Original Research Article

Study of acute kidney injury in snake bite patients in Salem district

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Abstract

Background: Snakebite poisoning is known to man since antiquity. The complications related to kidneys are observed in the majority of patients with a poisonous snake bite. Among the multifactorial cause for the pathogenesis of snakebite-induced AKI (SAKI), elevated oxidative, and carbonyl stress (CS) leading cause of kidney injury. Oxidative stress (OS) results in the modification of protein either directly through the oxidation of amino acid residues by reactive oxygen species (ROS) or indirectly by an increased generation of reactive carbonyl species. Although increased CS and protein modification has been extensively studied in both hyperglycemic and corticotropin-releasing factor and many cases of AKI, proteins damage due to OS and CS in SAKI has not been described well in literature.

Aim of the study: This study was an attempt to study the clinical profile of snakebite patients and evaluation of acute kidney injury in them.

Materials and methods: The study was conducted in 2018 at the Department of General Medicine, Government Mohan Kumar Mangalam Medical College, Salem. Fifty patients with snakebite induced acute kidney injury were selected randomly and their clinical profiles were assessed. AKI was evaluated using noninvasive methods.

Results: Out of 50 patients in the study, the majority were males (62%) with a mean age of presentation 43.8±12.63 years. The mean interval between snakebite and presentation to Hospital was 15.37 hours. 98% of patients presented with local signs of inflammation, 52% of patients presented with coagulation abnormality and 60% with decreased urine output.

Conclusion: Common manifestations of poisonous snake bite include cellulitis, abnormal coagulation profile and decreased urine output. Overall mortality due to snakebite induced AKI is 6%. Lapse of time in presenting to the hospital and abnormal coagulation profile are the predictors of poor outcome.

Key words

Introduction

Snake Bite Poisoning is 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 [1]. Recent estimates indicate somewhere between 1.2 million and 5.5 million snakebites worldwide each year, with 421,000-1,841,000 envenomations and 20,000–94,000 deaths [2]. Several educational and preventive actions should be taken in order to protect farm workers, who are the main victims of such accidents [3]. The complications related to kidneys are observed in the majority of patients with a 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 [4]. Snake venom is mostly watery in nature. It consists of numerous enzymes, proteins, amino acids, etc., Some of the enzymes are proteases, collagenase, arginine ester hydrolase, hyaluronidase, phospholipase, metalloproteinases, endogenous, autocoids, thrombogenic enzymes, etc.[5]. These enzymes also act as toxins on different tissues of the body and are grouped under neurotoxins, nephrotoxins, hemotoxins, cardiotoxins, cytotoxins, etc. resulting in organ dysfunction/ destruction [6]. Enormous clinical and experimental works have been published on the pathophysiology of snakebite in relation to different species of snakes Hyaluronidase allows rapid spread of venom through subcutaneous tissues by disrupting mucopolysaccharides, and 28 phospholipase A2 has an osteolytic effect on the red blood cell membrane and causes hemolysis. It also promotes muscle necrosis [7]. Thrombogenic enzymes promote the formation of a weak fibrin clot, which activities plasmin and results in consumptive coagulopathy and hemorrhagic consequences. The venom of some snakes causes neuromuscular blockade at pre or post-synaptic levels. In addition to the above, it causes endothelial cell damage which results in increased vascular permeability. In short, snake venom acts on various parts/systems/organs of the body. Venom also causes endothelial cell damage which results in increased permeability [8].

Materials and methods

The study was conducted in 2018 at the Department of General Medicine, Government Mohan Kumar Mangalam Medical College, Salem. Fifty patients with snakebite induced acute kidney injury were selected randomly and their clinical profiles were assessed. AKI was evaluated using noninvasive methods.

Inclusion criteria
- History of snake bite with signs of envenomation.
- Progressive elevation of serum creatinine >0.3 mg/dl from baseline, a percentage increase in the serum creatinine concentration of >50% or oliguria of fewer than 0.5 ml/kg/hr for more than 6 hours.

