



A PROSPECTIVE STUDY ON FACTORS INFLUENCING RENAL RECOVERY FOLLOWING SNAKE BITE INDUCED AKI IN A TERTIARY CARE HOSPITAL

Nephrology

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ABSTRACT

Background: Snake bite induced AKI is the well studied complication of snakebite. However the factors influencing recovery are less studied. This study is aimed at identifying these factors. **Materials and Methods:** About 83 dialysis requiring patients were included in the study. Age < 12 years, pregnant patients, patients with known CKD, patients with neurotoxicity also excluded. Clinical data and laboratory values were noted. They were divided into 2 groups based on dialysis dependency and duration of hospital stay. **Results:** The mean age of dialysis requiring patients was found to be 46 years. Among which 63% were males and 37% were females. About 80.2% patients' snakebite species were unidentified, while the remaining were from viperidae family. Bite to ASV time was ≤ 2 hours in 8.4% patients, 3-6 hours in 77.1% patients and > 6 hours in 14.5% patients and found to have near significant effect on recovery and significant effect on duration of hospital stay. Platelet count on day 1 was < 1 lakh in 48.2% patients, 1-1.5 lakh in 26.5% patients, > 1.5 lakhs in 25.3% patients. Lactate dehydrogenase (LDH) was found to be ≤ 1500 in 22.9% patients and > 1500 in 77.1% patients. Creatine phosphokinase (CPK) was found to be > 500 in 62.7% patients and ≤ 500 in 37.3% patients. Platelet count on day 1 and its decreasing trend, peak creatinine and LDH on day 1 and its increasing trend found to have significant impact on recovery and duration of hospital stay. **Conclusion:** Hence the timely initiation of ASV has early recovery from AKI and shorter duration of hospital stay. Platelet count, peak creatinine, and LDH count on day 1 and its trend during admission has significant impact on recovery.

KEYWORDS

Snakebite, acute kidney injury, hemodialysis (HD), lactate dehydrogenase.

INTRODUCTION:

Snakebite is the most common cause of tropical AKI [1]. About 5.4 million snake bites occur each year, resulting in 1.8 to 2.7 million cases of envenomation (poisoning from snake bites). There are between 81,410 and 1,37,880 deaths and around three times as many amputations and other permanent disabilities in the form of irreversible kidney damage each year [2]. The venomous snakes found in India belong to three families Elapidae, Viperidae and hydrophidae (Sea Snakes). The most common Indian elapids are Naja naja (Indian Cobra) and Bungarus caeruleus (Indian Krait), and snakes belonging to viperidae family are Daboia russalae (Russells' Viper) and Echis carinatus (Saw scaled viper) [3]. Viper bites are more common than other poisonous snakebites in human beings [4, 5]. AKI is a well documented complication of snakebite from viper bite. Enzymatic toxins in snake venom result in injuries to all kidney cell types including glomerular, tubulo-interstitial and kidney vasculature. Pathogenesis of kidney injury due to snake envenomation includes ischaemia secondary to decreased kidney blood flow caused by systemic bleeding and vascular leakage, proteolytic degradation of the glomerular basement membrane by snake venom metalloproteinases (SVMPs), deposition of microthrombi in the kidney microvasculature (thrombotic microangiopathy), direct cytotoxic action of venom, systemic myotoxicity (rhabdomyolysis) and accumulation of large amounts of myoglobin in kidney tubules [6].

Recovery from AKI depends on several patient factors and management factors which might lead to early or late recovery or dialysis dependency. This study is aimed at the identification of patient factors and treatment factors responsible for early or late recovery or dialysis dependency.

MATERIALS AND METHODS:

The study was conducted at the Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamil Nadu between July 2022 and June 2023.

Inclusion criteria:

All patients admitted with AKI following hemotoxic snake envenomation were followed and those who required dialysis were included in the study.

Defining criteria:

A diagnosis of snake bite was made from clinical history or with the presence of characteristic fang marks. AKI was defined according to KDIGO criteria either by urine output criteria or creatinine criteria. Snake bite species were identified as told by the patient or description as told by the patient or if dead snake has been brought by the patient's relatives.

Exclusion criteria:

Patients with age < 12 years, neurotoxic manifestations, non-dialysis requiring AKI, pregnancy, prior history of CKD (eGFR < 60 ml/min/1.73 m²), albuminuria > 30 mg/day, contracted kidneys, evidence of stones, cystic kidneys, hydronephrosis on USG, and abnormal urinary sediment, exposure to nephrotoxic drugs were excluded from the study.

