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Original Research Article

Socio-Demographic, Clinical Profile, Predictors and Outcome of Acute Renal Injury in Snake Envenomation

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Abstract

Introduction: Snakebites are a common reason for hospitalization in India. A recently published survey of snakebite deaths in India estimated that 45,900 people die from snakebites in India each year. Rajasthan, Uttar Pradesh, Andhra Pradesh and Bihar have the highest death rates. Local features of a snakebite include pain and swelling. Systemic features include tachycardia, hypotension, pulmonary edema, and renal failure. However, renal dysfunction is the most devastating manifestation associated with snakebite, particularly acute renal failure (AKI). This study was conducted to investigate the various factors that contribute to kidney injury in snakebite patients and to investigate the outcomes of snakebite patients with kidney injury.

Method: It is a prospective observational study on 100 snake bite patients. A snakebite is confirmed based on the patient's medical history and signs, bite marks (dental marks) at the claimed site, and possible identification of the snake (dead or alive - if purchased by patient or family). Patients were followed from admission until 3 to 5 days for the development of AKI, defined using urine output, serum creatinine, or glomerular filtration rate (GFR). Calculate GFR using the Cockcroft-Gault formula.

Results: In our study, mean age was 44.60 ±11.6 years. Male to female ratio was 1.56:1 with male dominance. The mean interval between snake bite and presentation was 15.37 hours. Lower limbs were the affected site in all patients and 48% were viper bite. Ninety-eight percent of patients had local signs of inflammation indicating the vasculo-toxic venom. A total of 84% patients had coagulation abnormality and 60% had decreased urine output which were associated with increase severity of AKI. There was need for haemodialysis in 12 patients. Twenty six patients had thrombocytopenia which was not associated with the severity of AKI.

Conclusion: From our study, we concluded that common manifestations of snakebite include cellulitis, coagulation abnormalities, and decreased urine output. The overall mortality rate from snakebite-induced ARI is 6%. Time to hospital admission and abnormal coagulation status are predictors of poor outcome in snakebite-induced acute kidney injury.

Keywords: Snake Bite, Acute Renal Injury, Viper, Cobra.

Introduction

Snake bite is a common hazard all over the world mainly in tropical and sub-tropical areas. India reports maximum snake bite related cases and deaths in one year. India reports almost 19.2 % poisonous bites or envenomation and 55% of all snake bite related deaths, that occur annually all over the world [1].

According to a recently published survey of snake bite related mortality in India 45,900 deaths occurs each year due to snake bite. Rajasthan, UP, AP and Bihar contribute the highest numbers of this mortality. Maximum number of deaths occurred in rural parts, especially during monsoon season and involve young males [2,3].

In India there are more than 250 species and subspecies of snakes, of which about 50 are poisonous [4]. The "big four" medically important species are Naja naja, Bungarus caeruleus, Daboia russelii and Echis carinatus [5]. Pain and swelling are the two most common presenting complaints in snake bite patients. Systemic findings include hypotension, tachycardia, pulmonary edema and deranged renal functions. Deranged renal function is the most devastating manifestation associated with snake bite, which present in form of Acute Kidney Injury (AKI).

In India, renal involvement is mostly seen with Russell viper (13%) and E. carinatus (32%). Oliguria or anuria generally develops within a few hours to as late as 96 hours after the snake bite [3]. On examination Urine may show gross or microscopic hematuria, hemoglobinuria and proteinuria (less than 500 mg/24 h) [6].

India is as country of varied cultural and social beliefs. due to notion and myths, human's motel to magico-religious treatment for snake chew which in addition cause postpone in in search of clinical treatment. as a result, there is a want for the health branch to disseminate the clinical factors related to snake bites to the community.

The aim of the present study is to study the various factors causing renal involvement in snake bite patients and to study the outcome of snake bite patients having renal involvement.

Material and Methods

This is a prospective observational study done on 100 snake bite patients admitted in department of General Medicine of Jawahar Lal Nehru hospital during September 2021 to September 2022. Ethical approval was taken for the study from institutional ethical committee and written informed consent was obtained. Snake bite was confirmed from patient's history and signs, presence of bite marks (fang marks) at the alleged site, identification of snake if possible (dead or alive-if bought by patient or relatives).

