

A STUDY OF CLINICAL PROFILE AND PREDICTORS OF POOR OUTCOME IN SNAKE BITE INDUCED AKI

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Abstract

Background: Acute kidney injury (AKI) is an important complication of snake bite and a major cause of mortality. To study the clinical profile of snake bite patients with AKI and identify the predictors of mortality, the current study was conducted. **Materials and Methods:** A retrospective record based study was conducted among 150 patients with snake bite induced AKI admitted in a tertiary care hospital for a period of 5 years. Data was collected from the case records and analyzed using SPSS version 20.0. A P value <0.05 was considered statistically significant. **Result:** The mean age of the participants was 41.7±14.9 years. Viper (hemotoxic) bites were the commonest (94.0%). Maximum bites were in the morning (41.3%), over lower limbs (77.3%). Commonly presented symptoms were pain (99.3%), cellulitis (96.7%), local edema (93.3%). 26.7% had anuria, 24.7% had oliguria. Only 24.0 % received early ASV within 6 hrs of snake bite. 41.4 % required hemodialysis and 8.7% ventilator support. Renal biopsy showed acute tubular necrosis (ATN) in 58.4%. Out of 150 study subjects, 94.3% recovered whereas 5.7% died. Number of deaths were significantly higher among hypotensive patients, who required ventilation, with less mean platelet levels, higher mean APTT levels and total counts (P<0.05). **Conclusion:** Most common clinical presentations were local effects followed bleeding manifestations, anuria, oliguria. Presence of hypotension, requirement of ventilator, lesser mean platelet, higher APTT and total counts were significant predictors of mortality.

INTRODUCTION

Snake bite is one of the common medical emergencies in many countries, especially in rural areas. Agricultural workers and children are the most affected. The incidence of snakebite mortality is particularly high in South-East Asian countries. Judicious use of ASV can considerably reduce mortality and morbidity.^[1]

Although there are more than 3000 species of snakes in the world, approximately 250 are enlisted by WHO as medically important because of their harmful venoms.^[2] Around 300 species of snakes are found in India of which 52 are venomous. Though 5-6 lakhs are the total number of bites, only 30% are venomous. There is a wide gap between the number of snake bite deaths reported from direct survey and official data.^[3] According to national statistics in India, 5% of all injury deaths and 0.5% of all deaths are reported to be due to snakebites which were more than 30-fold higher than the number declared from hospital records.^[4] The true burden of

mortality from snakebite has shown that there is one snakebite death for every two AIDS deaths in India.^[5,6] In 2017, in India the total number of cases and deaths due to snake bite were 1,42,366 and 948 respectively.^[7]

In India, the “big four” species : the Indian cobra (Naja naja), the Russell’s viper (Daboia russelii), the Indian saw-scaled viper (Echiscarinatus) and the Indian krait (Bungarus caeruleus) are present besides the other life threatening snakes.^[8]

Snakebite affects particularly the poorest members of society. Agricultural workers (including children aged 10–14 years) and people living in poorly constructed homes face the highest risk and often have limited access to education, health care and even footwear. When such people are bitten, the modern health care usually remain far from their reality.^[9]

AKI is a major cause of mortality and a significant complication of snake bite. Myotoxic or hemotoxic snakes like Russell’s viper, saw-scaled viper, hump-nosed pit viper, green pit viper, and sea-snake commonly lead to AKI. The pathological changes of

AKI include ATN, cortical necrosis, interstitial nephritis, glomerulonephritis, and vasculitis. Vasoactive mediators and cytokines cause hemodynamic alterations and direct nephrotoxicity accounting for the development of renal dysfunction. Hemorrhage, hypotension, disseminated intravascular coagulation (DIC), intravascular hemolysis, and rhabdomyolysis enhance renal ischemia leading to AKI. Incidence of AKI varies from 5% to 29% which depends on the species of snake bite and the severity of envenomation. The onset of AKI varies from few hours to as late as 96 h after the bite while duration of AKI after snake bite ranges from 2-3 weeks. ATN is a vital pathological correlate of AKI. 10% AKI is one of the preventable causes of mortality and morbidity,^[11,12] this study was conducted to elicit the clinical profile of the snake bite patients who developed AKI and identify the predictors of mortality.