Exclusion criteria
- Patients with pre-existing renal diseases with a history of snake bite.
- Patients with risk factors for developing the renal disease with a history of snake bite. (diabetes, hypertension, connective tissue diseases, chronic infection)

Data were collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations were undertaken. The purpose of the study was explained to the patient and informed consent obtained. Using non-invasive methods acute kidney injury in snake bite patients who fulfill the inclusion criteria was assessed. Patients were classified into three

stages of acute kidney injury proposed by Acute Kidney Injury Network which defines AKI as an "abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3 mg/dl from baseline, a percentage increase in the serum creatinine concentration ≥50% or oliguria of 0.5 ml/kg/hr >6 hours. The course acute kidney injury in three stages and the need for renal replacement therapy was assessed.

Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables, etc.

Results

Sixteen patients were in the age group of 41–50 years. The mean age was 43.8 years. Out of 50 patients included in this study, 31 were males (62%) and 19 (38%) were females (**Table – 1**).

Table - 1: Age distribution of patients studied.

Age group (years)	No. of patients	%
18-30 years	12	24.0
31-40 years	7	14.0
41-50 years	16	32.0
51-60 years	13	26.0
>60 years	2	4.0
Total	50	100.0

Table - 2: Snake bite site of patients studied.

Snake bite site	No. of patients (n=50)	%
Side of bite		
Left side	32	64.0
Right	18	36.0
Site of bite		
Leg	20	40.0
Foot	19	38.0
Toe	5	10.0
Calf	4	8.0
Shin	2	4.0

All bites were to the lower limb. 32 patients (64%) of patients had a snake bite to the left lower limb (**Table – 2**).

Table - 3: Distribution of lapse of time in hours of patients studied.

Lapse of time in hours	No. of patients	%
0-2 hours	7	14.0
2-5 hours	18	36.0
5-12 hours	11	22.0
12-24 hours	7	14.0
>24 hours	7	14.0
Total	50	100.0

Table - 4: Distribution of tourniquet application of patients studied.

Tourniquet application	No. of patients	%
No	19	38.0
Yes	31	62.0
Total	50	100.0

Table - 5: Identification of snake of patients studied.

Identification of snake	No. of patients	%
Not identified	26	52.0
Identified		
Viper	23	46.0
Cobra	1	2.0
Total	50	100.0

Table - 6: Symptoms of snake bite patients.

Symptoms	No. of patients (n=50)	%
Reduced urine output	30	60.0
Vomiting	19	38.0
Bleeding from the bite site	16	32.0
Bleeding from the gums	9	18.0
Hematuria	7	14.0

18 (36%) patients presented to the hospital within 2-5 hours of snake bite. Only 7 patients presented after 24 hours of snake bite to the hospital (**Table – 3**).

Table - 7: Vital statistics of patients studied.

Vital statistics	No. of patients (n=50)	%
Pulse		
<100	43	86.0
>100	5	10.0
Not recorded	2	4.0
Systolic blood pressure mmHg		
<120	34	68.0
>120	14	28.0
Not recorded	2	4.0
Diastolic blood pressure mmHg		
<80	29	58.0
>80	19	38.0
Not recorded	2	4.0

Table - 8: Clinical manifestations.

Clinical manifestation	No. of patients (n=50)	%
Fang mark	47	94.0
Signs of inflammation	49	98.0
Bleeding from the bite site	16	32.0
Peripheral pulses not felt	2	4.0

62% had applied tourniquet before coming to the hospital (**Table – 4**). Among 50 snake bites, only 24 (48%) had identified the snake as viper bites in 23 cases and cobra bite in 1 case (**Table – 5**). Thirty (60%) patients presented with reduced urine output, 19 patients (38%) with vomiting, 16 (32%) with bleeding from gums and 7 (14%) presented with hematuria (**Table – 6**).

Five patients (10%) had tachycardia and 2(4%) pulse was not palpable. Systolic blood pressure (SBP) was ≤120 mmHg in 34 (68%) and >120 in 14(28%). Diastolic blood pressure (DBP) was ≤80 mmHg in 29 (58%) and >80 mmHg in 19 (38%). Blood pressure was not recordable in 2 patients (**Table – 7**). On local examination 49 (98%) had signs of inflammation, 47 (94%) had fang mark, 16 (32%) had bleeding from bite site and in 2 (4%) patients peripheral pulses not felt (**Table – 8**).