Inclusion Criteria

- The patients with alleged history of snake bite having sign and symptoms of mild/ moderate/ severe and envenomation.

Exclusion Criteria

- Hypertensive or diabetic patients.
- Patients with active renal disease or pre-existing renal disease, hepatobiliary disease.
- patients on chronic non-steroidal anti-inflammatory drugs (NSAID) therapy or any other nephrotoxic drug therapy.
- Patients having no symptoms, signs of envenomation or no hematological, no neurological involvement.

A detailed history was recorded and clinical examination was done and using predesigned and pretested Performa.

Snake bite patients was classified as mild, moderate, or severe envenomation [7].

Mild: Local findings only (e.g., pain, local ecchymosis, non-progressive swelling).

Moderate: Progressive swelling, mild systemic features and/or laboratory abnormalities.

Severe: Respiratory distress, neurologic dysfunction, bleeding manifestation and/or cardiovascular instability. Patients was administered tetanus toxoid injection, if not received previously.

Polyvalent Anti-Snake Venom (ASV) was given to all patients. The dose was 5 vials (50 ml or 50 units) for mild envenomation cases, 6-10 vials (60-100 ml or 60-100 units) in the moderate cases and 10 vials (100ml or 100 units) in severe envenomation cases, as an intravenous infusion of normal saline over 60 - 120 minutes. Repeat ASV was given depending on 1st 20 min Whole Blood Clotting Time (WBCT) test done 6 hours after the 1 st ASV dose and subsequent ASV dosage was administered depending on subsequent 20 min WBCT test done 6 hourly till two consecutive 20min WBCT tests was normal.

In cases of Neuro-paralytic symptoms and signs, 10 vials (100 ml or 100 units) were given as first dose. If no response after 1 hour, 10 vials (100 ml or 100 units) were repeated. If there was no response after 2 hours, then, patient was observed for neuro-paralytic recovery, without any further ASV dose. All patients were managed with hydration, antibiotics, dopamine, diuretics, blood/blood products, renal replacement therapy as and when indicated.

The patients were followed up from admission for upto 3-5 days for development of AKI which was defined using urine output, serum creatinine or Glomerular Filtration Rate (GFR). GFR was calculate using Cockcroft-Gault formula [8,9]. Clinical observation and biochemical parameters were looked for and recorded using predesigned and pretested Performa during 3-5 days of follow up after the snake bite.

Clinical Parameters included was Fever, Heart rate, Blood pressure (Hypotension), Site of bite, Local tenderness, Local swelling, Progression of swelling, oozing from wound, Bleeding from wound, Wound complications (blister, gangrene and compartment syndrome), Bleeding manifestations (petechiae, purpura, ecchymosis and conjunctival hemorrhages), Regional lymphadenopathy and Neurological signs.

Laboratory Parameters recorded included

1. Urine output (in ml), Color of urine, Urine microscopy, Hemoglobinuria, and Proteinuria.
2. Blood Urea, Serum Creatinine, GFR, Total Leukocyte Count, Platelet count, International Normalized Ratio, Direct and total serum Bilirubin, Serum Potassium, Serum Sodium.

Snake-Bite Time and ASV Related Parameters:

1. Bite-to-initial ASV administration time,
2. 20 min WBCT Prolongation time and Total dose of ASV.
   For comparison, patients were classified into two groups based upon presence or absence of AKI (AKI and No-AKI). Further follow-up of the patient was done for 3-5 days.

Statistical Analysis

Continuous variables in the two groups were expressed as mean ± standard deviation. For comparison of categorical variables, Pearson's Chi-square test was used. Fischer exact test was used for small numbers. For continuously distributed variables, Student's 't' test for the significance of difference between the means of two independent samples was

used. P value of 0.05 or less was considered to be significant.

Results

This is a prospective hospital based observational study including 100 patients presented with alleged history of snake bite is undertaken to study the acute Kidney Injury. The Mean ± SD age of study group was 44.60 ±11.6. There were 62 males (62%) and 38 were females (38%) patients. Demographic profile is shown in table no. 2, rural were more than urban and most common profession was farming.