MATERIALS AND METHODS

A retrospective record based study was conducted among 150 patients with snake Bite induced AKI admitted in a tertiary care hospital in Mysuru for a period of 5 years. Ethical clearance was obtained from Institutional Ethical committee.

Inclusion Criteria

1. Definitive history of snake bite
2. Clinical picture consistent with snake bite; presence of fang marks/ cellulitis / coagulopathy/ neuroparalysis
3. Presence of AKI

Exclusion Criteria

1. Patients with pre-existent renal disease (serum creatinine > 1.5 mg/dL prior to snake bite or ultrasonography of abdomen suggestive of bilateral small kidneys/ loss of corticomedullary differentiation / obstructive nephropathy/other renal pathology).
2. Diagnosed cases of hypertension/diabetes mellitus.
3. Exposure to nephrotoxic drugs/toxins.

Operational Definition

Acute Kidney Injury: an abrupt absolute increase in the serum creatinine concentration of ≥ 0.3 mg/dL from baseline value measured after admission to the hospital or elsewhere after snake bite, before referring to our hospital, or a percentage increase in the serum creatinine concentration of ≥ 50 % above baseline, or oliguria of less than 0.5 mL/kg per hour for more than 6 hours Serum creatinine more than 1.5 mg/dL or oliguria (less than 400 mL/day of urine output).

Data collection: Data was collected from the case records regarding age, gender, type of snake bite, including the time and site of the bite, type of snake, presenting symptoms, time gap between the snake bite and the treatment, treatment details, any complications and outcome. Details of

Investigations like CBC, urine routine, blood urea, RBS, serum creatinine, electrolytes, BT, CT, PT, renal biopsy findings was collected.

Statistical Analysis: Data was entered in Microsoft Excel sheet and the analysis was done using SPSS version 20.0. Data was expressed in the form of frequencies and percentages. Chi-square test and Fisher's exact test was used to analyse the categorical variables. Independent samples 't' test and Mann-Whitney U test was used to analyse mean/median difference between continuous variables. A P value <0.05 was considered to significant.

RESULTS

The mean age of the study participants was 41.7 ± 14.9 years and it ranged from a minimum of 5 to 85 yrs. Majority (67.0%) of the study participants were males and Viper bites were the commonest (95.9%). Maximum bites were in the morning (41.3%). Most of them had lower limb bites (77.3%). More than 3/4th of the subjects had received delayed ASV [Table-1] 3.3% were given neostigmine and 18.0 % underwent fasciotomy.

The median (Range) bleeding time, clotting time, APTT and INR were 3.30 minutes (2 to 9 mins), 5.30 minutes (2 -36 mins), 34.0 seconds (11.40 to 180 seconds) and 1.16 (0.8 - 16) respectively. The median haemoglobin level was 11.2 gm% (11.0 – 18.2%), total count was 12,500 cells/ μ L (2610 – 14300/ μ L) and platelet count was 1.20 lakh cells / cu mm.

The most common presented symptom among the subjects with local effects were pain (99.3%) followed by cellulitis (96.7%) and local edema (93.3%). Among the neuroparalytic symptoms, most common presenting symptom was altered sensorium (4.0%), impaired consciousness and ptosis (2.7% each). Among the vascular symptoms, the most common manifestation was bleeding (36.7%) followed by haematuria (35.3%) and nearly 62.0% had bleeding at the site of wound. Among the renal manifestations 26.7% had anuria and 24.7% had oliguria. Other manifestations included vomiting (32.0%), basal crepts (25.3%), fever (14.0%) and respiratory distress (12.0%). [Graph-1] The mean systolic and diastolic BP was 120.3 ± 23.5 mm Hg and 76.30 ± 11.3 mm Hg respectively.

