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Original Research Article

Acute Kidney Injury Induced by Snake Bite and Its Outcome in a Tertiary Care Centre

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Abstract:

Background: The risk of an Indian dying from snakebite before age 70 is about 1 in 250, but notably higher in some areas. More crudely, we estimate 1.11–1.77 million bites in 2015, of which 70% showed symptoms of envenomation. Prevention and treatment strategies might substantially reduce snakebite mortality in India. The complications related to kidneys are observed in majority of patients with poisonous snake bite. Such renal failure, usually due to acute tubular necrosis, is frequently reversible. If bilateral cortical necrosis occurs, however the prognosis of renal recovery is grimmer. Hence this was conducted with the objective to determine risk factors associated with adverse outcome in patients with Acute Kidney Injury induced by snake bite. To determine association between treatment delay and outcome of Acute Kidney Injury.

Methodology: Data was collected using predesigned questionnaire by interviewing the patients or by verifying the records. Participants demographic, clinical details and investigation profile were recorded in proforma. Complete Blood Count, Bleed in g time, Clotting time, Urine Albumin, Sugar, Deposits including RBCs, Blood urea, serum creatinine, electrolytes, Electrocardiogram, USG abdomen, Other investigations were taken based on the clinical status of the patient. Patients were classified into three stages of acute kidney injury proposed by Acute Kidney Injury Network [Modified RIFLE Criteria]. Serum Creatinine clearance was estimated by Cockcroft's-Gault Equation. Data was entered into Microsoft excel data sheet and was analyzed using Epi Info version 7.2.6 software. p value of <0.05 was considered as statistically significant.

Results: In the study out of 100 subjects included, 30 subjects were recruited during Dec 2022 to Dec 23. 70 patient details were obtained from records during 2013 to 2022. Among these subjects, majority of them were in the age group 21 to 30 years (28%), males were 56%, Russel viper bites were 44%. Bite to needle time was <6 hrs. in 64%, 60% were Haematotoxic snake bites, 52% had elevated serum creatinine, 30% had bleeding manifestations, 70% had cellulitis, 40% had hypotension, 50% required dialysis and 38% had mortality. Mortality was highest among subjects with Raised serum creatinine and reduced eGFR (54.17% respectively). Other factors such as age, gender, type of toxicity, Bleeding Manifestations, Hypotension and dialysis were not significantly associated with mortality among AKI subjects. Among subjects who took >6 hrs for treatment had highest elevated serum creatinine (72.2%), reduced eFGR (72.2%), bleeding manifestations (55.56%), cellulitis (88.89%), hypotension (61.1%) need for dialysis (72.2%) and mortality (61.1%).

Conclusion: Raised serum creatinine levels and reduced estimated GFR levels were significantly associated with adverse outcome of death in Patients with Acute Kidney Injury in snake bite. Haematotoxicity, occurrence of cellulitis, bleeding manifestations, hypotension requirement of dialysis, elevated serum creatinine levels and reduced estimated GFR levels were significantly associated with bite to needle time of > 6 hours.

Keywords: Acute Kidney Injury, Snake Bite, Risk factors for AKI**.**

Introduction

Snake bite poisonings known to man since antiquity. Bite rates are highest in temperate and tropical regions where populations subsist by manual agriculture. In INDIA, a large proportion of snake bites occur when people are working barefoot in the fields or while walking at night. Recent estimates show that India has 1.2 million snakebite deaths (average 58,000/year) from 2000 to 2019. Nearly half occurred at ages 30–69 years and over a quarter in children < 15 years. Most occurred at home in the

rural areas. About 70% occurred in eight higher burden states and half during the rainy season and at low altitude. The risk of an Indian dying from snakebite before age 70 is about 1 in 250, but notably higher in some areas. More crudely, we estimate 1.11–1.77 million bites in 2015, of which 70% showed symptoms of envenomation. [1] Prevention and treatment strategies might substantially reduce snakebite mortality in India. [2]