Clinical course:

All patients with snake bite were treated with polyvalent ASV according to coagulopathy, cellulitis and other symptoms upto 30 vials. Further dosing was determined by local symptoms and hemotoxicity. Bite to ASV time (time interval between snake bite and administration of first dose of ASV) were recorded. Demographic, clinical and laboratory records were noted during hospital stay. All

patients clinical picture, CBC, RFT, LDH, CPK, urine output was monitored periodically and blood products transfused according to requirement. Patients were initiated on hemodialysis through temporary nontunneled catheter according to uremic symptoms and urine output. Bite to HD initiation time (time interval between snake bite and first hemodialysis initiation) were recorded. HD was continued based on uremic symptoms and weaned off based on improvement in urine output and improvement in uremia. Those who succumbed to death during the hospital stay were excluded from the study. Patients who did not show recovery in 21 days was planned for renal biopsy after obtaining consent. Based on days required for renal recovery (dialysis independency) patients were divided into two groups namely patients with early recovery (≤ 10 days) and patients with late recovery (>10 days). Similarly patient were divided based on the duration of hospital stay such as patient who stayed ≤ 15 days and >15 days. Clinical data were compared between both groups and analyzed.

Statistical analysis:

All categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as mean with 95% confidence intervals or median with interquartile range based on the normality of data. To find the significant difference between the bivariate samples in Independent groups the Independent sample t-test was used. To find the significance in qualitative categorical data Chi-Square test was used. In both the above statistical tools the probability value 0.05 is considered as significant level. The collected data were analysed with IBM SPSS Statistics for Windows, Version 29.0. (Armonk, NY: IBM Corp).

RESULTS:

About 98 patients with dialysis requiring AKI were registered, among which 15 patients succumbed to death. Remaining 83 patients' clinical data was recorded.

Demographics:

The age of patients admitted with dialysis requiring AKI ranged from 13 years to 70 years with mean age of 46 years with 10.8% belonged to ≤ 20 years group, 19.3% were from 21-40 years, 54.2% were from 41-60 years, 15.7% belonged to >60 years group. Among the patients, 63% were males and 37% were females. Among the demographic data 42% patients were from Salem, 19.8% from Namakkal, 14.8% from Krishnagiri, 12.3% from Kallakurichi, 6.1% from Dharmapuri, 2.5% from Athur and 2.5% from Erode. Among the site of bite, 93.9% in lower limb while 6.1% in upper limb. Viperidae family accounted for 19.2% of dialysis requiring AKI hemotoxic snake bites and was unidentified in 80.2% patients. 96.3% had no comorbidities and 3.7% had Diabetes mellitus as comorbidity.

Clinical data:

Bite to ASV time was ≤ 2 hours in 8.4% patients, 3-6 hours in 77.1% patients and > 6 hours in 14.5% patients. The mean bite to ASV time was 8.4 hours. 44.6% patients received ≤ 30 vials of ASV and 55.4% patients received > 30 vials of ASV. Fasciotomy was done in 5 patients in the period of 24-48 hours from bite. Bite to HD initiation time was 1 day in 7.2% patients, 2 days in 74.7% patients and 3 days in 18.1% patients. Iontropes was used in 23.5% of patients and not used in 76.5% of patients. Blood products were required in 32.1% patients and not required in 67.9% patients.

Laboratory investigation:

Hemoglobin in day1 was < 8 g/dl in 1.2% of patients, 8-12 g/dl in 53% patients, 12-16 g/dl in 32.5% patients and > 16 g/dl in 13.3% patients. Total counts in day1 were ≤ 11000 in 2.4% patients, > 11000 in 97.6% patients. Platelet counts in day 1 were < 1 lakh in 48.2% patients, 1-1.5 lakh in 26.5% patients, >1.5 lakhs in 25.3% patients. The mean creatinine while initiating hemodialysis was 3.2 mg/dl and the mean peak creatinine during the hospital stay was 7.1 mg/dl. Peak creatinine was ≤ 5 in 18.1% patients, 6-10 in 61.4% patients, >10 in 20.5% patients. LDH was found to be ≤ 1500 in 22.9% patients and > 1500 in 77.1% patients. CPK was found to be > 500 in 62.7% patients and ≤ 500 in 37.3% patients.