Among the findings of urine test, majority had albuminuria (72.0%) followed by pyuria (40.0%) and haematuria (35.4%). The median (range) of blood urea, serum creatinine levels were 100 mg/dl (17 - 415 mg/dl), 2.40 mg/dl (1 - 16 mg/dl) respectively. The median sodium and potassium levels were 136.0 mmol/L (115 - 145 mmol/L) and 4.2 mmol/L (2 – 8 mmol/L) respectively. Only 8.0% underwent renal biopsy, among whom, 16.6% had normal findings, 58.4% had ATN, 16.6% had patchy cortical necrosis, 8.4% had diffuse cortical necrosis. All the study subjects underwent Ultrasound

abdomen and it was found to be normal. 41.4 % required dialysis and 8.7% required ventilator support. Majority i.e., 94.3% recovered and 5.7% died. [Table2]

On comparing the baseline parameters like age, gender, time of bite, site of bite and manifestations like, bleeding, albuminuria, haematuria and hypotension among the outcome variables (recovered and died), it was found that the proportions of deaths were significantly higher among those with hypotension ($P<0.05$). Among the different treatment variables viz., administration of ASV, neostigmine, requirement of fasciotomy, dialysis and ventilation, higher proportion of deaths were significantly higher among those who required ventilation ($P<0.05$). Though, the median values of measures of hemostasis like, bleeding time (4.0 mins), clotting time (6.0 mins) and APTT (46.1 secs) were higher and platelets (0.51 lakhs) and INR (1.12) were lower among those who died, the difference was significant for the median levels of platelet and APTT ($P<0.05$). When the average (mean/median) values of other laboratory parameters were compared between the outcomes of recovery and death, haemoglobin levels and serum

potassium were marginally higher and blood urea, serum sodium, serum creatinine were slightly lower among those who died but the values did not vary significantly ($P>0.05$). However the total counts was found to be significantly higher (20685.0 ± 9946.61 cells/ μ L) among those who died ($P<0.05$). [Table-3]

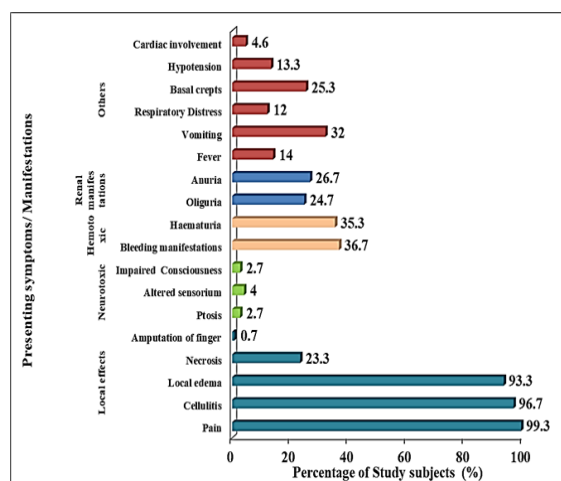


Figure 1: Symptoms among the study subjects

Table 1: Demographic and clinical characteristics of the study patients.

| Demographic particulars | n (%) |
|---|------------------------------------|
| Age in years | Mean \pm SD 41.67 \pm 14.89 |
| Gender | n (%) |
| Male | 100 (67.0) |
| Female | 50 (33.0) |
| Type of snake bite | n (%) |
| Hemotoxic | 141 (95.9) |
| Neurotoxic | 02 (1.4) |
| Hemotoxic & Neurotoxic | 04 (2.7) |
| Time of snake bite | n (%) |
| Morning (6:00 AM – 12:00 PM) | 62 (41.3) |
| Afternoon (12:00 PM – 4:00 PM) | 36 (24.0) |
| Evening (4:00 PM – 8:00 PM) | 29 (19.3) |
| Night (8:00 PM – 6:00 AM) | 23 (15.3) |
| Site of bite | n (%) |
| Upper Limb | 34 (22.7) |
| Lower Limb | 116 (77.3) |
| Time gap between bite to ASV administration | n (%) |
| Early (0-6 hrs) | 36 (24.0) |
| Delayed (> 6 hrs) | 114 (76.0) |