Laboratory data showed anemia with Hb <10 gm% in 27 (54%), Leukocytosis (Total count >11,000) in 8 (16%) and thrombocytopenia (platelet count <1.5 lakh) in 13 (26%) patients (**Table – 9**). Whole Blood Clotting Time (WBCT) was >20 minutes in 35 (70%) patients (**Table – 10**). Bleeding time was prolonged in 8 (16%) patients (**Table – 11**).

Mean levels of blood urea at baseline, at 24 hours (p value <0.001), on 2nd day and 3rd day were 61.01 mg/dl, 81.92 mg/dl, 74.26 mg/dl and 64.83 mg/dl respectively (**Table – 12**). Mean levels Serum Creatinine at baseline, at 24 hours (p-value <0.001), on 2nd day and on 3rd day were 2.32 mg/dl, 3.02 mg/dl, 2.94 mg/dl and 2.52 mg/dl respectively (**Table – 13**). All patients included in the study had elevated serum creatinine kinase levels with a mean of 266.58 U/L (Mean ± SD: 266.58±122.53) as per **Table – 14**.

PT-INR was prolonged (>1.2 seconds) in 17 (34%) patients and APTT was prolonged (>28 seconds) in 44 (88%) of patients (**Table – 15**). Mean levels of urine output at baseline, at 24 hours, on 2nd day and on 3rd day were 1205.40 ml/day, 1433.67 ml/day, 1742.20 ml/day and 1981 ml/day respectively with significant p-value (<0.001) as per **Table - 16**.

Twenty patients (40%) received 11-20 vials of ASV and ≥30 vials of ASV were given only for 2 patients. All patients received intravenous fluid (IVF) and 48 patients (96%) received antibiotics as supportive treatment. 7 patients were transfused blood and blood products. 3 patients (6%) were transfused FFP, 4 (8%) were transfused whole blood and one patient received platelet transfusion (**Table – 17**). Among 50 patients 6 (12%) required hemodialysis (**Table – 18**). Out of 50 patients studied, 43 (86%) improved and 7 had a poor outcome. Among those 7, 4 patients developed Chronic Kidney Disease (CKD) and 3 patients succumb to death (**Table – 19**).

Table – 9: Hematological parameters of patients studied.

Hematological parameters	Number of patients (n=50)	%	Mean ± SD
Hemoglobin (Hb in gms)			
<10.0%	27	54.0	9.40±2.08
>10.0%	23	46.0	
Total count			
<4000	4	8.0	8013.00±5214.13
4000-11000	38	72.0	
>11000	8	16.0	
Platelet count			
<1.5 lakh	13	26.0	1.95±0.83
>1.5 lakh	37	74.0	

Table - 10: WBCT in minutes of patients studied.

WBCT in minutes	No. of patients	%
<20	15	30.0
>20	35	70.0
Total	50	100.0

Table - 11: Bleeding time of patients studied.

Bleeding time	No. of patients (n=50)	%
Normal	42	84.0
Abnormal (Increased)	8	16.0
Total	50	100

Table - 12: Levels of blood urea of patients studied.

Blood urea	Min - Max	Mean ± SD	P-value from baseline
Baseline	15.00-198.00	61.01±39.99	-
24 hours	29.00-192.00	81.92±40.75	<0.001*
2nd day	22.00-188.00	74.26±42.69	0.016
3rd day	17.00-196.00	64.83±41.45	0.668

Table - 13: Levels of serum creatinine of patients studied.

Serum creatinine	Min - Max	Mean ± SD	P-value
Baseline	0.30-20.00	2.32±3.30	0
24 hours	0.90-21.00	3.02±3.58	<0.001**
2nd day	0.60-21.00	2.94±3.72	0.016
3rd day	0.60-18.00	2.52±3.24	0.472

Table - 14: Creatine kinase of patients studied.

Creatine kinase	No. of patients	%
Normal (Male: 25-90 U/L; Female 10-70 U/L)	0	0.0
Raised (Male >90 U/L; Female >70 U/L)	50	100.0
Total	50	100.0

Table - 15: PT INR and APTT of patients studied.

	No. of patients (n=50)	%
PT INR		
0.8-1.2	33	66.0
>1.2	17	34.0
APTT		
<28.0	6	12.0
>28.0	44	88.0

Table - 16: Urine output in ml/day of patients studied.