Patients were divided into 2 groups based on days of dialysis requirement and duration of hospital stay. 63.9% patients recovered in ≤ 10 days and 36.1% recovered in > 10 days with mean days of dialysis requirement was 10.1 days. 65.1% had hospital stay duration of ≤ 15 days and 34.9% had hospital stay duration of > 15 days with mean

duration of hospital stay was 14 days. Patient factors and laboratory investigations were compared between both groups and the same depicted in Table 1. Trend of hemoglobin, platelet counts and LDH during admission was compared with days of dialysis requirement and the same depicted in Figure 1a, 1b and 1c respectively. It also correlates with duration of hospital stay.

Renal pathology:

Among 83 patients, 4 patients was found to be dialysis dependency after 21 days hence planned for biopsy among which two patients found to have acute tubular necrosis, and one patient found to have renal cortical necrosis. One more patient was not willing. Among these patients, patient who was not willing and one patient with acute tubular necrosis became dialysis independent while the other two was discharged as dialysis dependent.

Outcome:

Among 83 patients, 81 patients discharged as dialysis independency while 2 patients discharged as dialysis dependent.

Table1: Comparison of patient factors and laboratory features between two groups based on recovery and hospital stay

		Early recovery	Late recovery	P value	Hospital stay(≤ 15 days)	Hospital stay(>15 days)	P value
Age (%)	≤ 20 years	17	0	0.121	16.7	0	0.109
	21-40 years	17	23.3		20.4	17.3	
	41-60 years	50.9	60		48.1	65.5	
	>60 years	15.1	16.7		14.8	17.2	
Sex (%)	Male	67.9	53.6	0.203	66.7	55.6	0.329
	Female	32.1	46.4		33.3	44.4	
Species of snakes (%)	Viperidae	20.8	17.8	0.087	20.4	18.5	0.086
	Unknown	79.2	81.2		79.6	81.5	
Bite to ASV time (%)	≤ 2 hours	9.4	6.7	0.058	9.3	6.9	0.045
	3-6 hours	83.1	66.6		83.3	65.5	
	> 6 hours	7.5	26.7		7.4	27.6	
No of vials of ASV (%)	≤ 30 vials	50.9	33.3	0.121	50	34.5	0.175
	>30 vials	49.1	66.7		50	65.5	
Bite to HD initiation time (%)	1 day	9.4	3.3	0.545	9.3	3.4	0.599
	2 days	71.7	80		72.2	79.3	
	3 days	18.9	16.7		18.5	17.2	
Requirement of blood products (%)	Yes	17	60.7	0.0001	18.5	59.3	0.022
	No	83	29.3		81.5	40.7	
Use of ionotropes(%)	Yes	24.5	21.4	0.754	25.9	18.5	0.458
	No	75.5	78.6		74.1	81.5	
Hemoglobin Day 1(%)	>16	15.1	10	0.609	16.7	6.9	0.245
	12-16	28.3	40		25.9	44.8	
	8-12	54.7	50		55.6	48.3	
	<8	1.9	0		1.9	0	
Total count day1 (%)	≤ 11000	3.8	0	0.533	3.7	0	0.540
	>11000	96.2	100		96.3	100	
Platelet count (%)	< 1 lakh	39.6	63.3	0.012	40.7	62.1	0.057
	1-1.5 lakhs	24.6	30		25.9	27.6	
	>1.5 lakhs	35.8	6.7		33.3	10.3	

Peak creatinine (%)	≤ 5	27.8	0	0.006	27.8	0	0.006
	6-10	51.9	79.3		51.9	79.3	
	>10	20.3	20.7		20.4	20.7	
LDH day1 (%)	≤1500	33.3	3.4	0.002	33.3	3.4	0.002
	>1500	66.7	96.6		66.7	96.6	
CPK day1 (%)	≤500	42.6	27.6	0.178	42.6	27.6	0.178
	>500	57.4	72.4		57.4	72.4	

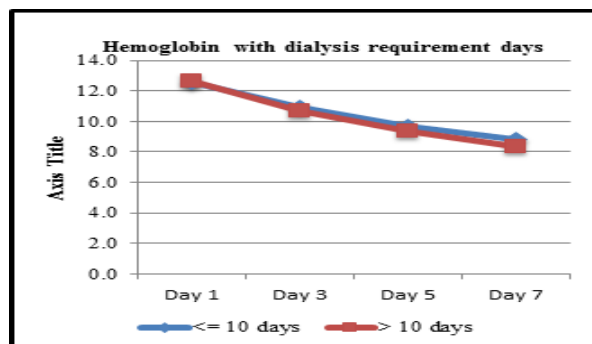


Figure 1a: Trend of hemoglobin plotted against hospital stay duration and compared between two groups.