The complications related to kidneys are observed in majority of patients with poisonous snake bite. Such renal failure, usually due to acute tubular necrosis, is frequently reversible. If bilateral cortical necrosis occurs, however the prognosis of renal recovery is grimmer.[3] Hence this was conducted with the objective to determine risk factors associated with adverse outcome in patients with Acute Kidney Injury induced by snake bite. To determine association between treatment delay and outcome of Acute Kidney Injury. [3]

Material and Methods:

Record based observational study was conducted among 100 Patients with patients developing Acute Kidney Injury following snake bite at Adhichunchanagiri Hospital and Research centre. BG Nagara. Nagamangala taluk. Mandya district. [4]

Inclusion Criteria: History of snake bite with signs of envenomation. Progressive elevation of serum creatinine >0.3mg/dl from baseline value measured at admission to the hospital after snake bite, or a percentage increase in serum creatinine level of ≥50 percentage above the baseline or b)Oliguria of less than 0.5ml/kg/hr for more than six hours or serum creatinine of more than 1.5mg/dl or oliguria(urine output less than 400ml/day)Patients with pre-existing renal diseases with or without history of snake bite, Patients with risk factors for developing renal disease with history of snake bite (connective tissue diseases, chronic infection). Chronic history of non-steroidal anti-inflammatory drugs (NSAIDS) intake. Contracted kidneys by abdominal ultrasound and Previous ultrasonography evidence of Chronic Kidney disease were excluded from the study. Study was conducted between December 2022 to December 2023 (1 year). Records of Snake bite induced AKI patients were examined from 2013 to 2022. Non-Probability sampling method was used to select the samples.

Sample Size: sample size calculation was done using most common presentation of AKI induced by snake bite i.e. Oliguria at 84% from the study by **Harshavardhanaetal**[4] Considering 99% confidence level, design effect of 1 and 10% absolute precision sample size calculated was 90 using the formula $n = Z_{1-\alpha/2}^2 \, p \, (100-p) / d^2$and with 10% non-response rate or incomplete date sample size was 100 and was included.

Method of Data Collection: Institutional Ethical clearance was obtained prior to the start of the study. Informed consent was obtained from all the patients fulfilling the inclusion criteria during study period. For record-based data consent was not taken. Data was collected using predesigned questionnaire by interviewing the patients or by verifying the records. Participants demographic, clinical details and investigation profile were recorded in proforma.

Evidence for Regional Envenomation: Site of snake bite was examined for presence of fang marks, cellulitis, bleeding from site of bite, local necrosis, blistering, gangrene, regional lymph node enlargement and evidence for compartment syndrome. All Vital signs looked for.

Evidence for Systemic Envenomation: Features of bleeding manifestations – gum bleeding, epistaxis, ecchymosis. Features of Neuroparalytic, Uremic symptoms.

Investigations: Complete Blood Count, Bleeding time, Clotting time, Urine Albumin, Sugar, Deposits including RBCs, Blood urea, serum creatinine, electrolytes, Electrocardiogram, USG abdomen, Other investigations were taken based on the clinical status of the patient.

Patients underwent physical examination daily. Pulse rate, Blood pressure, Urine output, Respiratory rate and features of envenomation were monitored daily. Blood specimen was taken every day till discharge or death to measure sodium, potassium, urea, creatinine, bleeding time, clotting time, platelets and for patients undergoing dialysis, pre-dialysis and post-dialysis Urea and Creatinine was measured. All the patients received treatment as per standard protocol for snake bite. [5]

Patients were classified into three stages of acute kidney injury proposed by Acute Kidney Injury Network [Modified RIFLE Criteria] [6] which defines AKI as an "abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥ 0.3 mg/dl (26.4µmoles/l) from baseline, a percentage increase in the serum creatinine concentration of ≥50 % or oliguria of <0.5 ml/kg/hr > 6 hours. Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m^2 with in the first 72 hr after snakebite was defined as AKI.

