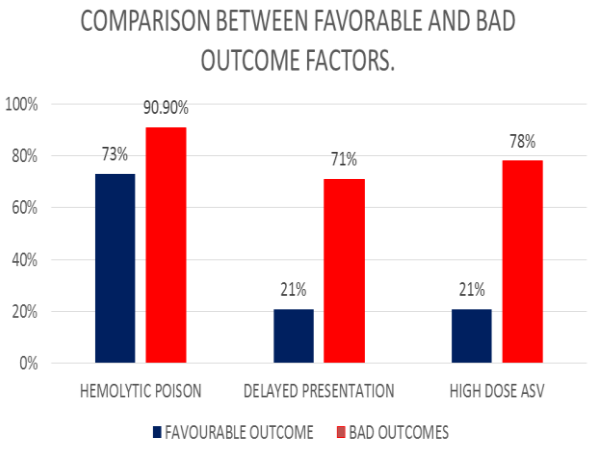

Figure 1: Comparison between factors among patients with favorable and bad outcomes.

Table 1: Inclusion and Exclusion Criteria for Outcome Analysis of Snakebite Patients.

INCLUSION CRITERIA
• **Hospital admitted patients age >18 years** • **History of snakebite** • **Clinical and/or laboratory signs of systemic envenomation.**
EXCLUSION CRITERIA
• **Inpatients with history of snakebite, but no objective clinical or laboratory evidence of systemic envenomation.** • **Patients with multiple comorbidities.**

Table 2: Case Definitions.

Acute Kidney Injury.
• **Rise from baseline creatinineof 0.3 mg% within 48 hrs** • **At least 50% rise from baseline creatinine within 1 week** • **Reduction in urine output <0.5 ml/kg/hr fro 6 hours**
Multiorgan Dysfunction Syndrome
Clinical or laboratory evidence of progressive dysfunction in 2 or more organs or organ systems that is induced by a variety of acute insults.
Respiratory failure requiring prolonged support.
Failure of respiratory function following snakebite requiring ventilator support for > 72 hours
Compartment Syndrome.
Clinical syndrome wherein the tissue pressure within a closed muscle compartment exceeds the perfusion pressure and results in muscle and nerve ischemia.

Table 3. Principle Adverse Outcomes of Venomous Snakebite And Their Associations.

Outcome	Number(n=200) N(%)	Clinical association	Significance P value	Management issues	Significance p value
AKI requiring Hemodialysis	22(11%)	• Hemotoxic poison(20/22) • Delayed presentation(9/22) • Shock(8/22) • Dehydration(8/22) • Hematuria(8/22).	<0.01 <0.05	• High dose ASV(20/22) • Inadequate IV hydration(12/22) • Nephrotoxic drugs(8/22)	<0.001 <0.05
Resp Failure with prolonged support	13(6.5%)	• Delayed presentation(10/13) • Krait bite(8/13) • Aspiration pneumonitis(5/13)	<0.05 <0.05	• Weaning protocol not followed(12/13) • Delayed initiation of vent support(6/13)	<0.01
Multi Organ Dysfunction syndrome(MODS)	8(4%)	• Hemotoxic poisoning100% • AKI 100% • Delayed presentation 100% • Shock 100% • DIC 75%.	<0.001 <0.001 <0.001 <0.01 <0.001	• High dose ASV(7/8) • FFP(6/8)	<0.01
Compartment Syndrome	5(2.5%)	• Hemotoxic poisoning(4/5) • Delayed presentation(2/5)	<0.05	• Pressure monitoring not done(2/5). • Delayed fasciotomy(2/5).	
Death	7(3.5%)	• MODS 100% • Shock 100% • Hemotoxic poisoning(6/7) • Delayed presentation(5/7)	<0.001 <0.001 <0.01	• High dose ASV(6/7) • Vent support(5/7)	<0.01

DISCUSSION

Envenomings and deaths resulting from snakebites are a particularly important public health problem in the rural tropics. The poisoning can manifest in multitude ways, the final outcome being highly unpredictable. The scenario is further complicated by sociodemographic factors and available health infrastructure. Though previous research studies have attempted to predict the outcome in venomous bites, their findings cannot be extrapolated to all snakebites due to obvious reasons.[5,6,7]

Hence regional studies are absolutely essential to draw guidelines and protocols for the health hazard. The Indian scenario is dominated by the "big four poisonous snakes namely, common cobra (Najanaja), common krait (Bungarus caerulus) and viperidae including Russell's viper and saw scaled viper.[8] Given this situation, an outcome based analysis of systemically envenomed patients would help refine our knowledge and customize the management plan to fit our needs.

A lot of important associations were identified in this study which are potential predictors of mortality and other adverse outcomes. Based on their frequency and severity, five crucial adverse outcomes were considered in detail, namely Acute Kidney Injury[AKI] requiring hemodialysis, respiratory failure requiring prolonged ventilator support, compartment syndrome, Multi Organ Dysfunction Syndrome[MODS] and death. Several important predisposing factors were identified from this study which correlated well with adverse outcome.