ASV - Anti-Snake Venom

Table 2: Characteristics of the study subjects based on manifestations of acute kidney injury (AKI)

| Characteristics related to AKI | n (%) |
|--|-------------------|
| Presence of abnormal urinary findings | n (%) |
| Haematuria (n=150) | 53 (35.4) |
| Pyuria (n=150) | 60 (40.0) |
| Albuminuria (n=150) | 108 (72.0) |
| Findings of RFT | Median (Range) |
| Blood Urea (mg/dL) | 100.0 (17 - 415) |
| Serum Creatinine (mg/dL) | 2.40 (1-16) |
| Sodium (mmol/L) | 136.0 (115 - 145) |
| Potassium (mmol/L) | 4.20 (2-8) |
| Renal biopsy findings (n=12) | n (%) |
| Normal | 2 (16.6) |
| Acute tubular necrosis | 7 (58.4) |
| Patchy cortical necrosis | 2 (16.6) |
| Diffuse cortical necrosis | 1 (8.4) |
| Management of Complications of AKI | n (%) |
| Requirement of Dialysis | 62 (41.4) |

| | |
|----------------------------|------------|
| Requirement of Ventilation | 13 (91.3) |
| Outcome¥ | n (%) |
| Died | 8 (5.7) |
| Recovered | 133 (94.3) |

¥ n=141 as 9 subjects were discharged against medical advise

Table 3: Significant predictors of mortality among those with snake bite induced AKI

| Significant Predictors | Recovered (n=133) | Death (n=8) | P-value |
|-------------------------------------|------------------------|-----------------------|----------|
| Hypotension.ª | | | |
| Yes | 13 (76.5) | 04 (23.5) | 0.01* |
| No | 120 (96.8) | 04 (03.2) | |
| Requirement of Ventilation.ª | | | |
| Yes | 04 (36.4) | 07 (63.3) | <0.0001* |
| No | 129 (99.2) | 01 (0.8) | |
| Median Platelet levels (lakhs)¥ | 1.28 (0.08 – 4.90) | 0.51 (0.05 – 3.85) | 0.03* |
| Median APTT levels (secs) ¥ | 33.65 (11.40 – 300.0) | 46.1 (34.10 – 180.0) | 0.002* |
| Mean Total Count in cells/ μ L§ | 13486.65 \pm 6548.73 | 20685.0 \pm 9946.61 | 0.004* |

*indicates statistical significance at P<0.05; ªexpressed in n(%) &Fisher’s exact test applied; ¥expressed inMedian (Range) &Mann Whitney U test applied; §expressed inMean \pm SD&Independent t- test applied

DISCUSSION

Snake bite is an important preventable cause of acute kidney injury (AKI).¹²Both the protein and the non-protein component in the snake venom further complicated by the inflammatory response of the victim's body results in the toxic effect. The polypeptides which are smaller molecules absorbed into systemic circulation exerts a systemic toxicity in the organs with rich blood supply like kidney resulting in acute kidney injury.¹³ Thus to elicit the clinical profile of the patients admitted in our hospital and determine predictors of mortality the study was conducted.

Vikrant S et al., found mean age of 42.2 \pm 15.1 years among the study subjects and was comparable to our study subjects.¹⁰Meenakshi B et al., reported majority (67.0%) as males and is in line with our study findings¹⁴and in addition, males are more involved in outdoor activities compared to females. Most of the cases were viper bites and lower limb was the commonest site of bite as recorded by Mukhopadhyay P et al., and are similar to our findings.¹²Morning hours was the commonest hour of maximum bites and pain at local bite site (74.3%) was the common presenting symptoms which were noted in conjunction to our study.¹⁵Pore SM et al., observed that 70.0% had received early ASV administration,¹⁶ however in our study less than 25.0% received early ASV within 6 hours of snake bite and differences may be due to difference in the distances of location of the health care facilities, the knowledge of the bystanders or the patient attendants and availability of ASV in smaller hospitals located nearby.