Urine output in ml	Min - Max	Mean ± SD	P-value
Baseline	15.00-4000.00	1205.40±1010.72	-
24 hours	50.00-3500.00	1433.67±945.29	<0.001**
2nd day	60.00-3000.00	1742.20±929.42	<0.001**
3rd day	100.00-3500.00	1981.00±874.98	<0.001**

Table - 17: ASV vials given for patients studied.

ASV vials were given	No. of patients	%
Not given	10	20.0
1 to 10	7	14.0
11 to 20	20	40.0
21 to 30	11	22.0
>30	2	4.0
Total	50	100.0

Table - 18: Need for hemodialysis of patients studied.

Need for hemodialysis	No. of patients	%
No	44	88.0
Yes	6	12.0
Total	50	100.0

Table - 19: End results of snakebite patients studied.

End results	No. of patients	%
Improved	43	86.0
CKD	4	8.0
Death	3	6.0
Total	50	100.0

Comparison between good outcome (recovered from AKI) and poor outcome (not recovered from AKI) shows significant p-value for 'lapse of time in hours' in presenting to the hospital after snake bite (p-value 0.005) and 'alternative treatment taken' before coming to the hospital (p-value 0.001) as per **Table - 20**.

Patients who had poor outcomes after snake bite induced AKI presented with reduced urine output in 85.7%, vomiting in 57.1%, hematuria in 28.6% and signs of inflammation in 100% when compared to patients with a good outcome without significant p-value (**Table – 21**). Forty-two patients (84%) were in Stage I AKI, 2 (4%) were in Stage II and 6 (12%) patients were in Stage III AKI (**Table – 22**).

Discussion

The kidney, a highly vascularized organ with excretory function, is prone to venom toxicity as an innocent bystander. AKI, the most significant of all the renal manifestations, has been reported with varying frequency in different studies. In our study, we studied the demographic and clinical predictors of developing AKI in snakebite victims. Males were more commonly the victims of snake bites, probably due to their more outdoor activities in the field [9]. However, there was no significant association of gender of the patient and the development of AKI after snake bite (P > 0.05). Patients who developed AKI were mostly older than those who did not develop AKI (34 ± 1.64 vs. 32 ± 1.62) (P < 0.05) [10]. Cerda J., et al. also found an increased incidence of AKI in the older age group. This could be due to declining renal reserve with age. Our snakebite patients hailed predominantly from the rural population as Barabanki is predominantly an agricultural district and people working in the fields are more exposed to snakes. However, the development of AKI was not significantly related to the residence of the patient independently as compared to other factors [11]. An important observation was that a significant number of patients (42.75%) took nonmedical treatment before coming to the hospital demonstrating the prevalent customs in the population. This is an important contributing factor for the development of various complications of snakebite including renal failure because of prolongation of bite to ASV time. The increased time interval between bite to the administration of ASV (bite to needle time) had a direct correlation with the development of AKI (P < 0.05) [12]. Delay in the administration of ASV increases the risk of developing AKI. The venom continues to produce damage until it is neutralized. Early administration of anti-venom could reverse all clinical manifestations of snakebite. Causes of delay in seeking proper medical treatment could be due to lack of awareness of the importance of early medical treatment of snakebite patients and consulting local healers using charms and other nonmedical treatment in snake bite as well poor transportation facilities in rural areas. Snakes that cause renal failure are either myotoxic or hemotoxic but venom may have direct

nephrotoxicity [13]. Among land snakes, there are five important venomous species in India. They are neurotoxic Elapidae, including common Cobra (Naja naja), King Cobra (Ophiophagus hannah), and Krait (Bungarus caeruleus, Bungarusfasciatus); and vasculotoxic Viperidae, Russell's viper (Daboia russelii), and saw-scaled viper (Echis carinatus) [14].

Table - 20: Association of clinical variables according to outcome.