Table 1: Distribution of patients according to age groups

Age group (years)	No. of Patients	%
18 - 20	5	5
21 - 30	19	19
31 - 40	14	14
41 - 50	32	32
51 - 60	26	26
61 - 70	4	4
Total	**100**	**100**

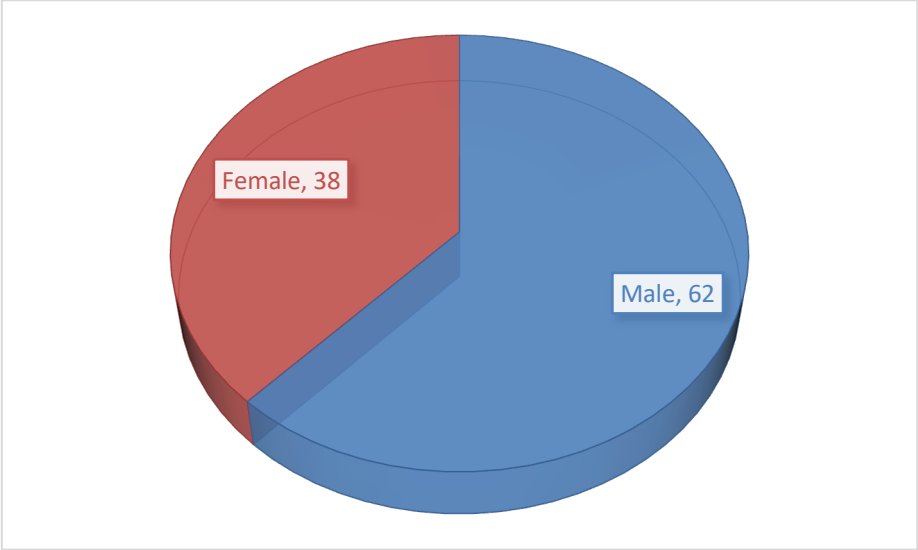

Figure 1: Distribution of cases according to sex

Table 2: Demographic distribution of patients studied

Demographic	No. of Patients	%
Urban	22	22%
Rural	78	78%
Occupation		
Farming and mining	52	52%
Household work	38	38%
Private Job	10	10%
Total	**100**	**100.0**

All the patients had bite in lower limbs. In 64 patients snake bite was to left lower limb. Thirty-six patients visited the hospital within 2-4 hours of snake bite and fourteen patients visited after 24 hours of snake bite. Forty-eight (48%) patients or their attendants identified the snake, in 46 cases as viper and 2 cases as cobra bite.

Presentation of patients is shown in table no. 3. Most common presentation was reduced urine output in sixty (60%) patients. On local examination, 97 patients shown signs of inflammation, 93 patients had visible snake fang marks, 33 patients had active bleeding at the bite site, and 4 patients had no palpable peripheral pulse. On general examination, we found tachycardia in 12 patients and no palpable pulse in 4 patients. Systolic blood pressure was ≤ 120 mmHg in 64 and > 120 mmHg in 32. Diastolic blood pressure was ≤80 mmHg in 54 patients and ≤ 80 mmHg in 42 patients. Blood pressure could not be recorded in 4 patients.