Hematuria and proteinuria are the clinical manifestations of kidney damage caused by snake bite and the pathogenic mechanism involved in snake-bite induced AKI are not clear and it has been suggested that Disseminated intravascular coagulation (DIC) could cause hemoglobin deposition in kidney tubules and lead to degenerative necrosis.¹⁷ Few case reports have

mentioned pus cells in urine examination among snake bite patients.^{18,19}According to Vikrant S et al., the mean blood urea levels were 169 mg/dl, creatinine levels were 7.2 mg/dl and in our study we did not find such a high average of creatinine levels.²⁰ The median blood urea and serum creatinine levels in the current study were 100 mg/dl and 2.40 mg/dl respectively. The median sodium and potassium levels were 136.0 mol/L and 4.2 mmol/L respectively in our study which are similar to the findings by Vikrant S et al.¹⁰In our study, 41.4 % required dialysis and 8.7% required ventilator support, whereas Bhalla G et al., noted that 9.2% and 25.0% of poisonous snake bites required hemodialysis and ventilator support respectively. The proportions according to Bhalla G et al., were less which may be due to the consideration of different snake bites.²¹Vikrant S et al., have recorded the histopathological findings among 25.0% who underwent renal biopsy among whom majority i.e., 91.0% had ATN and renal cortical necrosis (RCN) which was patchy involving 35%-40% of cortical segment was present in one patient (5.0%) whereas in our study, 8.0% of them underwent renal biopsy among whom, 58.4% had ATN, the commonest manifestation and 16.6% had patchy cortical necrosis. 9.0% expired in their study and 5.3% expired in our study.¹⁰

In our study, among the baseline characteristics like age, gender, time of bite, site of bite and manifestations like, bleeding manifestations, albuminuria, haematuria and hypotension were significantly associated with death and is in line with the study findings by Raj R et al., and Harshavardhan L et al., it was found that the proportions of deaths were significantly higher among those with hypotension (P<0.05).^{15,22} Similarly requirement of ventilator support was significantly associated with occurrence of death indicating the severely impaired respiratory mechanics and critical illness. Vikrant S et al., found that platelet count was lesser among those with an outcome of death however it was not significant. In our study it was in correspondence except for

significance.¹⁰ Huang MJ et al., found increased APTT among those with AKI like-wise in our study increased APTT was significantly higher among those with an outcome of death in patients with AKI but for the significance.^[23] Aye KP et al., have found WBC to be significantly associated with the occurrence of AKI with an odds ratio of 3 and similarly in our study death was associated with raised WBC among the patients with AKI and the findings of WBC and ICU support (ventilator support) are in line with the findings by Vikrant S et al.^[10,24]

However, drawing any solid inferences which can be generalized is difficult from this study in view of the shortcomings, such as the smaller study population. Multi-centric studies involving a large number of patients are indicated to identify the actual determinants and predictors of long-term renal dysfunction.

CONCLUSION

Pain followed by cellulitis and local edema was the commonest local effects reported in more than 90.0% of the study subjects. Only 24.0 % of the subjects received early ASV. More than one third had bleeding and hematuria. Nearly a quarter of those with AKI had manifestations of anuria and oliguria. The medians of blood urea and serum creatinine levels were 100 mg/dl and 2.40 mg/dl respectively. As an intervention, 41.4 % required dialysis and 8.7% required ventilator support. Among 8.0% of renal biopsies, 58.4% had acute tubular necrosis, 16.6% had patchy cortical necrosis, 8.4% had diffuse cortical necrosis. Nearly 6.0% died as a result of acute kidney injury.

Occurrence of death among those with acute kidney injury was significantly associated with the presence of hypotension and requirement of ventilator support. The mean platelet levels were significantly lesser and APTT levels and total counts were significantly higher among those who died respectively.

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