Clinical variables	Outcome		P-value
	Good (n=43)	Poor (n=7)	
Age in years			
<40	18(41.9%)	1(14.3%)	0.229
>40	25(58.1%)	6(85.7%)	
Gender			
Male	27(62.8%)	4(57.1%)	1.000
Female	16(37.2%)	3(42.9%)	
Site of bite			
Leg	18(41.9%)	2(28.6%)	0.687
Foot	14(32.6%)	5(71.4%)	0.093+
Toe	5(11.6%)	0(0%)	1.000
Calf	4(9.3%)	0(0%)	1.000
Shin	2(4.7%)	0(0%)	1.000
Lapse time in hours			
0-2 hours	7(16.3%)	0(0%)	
2-5 hours	18(41.9%)	0(0%)	
5-12 hours	10(23.3%)	1(14.3%)	0.005**
12-24 hours	4(9.3%)	3(42.9%)	
>24 hours	4(9.3%)	3(42.9%)	
Alternative treatment			
No	40(93%)	2(28.6%)	<0.001**
Yes	3(7%)	5(71.4%)	
Identified snake			
Not identified	24(55.8%)	2(28.6%)	0.239
Identified	19(44.2%)	5(71.4%)	
Tourniquet application			
No	16(37.2%)	3(42.9%)	1.000
Yes	27(62.8%)	4(57.1%)	

Table - 21: Association of clinical symptoms according to outcome.

Clinical symptoms	Outcome		P-value
	Good (n=43)	Poor (n=7)	
Signs of inflammation	42(97.7%)	7(100%)	1.000
Reduced urine output	24(55.8%)	6(85.7%)	0.219
Vomiting	15(34.9%)	4(57.1%)	0.404
Bleeding from bite site	15(34.9%)	1(14.3%)	0.406
Bleeding from the gums	8(18.6%)	1(14.3%)	1.000
Hematuria	5(11.6%)	2(28.6%)	0.250

Table - 22: Stage of AKI of patients studied.

Stages of AKI	Number of patients	%
Stage I	42	84.0
Stage II	2	4.0
Stage III	6	12.0
Total	50	100.0

Acute renal failure is an important complication of Russell's viper and saw-scaled viper species of snakes in India. Up to 70% of the protein content of viper venom is phospholipase A2, present in the form of at least seven isoenzymes Possible clinical effects of the enzyme include hemolysis, rhabdomyolysis, presynaptic neurotoxicity, vasodilatation and shock, the release of endogenous autacoids, and interaction with monoamine receptors. Interestingly, Vaidya, et al. [15] found geographical variation in the clinical manifestations, reflecting differences in venom composition. In our study, we noticed that those patients who subsequently developed acute renal injury had predominant complaints of GIT symptoms such as abdominal pain, tenderness, and vomiting. Abdominal pain, thought to be caused by submucosal hemorrhages in the stomach, has long been recognized as an important and early symptom of venomous snake bite. Abdominal pain and vomiting may denote the severity of envenomation. Vomiting can be a part of the autonomic symptoms of snakebite. Jorge et al. 1997 report severe envenomation are associated with several autonomic symptoms such as vomiting, nausea, sweating, and abdominal colic [16]. Mehta, et al. found that the risk of death was six times higher for those snakebite patients with a history of vomiting. The most striking abnormalities following bites by Russell's viper and Echis carinatus are bleeding and coagulation defects [17]. In vivo, if the venom dose is large, massive intravascular clotting can stop the circulation and cause rapid death. With smaller doses of venom, such as those typically injected in humans, there is a continuous activation of fibrinogen, producing fragile fibrin more susceptible to lysis than is ordinary fibrin [18]. The venom thus destroys fibrinogen as quickly as the liver provides it, and as a consequence, the blood either fails to clot or clots poorly. The final coagulation disturbance depends on the balance among the activity of procoagulant, anticoagulant, and fibrinolytic and fibrinogenolytic components of the injected venom. Russell's viper venom selectively activates Factor X. Echis carinatus venom, besides activating Factor X, also accelerates the conversion of prothrombin to abnormal thrombin [19, 20].

Conclusion

Acute renal failure complicates the course in 5% to 30% of victims of severe viper poisoning. The alterations include a varying degree of bleeding, hypotension, circulatory collapse, intravascular hemolysis, and disseminated intravascular coagulation with or without microangiopathy. Direct cytotoxic action of snake venom on the kidney is suspected, but convincing evidence is still lacking. Severe hypocomplementemia is consistently present, but I doubt its role in the causation of renal lesions. Hypersensitivity to venomous or anti venomous protein occasionally causes acute renal failure. Common manifestations of poisonous snake bite include cellulitis, abnormal coagulation profile and decreased urine output. Overall mortality due to snakebite induced AKI is 6%. Lapse of time in presenting to the hospital and abnormal coagulation profile are the predictors of poor outcome in snake bite induced acute kidney injury.

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