Serum Creatinine clearance was estimated by Cockcroft's-Gault Equation:(140-Age)/Serum creatinine*weight/72. [7]

Definition of Acute Kidney Injury:

Classification of Acute Kidney Injury– Modified RIFLE Criteria		
Stage	Serum Creatinine Criteria	**Urine Output Criteria**
1(Risk)	Increase of ≥ 0.3mg / dL or 1.5–2-fold increase of the baseline	**<0.5 ml / Kg /h>6hr**
2(Injury)	**Increase to 2–3-fold of the baseline**	**<0.5ml / Kg / h for>12hr**

Data was entered into Microsoft excel data sheet and was analyzed using Epi Info version 7.2.6 software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. **p value** (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. [**8,9]**

Results:

In the study out of 100 subjects included, 30 subjects were recruited during Dec 2022 to Dec 23. 70 patient details were obtained from records during 2013 to 2022. Among these subjects, majority of them were in the age group 21 to 30 years (28%), males were 56%, Russel viper bites were 44%. Bite to needle time was <6 hrs in 64%, 60% were Haematotoxic snake bites, 52% had elevated serum creatinine, 30% had bleeding manifestations, 70% had cellulitis, 40% had hypotension, 50% required dialysis and 38% had mortality [Table 1].

Table 1: Profile of subjects

	Age	Frequency(n)	Percent (%)
Age (years)	11-20	16	16.0
	21-30	28	28.0
	31-40	14	14.0
	41-50	18	18.0
	51-60	12	12.0
	61-70	12	12.0
Gender	Male	56	56.0
	Female	44	44.0
Type of snake	Russel Viper	44	44.0
	Saw Scaled Viper	16	16.0
	Unknown	40	40.0
Bite to needle	>6Hour	36	36.0
	<6Hour	64	64.0
Type of toxicity	Haematotoxic	60	60.0
	Neurotoxic	40	40.0
Serum Creatinine	Elevated (≥50% or >0.3mg/dl from base-line value)	52	52.0
eGFR	Reduced	48	48.0
Bleeding manifestations		30	30.0
Cellulitis		70	70.0
Hypotension		40	40.0
Dialysis		50	50.0
Outcome	Survived	62	62.0
	Death	38	38.0

In the study factors such as raised serum creatinine, reduced eFGR, presence of cellulitis was significantly associated with Mortality. Mortality was highest among subjects with Raised serum creatinine and reduced eGFR (54.17% respectively). Other factors such as age, gender, type of toxicity, Bleeding Manifestations, Hypotension and dialysis were not significantly associated with mortality among AKI subjects [Table 2].

Table 2: Association between Outcome and Factors

Variables		Outcome of snake bite				χ^2Value	*P*-Value
		Survived (n =		Died (n = 38)			
		Count	%	Count	%		
Age	<40yrs	36	64.29	20	35.71	0.282	0.595
	>40yrs	26	59.09	18	40.91		
Gender	Males	34	60.71	22	39.29	0.089	0.765
	Females	28	63.64	16	36.36		
Type of toxicity	Neurotoxic	28	70.00	12	30.00	1.811	0.178
	Haematotoxic	34	56.67	26	43.33		
Serum Creatinine	Normal	40	76.92	12	23.08	10.24	0.0013*
	Elevated	22	45.83	26	54.17		
Estimated GFR	Normal	40	76.92	12	23.08	10.24	0.0013*
	Reduced	22	45.83	26	54.17		
Bleeding Manifestations	Present	16	53.33	14	46.67	1.366	0.41
	Absent	46	65.71	24	34.29		
Cellulitis	Present	38	54.29	32	45.71	5.894	0.015*
	Absent	24	80.00	6	20.00		
Hypotension	Present	22	55.00	18	45.00	1.387	0.238
	Absent	40	66.67	20	33.33		
Required Dialysis	Yes	28	56.00	22	44.00	1.528	0.216
	No	34	68.00	16	32.00		

In the study bite to needle time was significantly associated with Serum creatinine, Estimated GFR, Bleeding manifestations, Cellulitis, Hypotension, need for dialysis and outcome. I.e. among subjects who took >6 hrs for treatment had highest elevated serum creatinine (72.2%), reduced eFGR (72.2%), bleeding manifestations (55.56%), cellulitis (88.89%), hypotension (61.1%) need for dialysis (72.2%) and mortality (61.1%) [Table 3].