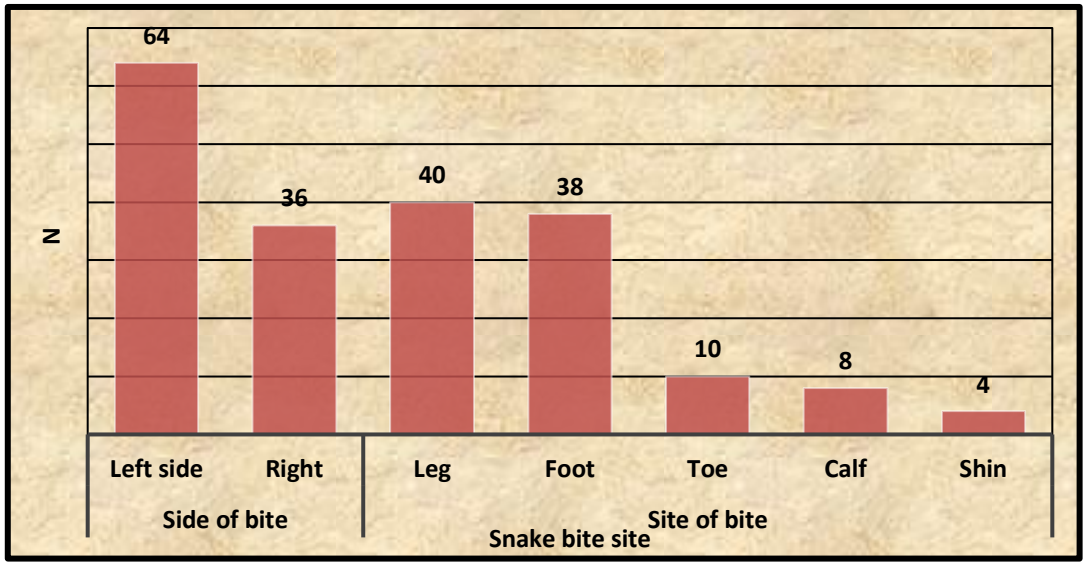

Figure 2: Snake bite site of patients studied

Table 3: Distribution of cases according to symptoms of patients

Symptoms	No. of Patients (n=100)
Decreased urine output	61
Nausea and Vomiting	38
Bite site bleeding	30
Gum Bleeding	16
Hematuria	15

Table 4: Hemogram values of the study group

Hematological Values	No. of Patients (n=100)	Mean ± SD
Hemoglobin (Hb in gm%)		9.40±2.08
< 10	53	
> 10	47	
Total WBC count (in cells / dl)		8009.00±5214.13
< 4000	8	
4000 -11000	73	
> 11000	15	
Platelet count		1.85±0.83
< 0.15 x 10^6	25	
> 0.15 x 10^6	75	

On lab investigation, as shown in table no. 4, anemia was seen in 53 patients, Leukocytosis was there in 15 patients and thrombocytopenia was reported in 25 patients. Whole Blood Clotting Time (WBCT) was done for all the patients. WBCT >20 minutes was seen in 71 patients. Bleeding time was prolonged in 17 patients. The trend of change of serum urea and serum creatine from baseline (on admission), 24 hrs after admission, 2nd day and 3rd day is shown in Table no. 5. The increase of serum urea was statistically significant after 24 hrs (p-value < 0.001). Similarly increase in serum creatinine was also found statistically significant on 24 hrs (p-value < 0.001). Elevated serum creatinine kinase levels were reported in all the patients, with a mean of 264.58±122.53. PT-INR was normal (0.8-1.2 seconds) in 66 patients and was prolonged (>1.2 seconds) in 34 patients. aPTT was normal (<28.0) in 12 patients and was prolonged (≥ 28.0) in 88 (88%) patients.

Table 5: Trend of change of serum urea and creatinine in study group

Parameter	Baseline	After 24 hours	2nd day	3rd day
Urea	60.98	81.96	73.99	65.01
Creatinine	2.30	3.05	3.01	2.56

On ultrasound examination, normal study was reported in 65 patients and in 35 patients showed normal sized kidney with alteration in cortical echo texture.

For the treatment by Anti Snake Venom, 20 patients did not receive ASV, 14 patients received 1-10 ASV vials, 40 patients were given 11-20 ASV vials, 22 patients received 21-30 ASV vials and ≥30 vials of ASV were given only for 4 patients. Blood transfusion was given to 16 patients. FFP transfusion was given to 6 patients. Whole blood to 8 patients and two patient received platelets transfusion. Among 100 patients 12 required hemodialysis.