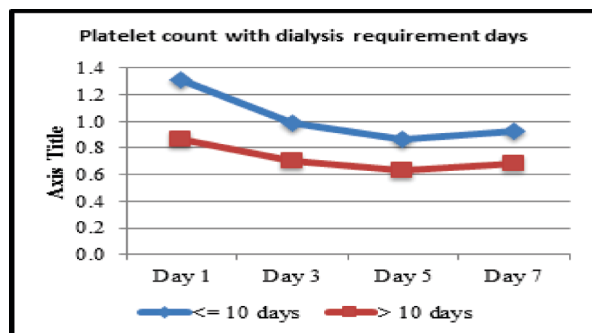


Figure 1b: Trend of platelet count plotted against hospital stay duration and compared between two groups.

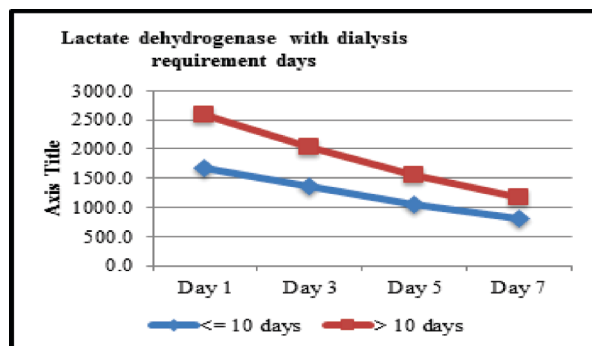


Figure 1c: Trend of LDH plotted against hospital stay duration and compared between two groups

DISCUSSION:

Snake bite induced AKI is a well recognized complication but factors influencing its recovery are less explored.

Demographics:

In our study, age group who had dialysis requiring AKI was mostly 41-60 years which correlated with most previous studies [7-9] except for one study [10] from China where the mean age of the patient was 66 years. This could be due to lower renal reserve when compared with people of younger age group. In our study most commonly dialysis requiring patients were males which correlate with previous studies [7-10] because they are the most working individuals in the farm area and hence high risk of developing AKI. Almost 90% of the patients were from rural areas which is similar to most of previous studies [10] because of the increased floral density. Most of the bite sites were in the lower limb similar to most of the previous studies [11] which may be because most snake-bites happen when the snake is trodden on, either

in the dark or in undergrowth, and bite happen to someone who is bare-footed or wearing only sandals. Farmers and field workers should be educated to use long boots and leave the snakes undisturbed in the fields to prevent snakebites [7]. In our study, most of the snake bite species were unidentified which impede the investigation of the epidemiology of species-specific biological behavior of envenomation [9] and also the species-specific characteristics of AKI. Most patients were found to have no co morbidities and hence the development of AKI is exclusively secondary to snake bite.

Clinical data:

In our study most patients received ASV between 3 to 6 hours. This is the much debated factor influencing development of AKI, systemic symptoms, and also recovery from AKI. Athappan et al., [11] found that bite to needle time more than 2 hours (OR 2.10, $P = 0.001$) was an independent risk factor for the development of AKI. Kalantri et al., [12] noted mean bite to hospital time of 5.6 hours associated with survival from snake bite. On the contrary, Danis et al., [13] and Priyamvada et al., [8] observed that there was no association of bite to hospital time with development of AKI. The bite to hospital time varies depending on the availability of medical facilities and the settings in which the study has been done. Snake venom, which is responsible for almost all the complications of snake bite, must be neutralized as soon as possible with ASV [14]. In our study, for recovery it was found to be near significant ($p = 0.058$) and for duration of stay it was found to be significant ($p = 0.045$). More than half of patients received more than 30 vials of ASV and not found to be significant with both the outcome. This may be due to further dosage was determined by the local symptoms and hemotoxicity and not by renal failure. Surgical intervention in the form of fasciotomy was done for 5 patients within 24-48 hours from the snakebite. This does not found to have impact on dialysis requirement and hospital stay. Ionotropes and blood products were required in around one fourth of patients. Both are due to direct effects of snake venom namely capillary leak, hemolysis and coagulopathy. Among these two, blood products usage was found to significantly impact dialysis dependency and dialysis recovery. Blood products were used in 32.1% patients in our study which is dissimilar to Sanjay vikrant et al., [7] and Naqvi R., [18] which showed 88.6% patients and 65.2% patients respectively. Hypotension was found in 23.5% patients in contrary to other studies [7, 14] where it was 4.5% and 8.12% respectively.