Table 3: Association between Bite to Needle time and Factors

		Bite to needle				χ^2Value	*P*-Value
		>6Hour (n = 36)		<6Hour (n =64)			
		Count	%	Count	%		
Type of toxicity	Neurotoxic	6	16.67	34	53.13	12.76	0.0003*
	Haematotoxic	30	83.33	30	46.88		
Serum creatinine	Elevated	26	72.22	22	34.38	13.22	0.0002*
	Normal	10	27.78	42	65.63		
Estimated GFR	Reduced	26	72.22	22	34.38	13.22	0.0002*
	Normal	10	27.78	42	65.63		
Bleeding manifes-tations	Yes	20	55.56	10	15.63	17.49	<0.001*
	No	16	44.44	54	84.38		
Cellulitis	Yes	32	88.89	38	59.38	9.55	0.0019*
	No	4	11.11	26	40.63		
Hypotension	Yes	22	61.11	18	28.13	10.44	0.0012*
	No	14	38.89	46	71.88		
Dialysis	Yes	26	72.22	24	37.50	11.11	0.0008*
	No	10	27.78	40	62.50		
Outcome	Death	22	61.11	16	25.00	12.75	0.0003*
	Survived	14	38.89	48	75.00		

Discussion:

Snake-bites are one of the common reported morbidities in tropical countries, especially during some specific seasons. [10,11] Seasonal peaks of snake-bite incidence usually coincide with increase in agricultural activity or seasonal rains, may be over lapping with unusual movement and activity by snakes. Snake bites and snake bite related fatal incidence speak during the monsoon season in India, [12,13] According to the estimates in India, each

year at least 81,000 snake envenoming and 11,000 fatalities occur. [14]

Majority of the Indian patients are victims of Russell's viper. [15] Though bites from all the venomous snakes cause AKI, a significant proportion of these cases results from viper bites. Snake venom is a complex poison consisting of hundreds of different proteins: Enzymes (PhospholipaseA2), polypeptide toxins and non-toxic proteins. [11] Following the viper bites, various systemic symptoms occur as a result of coagulopathy, haemolysis, acute kidney injury, a generalized increase in capillary permeability, rhabdomyolysis, neurotoxicity etc. [11]

The kidney being a highly vascularized organ with excretory function is prone to toxicity of the venom and acute kidney injury is the most significant of all the renal manifestations. [11,16,17] AKI in snakebite constitutes 3.0% of total AKIs in India. [18] As a result of intravascular haemolysis and rhabdomyolysis, haemoglobinuria and myoglobinuria develops thus contribute importantly to the development of AKI after snake bite. [16] Tubular and cortical necrosis are also the important causes of AKI and is usually reversible, until acute cortical necrosis occurs. [4,19] Renal failure can be catabolic, hence increases blood urea nitrogen, serum creatinine and serum uric acid levels. [16]

Intravascular haemolysis can be more fatal when combined with other adversarial factors such as dehydration, hemorrhage or hypotension. Bleeding and circulatory collapse in snake-bite victims is usually due to DIC. [20] Hypotension is another important factor to cause ARF. [21] Russell's viper can cause hypotension and collapse by releasing bradykinin. [20]

Increased time interval between bite to the administration of ASV (bite to needle time) increases the risk of developing AKI. Until the venom is neutralized, it continues the damage. [22]

Naqvi R reported the age group of the patients developing AKI secondary to snake bite ranging from 6 - 70 years similar to the present study wherein the age group ranged between 11-70 yrs. [10] The victims in a study by Monteiro FNP et al., were predominant in 20–29 year and 40-49 year age group as the predominant snake bite victims [23] similar to our study where we noted a predominant age group of those with AKI following snake bite as 21-30 years. Harshavardhan L et al., also found majority with AKI among with younger age group of 20-40 years. [4]