Among all adverse outcomes AKI ranked first with an astounding 73% of cases fulfilling the diagnostic criteria for AKI. However our focus was only on oliguric AKI severe enough to need hemodialysis. Only 22(11%) of the cases studied suffered this complication. Nevertheless, AKI after snake bite was significantly associated with hemotoxic envenomations($p<0.01$) and occurrence of hematuria($p<0.05$). Likewise, high dose ASV was a very common forerunner of AKI($p<0.001$) as was inadequate intravenous hydration($p<0.05$). Previous literature on the subject revealed that AKI is a common complication of snake bite.[9] The probable causes for this occurrence are venom induced nephrotoxicity, ASV associated immune reaction, rhabdomyolysis, hemoglobinuria, dehydration, NSAID use for pain, DIC,etc.[10] Akin to these reports, we also identified significant association of AKI with snakebite. In addition, evidence from our study suggest that AKI is a predictor of poor outcome. The modifiable factors which could alter the outcome favorably include correction of dehydration by intravenous fluids and restricting the dosage of ASV.[10,11]

Respiratory failure occurred in 17.5% of our cases, however those requiring prolonged ventilatory support were only 6.5%. Though it was a common complication of neurotoxic envenomation, only those who required prolonged support were associated with bad outcome. The reasons for such a phenomenon was hypothesized to be due to an evolving process of ARDS or MODS presenting as respiratory failure. We searched available literature on the topic and found that the commonest mode of death after neurotoxic envenomation was respiratory failure[12,13,14] Addressing important issues like adhering to the weaning protocol, strict airway hygiene and early initiation of ventilator support could have a beneficial effect on the dismal outcome these patients face.[14,15,16]

Compartment syndrome occurred in 2.5% of our cases and had a significant association with hemotoxic envenomation in general and Russel's viper bite in particular. Among the neurotoxic bites, only cobra envenomation resulted in gross tissue necrosis and edema. Many studies have highlighted the need for intracompartmental pressure monitoring in such patients.[10,17] Resource constraints and huge work burden hinder proper care of these patients. Protocol based pressure monitoring and timely intervention could tilt the table against their grim outlook.

Multi Organ Dysfunction Syndrome[MODS] is a continuum, with incremental degrees of physiologic derangements in individual organs; it is a process rather than a single event.[18] It is a forerunner of death in snake bite as revealed in our observation. In our series, MODS occurred in 8 patients and all but one died. Inflammatory mediator release becomes a self-stimulating process, and release of other such mediators, including interleukin (IL)-1, platelet activating factor, IL-2, IL-6, IL-8, IL-10, and nitric oxide (NO), further increases cytokine levels. This leads to continued activation of polymorphonuclear leukocytes (PMNs), macrophages, and lymphocytes; proinflammatory mediators recruit more of these cells.[19,20] Once established it becomes a self perpetuating vicious cycle involving failure of multiple organ systems finally culminating in death.[21] We observed that MODS was associated significantly with hemotoxic envenomation($p<0.001$), AKI($p<0.001$), DIC($p<0.001$) and high dosage of ASV($p<0.001$). There were few if any interventions which could modify the outcome in MODS.[21]

Mortality in snake bite is reflector of the efficiency of health infrastructure. We recorded a death rate of 3.5% at our institute. This is an overestimate since we considered only systemically envenomed patients, who constitute a minority of all snake bite cases. However important observations herein include a significant association with hemotoxic envenomation, MODS and high dose ASV usage. Research findings from other institutes in the country reveal a strong correlation between high dose ASV and death[888]. Given the hopeless situation in altering MODS, the only possible intervention to reduce mortality is to restrict the dose of ASV to less than 16 vials.[22,23,24,25]

CONCLUSION

Snake bite is one of the neglected tropical diseases and an important cause for loss of life and productivity. After the index event of a venomous bite several extrinsic factors come into play which determine the final outcome. In our study we identified a few modifiable factors which are a significant cause for dismal outcome in snake bite in our geographic region. These include delayed presentation, occurrence of DIC, MODS, dehydration and usage of high dose ASV. Based on this observation the following recommendations are being

put forward to enable better and evidence based management of such patients.

- Proper attention should be directed towards avoiding and correcting dehydration in snake bite patients, so that the prerenal component of AKI is appropriately addressed.
- Early respiratory support should be norms to patients suffering respiratory failure. Weaning protocol should be strictly adhered to inorder to prevent complications like ventilator associated pneumonia , deep vein thrombosis, etc.
- Intensive monitoring of all vital organ functions for those who suffer AKI, respiratory failure or DIC should be practiced to prevent them from deteriorating into MODS. Such patients with single organ dysfunction are best screened early and brought into an intensive care facility to reduce mortality.
- DIC should be anticipated and managed energetically in all cases of hemotoxic envenomation.
- Finally, in accordance with multiple previous research evidence it is recommended to keep the dose of ASV to <16 vials for a favorable outcome.

ACKNOWLEDGEMENT

The authors acknowledge the help and support of all staff of the Department of Internal Medicine and Medical Records Department in the conduct of this study.

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