Laboratory investigations:

Hemoglobin on day1 found to be 8-12 g% in more than half of patients and this may be due to either baseline lower level or due to hemolysis. Hemoglobin was recorded over the duration of hospital stay and found to be decreasing in all most all patients probably due to venom and sepsis induced hemolysis and the same plotted against hospital stay and compared between both groups (early and late recovery) found to be not significantly deciding recovery from AKI and duration of hospital stay. Total counts on day 1 found to be > 11000 in almost all patients. This may be due to bite site infection. Total counts found to be increasing in almost all of the patients followed by a fall and this not found to be significantly affecting the dialysis dependency or the duration of hospital stay. This may be due to the local infection of the bite site or non-tunneled catheter infection which has been used as HD access. Platelet count found to be less than 1 lakh in nearly half of patients which may be due to hemolysis and hemotoxicity as like most other previous studies [15]. Platelet counts were recorded during admission and plotted against the days of hospital stay. It was found to be more decreasing in the patient group who required dialysis more than 10 days and the same holds good for duration of hospital stay. Peak creatinine was found to be between 6 and 10 among patients requiring dialysis more than 10 days and this was found to be significant. This may be due to the severity of acute tubular necrosis or possibility of renal cortical necrosis.

Lactate dehydrogenase on day1 was found to be > 1500 in 77.1% patients and remaining had within 1500. LDH was measured periodically during admission and plotted against the days of hospital stay and it was found to be increasing. The graph was compared between two groups and it was found that patients requiring dialysis more than 10 days had more increasing trend of LDH and found to be significant and the same holds good for duration of hospital stay. LDH, class of oxidoreductases is an important enzyme of the anaerobic metabolic pathway. The function of the enzyme is to catalyze the reversible conversion of lactate to pyruvate with the reduction of NAD^+ to NADH and vice versa. LDH exhibits five isomeric forms

assembled in tetramers of either of the two types of subunits, namely muscle (M) and heart (H). The isoforms called isozymes are named LDH-1 through LDH-5, each having differential expression in different tissues. Among which Isozyme LDH-4 has one heart and three muscle subunits (1H3M) and is the primary isozyme present in the kidneys [16]. Upon tissue damage, the cells release LDH due to loss of cytoplasm into the bloodstream. Depending upon the type of tissue injury, the enzyme can remain elevated for up to 7 days in the bloodstream. LDH assays can measure the amount of LDH present in the serum that leaks from the tissues when damaged. But routine isozyme measurement is usually unavailable in clinical laboratories; hence it is a non specific test. The presence of high concentrations of vitamin C may lead to a falsely low LDH result. On the other hand, the presence of anesthetics, aspirin, alcohols, and certain narcotics, and procainamide may falsely increase the LDH result.

Rhabdomyolysis was seen in 62.7% patients as compared to 100% in a study by Pinho et al [17]. It might have been missed in some of them due to delayed arrival at our hospital. Majority of our patients had both hemolysis and rhabdomyolysis contributing to the development of AKI. However it was not found to be significantly affecting either the hospital stay or dialysis requirement.

Renal pathology:

The renal lesions of clinical significance in envenomed patients are Acute Tubular Necrosis (ATN), and patchy or diffuse Renal Cortical Necrosis (RCN). Glomerulonephritis, Acute Interstitial Nephritis (AIN), and papillary necrosis have been reported in rare patients. Tubulointerstitial lesions, predominantly ATN, are observed in 70% to 80% of patients with AKI [18]. Biopsies carried out early reveal morphological features of severe acute tubular injury with intratubular pigmented granular casts. Varying degree of acute tubulointerstitial nephritis and interstitial edema may be found. Late biopsies reveal regenerating tubular epithelium [18]. AIN was considered to be a rare after snake bite but according to recent studies AIN after snake bite is not uncommon [19]. Most of the patients of ATN and AIN recover by few weeks, with the help of renal replacement therapy, but who develops RCN requires renal replacement therapy on a long term basis.

In our study 2 patients found to have acute tubular necrosis and 1 patient found to have renal cortical necrosis. In our study patients who were biopsied were very low to be compared with other studies.

CONCLUSION:

Hence awareness about snakebite and preventive strategies to be educated to the farmers and field workers. Importance of early presentation to hospital also to be educated. Timely initiation of ASV following snakebite has near significant impact on recovery from AKI. Bleeding tendencies has worse outcome in recovery. Monitoring of platelet count and LDH gives significant information about the recovery.

Limitations:

The study is limited to the hospital stay and further follow up after discharge is required. In our study the recovery criteria was dialysis independency, returning of creatinine to baseline was not taken into account. LDH not a specific enzyme for renal injury as specific isozyme measurement not widely available

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