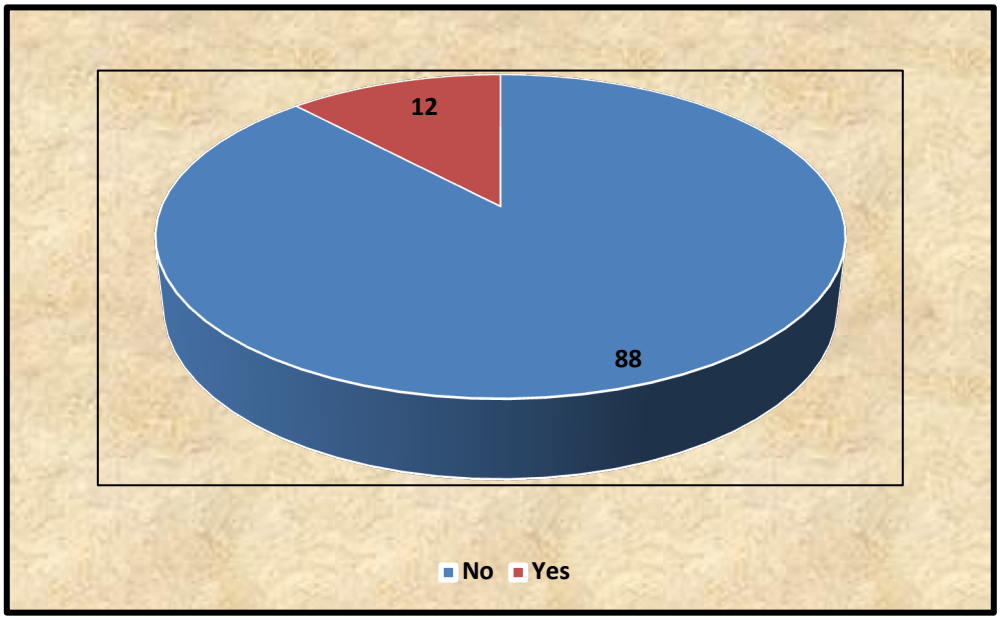

Figure 3: Patient distribution on basis of hemodialysis.

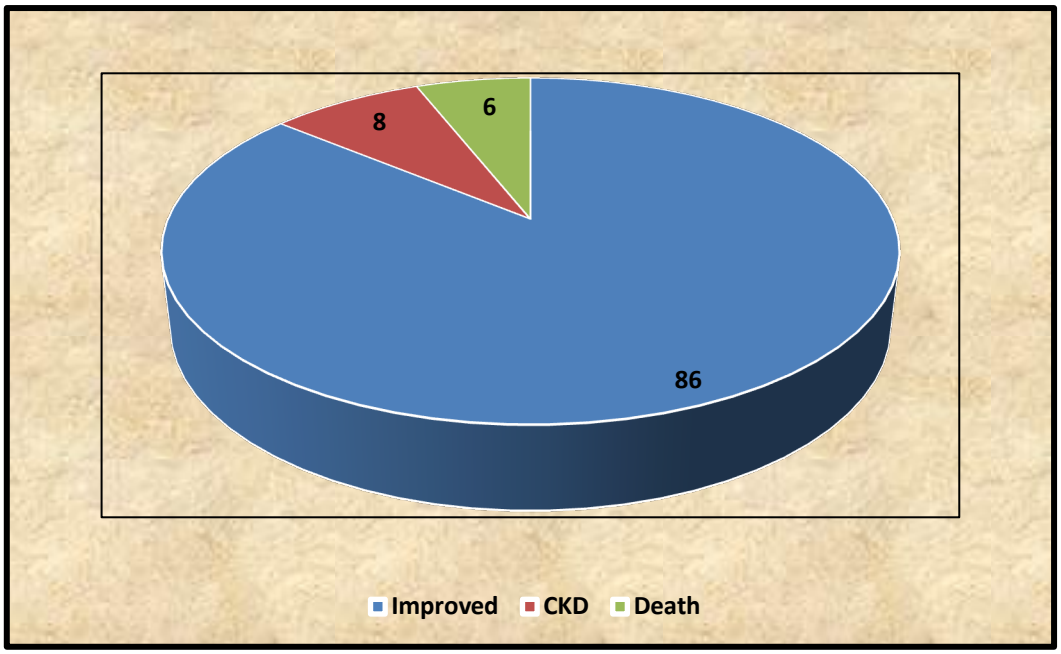

Figure 4: Distribution of cases according to end result

Comparison of good outcome (recovery from ARI) and poor outcome (no recovery from ARI) showed significant p-values (p-value = 0.004) for 'time in hours' and 'treatment alternative previously followed" in the hospital (p-value < 0.001). Comparison of the laboratory parameters of the good and bad results groups showed a significant p-value for the PT-INR (0.020). We found 84 patients (84%) with stage I ARI, 4 (4%) with stage II ARI and 12 (12%) patients with stage III ARI. [Figure 5]