Majority i.e., 56.0% were males and 44.0% were females in the current study. The major proportion of those who developed AKI following snake bite were Males as noted by Singh RR et al. [22] Study by Wei Liet al., has noted majority i.e., 59.7% males and 40.3% females presented with snake bite [24] and the findings by Singh RR et al and Wei Li et al are in parallel with the current study findings. [22,24]

Majority of the snake bites in the present study were by the Russel viper similar to the findings by Athappan G et al., where majority had viper bites. [20] Kohli HS and Sakhuja V have reported 13 to 32% incidence of Acute renal failure following Russell's viper bite in India. [25] Russell's viper is responsible for 30–40% of the snake bites in Srilanka. [26] in our study Russel viper bites i.e. 44 % more commonly associated with the development of AKI. [4]

36.0% of the patients with AKI had bite to needle time > 6 hours. Among those with bite to needle time > 6 hours presented late in the present study 72.2% had developed AKI which is comparable to the study findings conducted by Badgal A et al, [27] in his study whose bite to needle time > 6 hours that is 112 patients had developed AKI (72%).

Majority i.e., 60.0% were having haematotoxicityand 40.0% were having neurotoxicity. The varied pattern of syndromes across India indicates predominance of haematotoxic viper bites in south India and neurotoxic elapid bites in north India.[17] Similarly predominant manifestation was haematotoxicity in our study. Among the venomous snake bites among the patients with snake bite belonging to study group of Ishfaq A et al., majority had haematotoxicity. [28] All those with Russel Viper bites had haematotoxicity in the present study and Monteiro FNP et al., also reported 100% of them having haematotoxicity among the cases they had studied. [23]

30.0% of the study subjects had bleeding manifestations in the current study and are in congruence to the study findings by Athappan G et al and HarshavardhanL et al where 27.7% and 38.8% demonstrated bleeding manifestations among the subjects with AKI respectively. [4,20]

Majority i.e., 35 patients (70.0%) study subjects presented with cellulitis among the study subjects with snake bite and 15 patients (30.0%) of the did not have cellulitis.

40.9 % developed cellulitis according to a study conducted by Naqvi R et al. [10] Nearly 92.0% of them developed cellulitis in a study conducted by Harshavardhan L et al. [4]

52.0% of them had elevated serum creatinine of ≥ 50% or >0.3mg/dl from baseline value and reduced GFR. The study findings by Badgal A et al., reported 3.6% of those with AKI had doubled serum creatinine or urine production less than 0.5ml/kg/hr for 12 hours. The difference may be due to, the difference in the criteria for consideration of AKI

(where even rise of >0.3mg/dl of creatinine values from the baseline is also included among 54.0% in the current study) and bite to needle time of the patients.2752.0% of the study subjects in the present study had reduced estimated glomerular filtration rate. As reported by Das SN et al., 58.0% of the patients with reduced GFR among the cases of AKI following snake bite, had >50.0% reduction in GFR. [29]

Burdmann EA et al., in an experimental model (a model of snake bite-induced ARF) following venom administration in rats extracted by one of the Viperidae snake family has noted acute and significant decrease in the glomerular filtration rate was achieved. Ischemia and intravascular hemolysis are the important pathogenic factors causing a decrease in the glomerular filtration rate. [30]

The present study recorded hypotension among 40.0% of the patients. Similarly, Singh RR et al., noted hypotension among45.2%ofthe patients with AKI.

The proportion of study subjects requiring the dialysis and not requiring the dialysis were equal (50.0%) in our study and 45.3% of them with ARF required dialysis as noted by Athappan G et al. Vikrant S et al., noted that 75.0% of them with AKI required dialysis. [11,20] The slight difference may be due to difference in the severity of AKI of the study subjects.

Majority (62.0%) of the study subjects survived the snake bite and 38.0% of the study subjects died as a result of snake bite. Patil TB et al., has noted in their study that 29.8% of them died which is nearly comparable to our study findings.103 9.1% died among those with AKI following snake bite as reported by Vikrant S et al.11 The differences may be due to difference in the severity of AKI among the patients.

In the present study there was no significant statistical association of age and gender with the outcome of snake bite which is similar to the findings by Naqvi R [10] and Harshavardhan L et al. [4]

Among the study population who died, majority had haematotoxicity. However, the number of patients with haematotoxicity was more compared to neurotoxicity and was not significantly associated. Among those who died with known snake bites majority, had Russel viper bites. It is a known fact that Russel viper bite is associated with development of more of haematotoxicity. [11]

In the present study cellulitis was significantly associated with Mortality. Were as in the study conducted by Harshavardhan L et al., where in 98.9% had cellulitis and it was not significantly associated with the outcome of death. [4] Similarly, Pail TB et al., was also not significantly associated with the death. [21] Harshavardhan L et al., has noted that bleeding manifestations were not significantly associated with the outcome of death which is similar to the current study findings however proportion with hypotension were significantly higher among those who died which is not in parallel to the current study findings. [4] This difference may be due to the difference in the severity of haemorrhagic manifestations among the study subjects in two different study settings. Vikrant S et al., has also noted that the difference among the proportion of those who underwent dialysis following AKI was not statistically significantly different among those who survived and died which is analogous to the current study finding. [11]

Among the study subjects in the present study with the adverse outcome of death, the proportion of those with elevated serum creatinine levels and those with reduced estimated GFR were significantly higher compared to those with normal serum creatinine levels and reduced estimated GFR respectively ($P<0.05$). Harshvardhan L etal., has noted significant increase in the mean values of serum creatinine among those who died of AKI. [4] Wei Li et al., noted that 6.2% died among those with raised serum creatinine concentration and with AKI. [24] However 68.4% died in our study, Pinho F-MO et al., has reported death among 10.3% of them with reduced GFR. [30] Ischemia related to glomerular coagulation and intravascular haemolysis is the most vital pathogenic factors in causing a decrease in the glomerular filtration rate. [31]

Kumar KP et al., has reported that the blood creatinine level in the majority of viper bite cases was found to be increased after the sixth hour and that increased creatinine level caused the renal failure.[32] It was noted by Dharod MV et al., that patients who developed AKI had a significantly longer bite-to-hospital time, compared to those who did not develop AKI[33] and similarly, Athappan et al., found that bite to needle time more than 2 hours was an independent risk factor for the development of AKI Snake venom, which is responsible for almost all the complications of snake bite, must be neutralized as soon as possible with ASV. [20] Similarly in the present study, the proportion of those with increased creatinine, reduced GFR and requirement of dialysis was significantly associated with bite to needle time > 6 hours, like in our study those patients with more than 6 hours had raised creatinine levels and reduced eGFR and had been taken to dialysis.

Saravu K et al., reported that the severity of graded manifestations increased as the bite to needle time increased. Patients, who presented late, had delayed administration of ASV and required more aggressive therapies (mechanical ventilator support). [33] Patil HV etal., found the positive

correlation for occurrence of complications and mortality with needle to ASV time. [34] The early institution of ASV has been beneficial in preventing complications, irrespective of the severity of systemic envenomation. [35] These findings are similar to our study findings wherein, the complications like Cellulitis, bleeding manifestations, hypotension and mortality were more associated with late presentation or (bite to needle time>6hrs). [33]

Conclusion:

From the study findings it was concluded that Raised serum creatinine levels and reduced estimated GFR levels were significantly associated with adverse outcome of death in Patients with Acute Kidney Injury in snake bite. Haematotoxicity, occurrence of cellulitis, bleeding manifestations, hypotension requirement of dialysis, elevated serum creatinine levels and reduced estimated GFR levels were significantly associated with bite to needle time of > 6 hours. Hence snake venom responsible for most of the complications must be neutralized as early as possible is well established.

Limitation: Sampling procedure being purposive, the selection of representative sample and generalizability becomes a limitation. Hence, the study needs to be conducted in a larger sample and in a community-based setting to generalize the obtained results. Few patient's data was obtained from Records hence prospective studies to be conducted.

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