Table 6: Comparison of Clinical parameters with outcome

Clinical Parameters studied	Patient's Outcome				P-value
	Good (n=84)		Poor (n=16)		
	No. of Cases	Percent	No. of Cases	Percent	
Age in years					
<40	36	43%	4	25%	0.22
>40	48	57%	12	75%	
Gender					
Male	52	62%	9	56%	1
Female	32	38%	7	44%	
Site of bite					
Leg	35	42%	5	31%	0.413
Foot	30	36%	8	50%	0.293
Toe	8	10%	2	13%	0.72
Calf	8	10%	0	0%	0.188
Shin	3	4%	1	6%	0.719
Lapse time in hours					
0-2 hours	14	17%	0	0%	0.004
2-5 hours	35	42%	1	6%	
5-12 hours	19	23%	3	19%	
12-24 hours	8	10%	6	38%	
>24 hours	8	10%	6	38%	
Alternative treatment					

No	78	93%	6	38%	<0.001
Yes	6	7%	10	63%	
Identification of snake					
No	47	56%	5	31%	0.177
Yes	37	44%	11	69%	
Tourniquet application					
No	31	37%	7	44%	0.051
Yes	53	63%	9	56%	

Table 7: Correlation of outcome and clinical symptoms

Clinical symptoms	Outcome		P value
	Good(n=84)	Poor(n=16)	
Inflammation	84 (100%)	16 (100%)	1
Decreased urine output	48 (55.8%)	12 (85.7%)	0.219
Nausea and Vomiting	30 (34.9%)	8 (50.0%)	0.404
Bite site bleeding	30 (34.9%)	2 (14.3%)	0.406
Gum bleeding	16 (18.6%)	2 (14.3%)	1
Hematuria	10 (11.6%)	4 (28.6%)	0.250

Table 8: Correlation of outcome and lab parameters

Lab parameters	Outcome				P value
	Good (n=84)		Poor (n=16)		
PT INR					
0.8 - 1.2	67	80%	3	19%	0.0001
> 1.2	19	23%	11	69%	
APTT					
< 28.0	16	19%	0	0%	0.079
> 28.0	70	83%	14	88%	
ASV vials given					
Not given	13	15%	7	44%	0.18
01-Oct	13	15%	1	6%	
Nov-20	33	39%	7	44%	
21 - 30	20	24%	2	13%	
> 30	4	5%	0	0%	
Platelet count					
< 1.5 lakh	22	26%	4	25%	0.813
> 1.5 lakh	64	76%	10	63%	

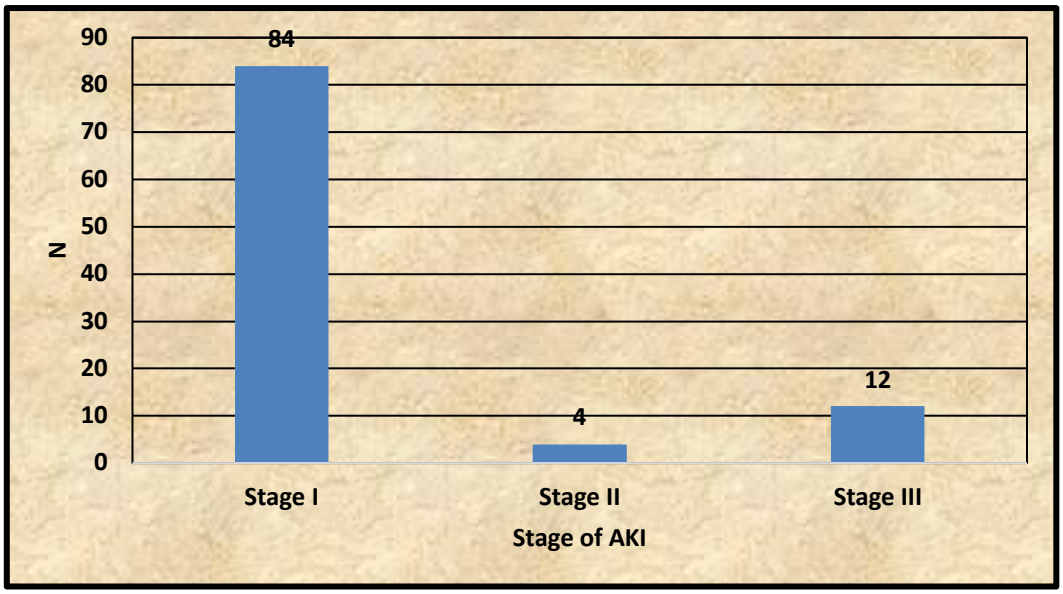

Figure 5: Stage of AKI of patients studied

Discussion

Snakebite is a major health problem with the highest prevalence in Asia. Clinically renal injury manifest as proteinuria, haematuria, pigmenturia and renal failure. Kidney disease is often caused by poisonous snakes or snakebites. [7] Acute renal failure mainly occurs after bites from vipers, sea snakes and vipers, but a large proportion of cases are caused by bites from venomous snakes. The Current Study is a prospective clinical study of 100 snakebite patients, conducted to study acute kidney injury with the aim of investigating the various factors that contribute to kidney damage in snakebite patients and to study the outcome of renal damage in patients with snakebite.

The average age of cases in our study was 44.60 years, with the majority (32%) in the 41-50 age group. Men represented 62% and women 38%. In the study by Kumar *et al* [8], the mean age of the patients was 28 ± 0.151 years and 90 (83.36%) men and 22 (19.64%) women. Male dominance may be because males generally go to ground daily, are more active at night, and travel more, while females spend most of their time in and around the house and enclosure. In a study by Kulkarni *et al* [9] showed 633 cases, of which 433 (68.40%) were men and 200 (31.60%) are women.

In our study 84% patients were in Stage I AKI, 4% were in Stage II and 12 (12%) patients were in Stage III AKI. Out of these patients studied, good improvement was seen in 84% patients, while 16 showed poor recovery. Among those 16 with poor outcome, 10 patients developed chronic kidney disease (CKD) and 6 patients did not survive. And, on comparing between good outcome (recovered from AKI) and poor outcome (not recovered from AKI), the present study showed statistical significance for 'lapse of time in hours' in first visit to the hospital after the snake bite (p-value = 0.004), alternative treatment taken before coming to the hospital (p-value < 0.001) and significant p-value for PT-INR (p-value < 0.001). All other parameters are comparable but not statistically significant. In concordance with our results study conducted by Patil *et al* [10] showed that in the cases of snake bite AKI developed was in 20.48%, whereas in another study by Ali *et al* [11] observed that 17% cases of snake bite were get complicated by AKI. Therefore, in our study, the snakebite mortality rate was 6%. In another study by Kulkarni *et al* [12], mortality was observed in 5.2% of patients. Athappan *et al* [13] studied a total of 1548 cases, 159 patients developed AKI, of

which 36 disappeared. Therefore, the mortality rates described in various studies vary from 2.5% to 25%. Hemoglobin less than 10 g, polymorphonuclear leukocytosis on day 1, thrombocytopenia, deranged prothrombin time and partially activated prothrombin time, INR, prolonged WBCT 20 minutes, serum creatinine and albuminuria are the parameters and indicators of coagulation and renal failure, which are well-established indicators of Mortality.

In our study all the snake bites were inflicted to the lower limb. A similar observation was reported in a study, which was done by Viramani *et al* [14] This is obvious as most snake bites occur while working day hours when people have upright posture. Therefore, this also shows that use of protective footwear can reduce the snake bites.

In our study, 36% of patients visited hospital within 2-4 hours of a snakebite, followed by 22% within 5-12 hours. Only 14 patients went to hospital 24 hours after the snakebite. A total of 62% patients had a tourniquet applied before coming to the hospital. Of 100 snakebites, 48% of the patients or their attendants identified the snake. Snakebites 46 were identified as viper bite and 2 as cobra bites. In 52% cases, snakes were not identified. In the study by Chakraborty *et al* [15], the mean hospitalization time for a bite was 5.13 ± 5.97 hours. The average length of hospitalization was estimated at 6.44 ± 4. 09 days.

In our study on snakebite, 61% of patients had reported decreased urine output, 38% had vomiting, 30 had bleeding at the bite site, 16 had bleeding from the gums, 15 complaint of Hematuria. In the USG abdomen, 34% of patients showed changes in renal cortical echogenic structure, while the kidneys were normal in size. In a study of current symptoms by Pillai *et al* [16], 47.1% of patients had decreased urination and 42.9% had fever. In 71.4% of patients, no renal parenchymal changes were observed on ultrasound, while the remaining patients (28.6%) had grade 1 renal parenchymal changes. Mahajan *et al* [17], reported oliguria in 71.1% of patients. In the study by Chakraborty *et al* [15], cellulitis (67.83%) and vomiting (53.84%) seemed to be the most frequent on the list, whereas only 3 cases (1.04%) of seizures have been reported, making this one of the rarest symptoms.

In present study on vital examination, we found tachycardia in 12 patients and no palpable pulse in 4 patients. Systolic blood pressure was ≤ 120 mmHg in 64 and > 120 mmHg in 32. Diastolic blood pressure was ≤80 mmHg in 54 patients and ≤ 80 mmHg in 42 patients. Blood pressure could not be recorded in 4 patients.

Anemia with Hb <10 gm% was found in 53, Leukocytosis in 15 and thrombocytopenia in 25 patients. Whole Blood Clotting Time (WBCT) was >20 minutes in 70 Patients. And Bleeding time was prolonged in 16 patients. PT-INR was prolonged (>1.2 seconds) in 34 patients and APTT was prolonged (>28.0 seconds) in 88.

In a study by Patil BT *et al* [10], 29.8% of patients had hematuria and 22.8% had other bleeding manifestations. Meshram *et al* [18] also observed hypotension and acute renal failure during vasotoxic venom poisoning and respiratory failure during neurotoxic bites. In Paul and Dasgupta [19] study 59.

06% of snakebite patients had a 20-minute WBCT > 20 minutes. Athappan *et al* [13] showed in their study that the presence of hemorrhagic manifestations was identified as an independent predictor of poor prognosis in snakebite patients. Hemorrhagic signs are those of coagulopathy, which in our study was a WBCT of 20 minutes > 20 minutes. Several thrombin-promoting enzymes are found in the venoms of venomous snakes and activate different steps in the coagulation cascade leading to the state of disseminated intravascular coagulopathy (DIC).

Bleeding tendencies can also lead to severe blood loss, leading to low blood pressure, which in turn can lead to kidney damage or kidney damage if not present.

DIC plays an important role for the development of ARI in patients with snake bite which is evident from the fact that there is presence of fibrin thrombi in renal microvascular glomerular capillaries. Microangiopathic hemolytic anemia, and thrombocytopenia also favors this hypothesis. Therefore, bleeding tendency secondary to DIC is an important factor in the development of AKI in snakebite patients, especially venomous viper snakebite patients.

In snake bite the level of urea increases from base line (60.98±39.99 mg/dl) to 81.96 mg/dl at 24 hours, 73.99 mg/dl at 2nd day. This increase in statistically significant (P-value <0.001; 0.016 respectively). Similarly, mean levels of Serum Creatinine at baseline was 2.30 mg/dl and increases at 24 hours to 3.05 mg/dl, and 2nd day of snake bite mean creatinine was 3.01 mg/dl. This increase in statistically significant (P-value<0.001; 0.016 respectively). And all patients included in the study had elevated serum creatinine kinase levels with a mean of 264.58 U/L.

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In our study 40% of the patients received 11-20 vials of ASV followed by 22% patients who received 21-30 vials.

Supportive treatment was given to all patients in form of Intravenous fluid (IVF) and 96% patients were given antibiotics. To sixteen patients blood and blood products transfusion was given. However only 12% required hemodialysis.

In the study by Meshram *et al* [18], most received primary treatment from medical staff, and 6.52% patients by rural health workers, however only 36.96% of patients received ASV. A total of 2.17% received the application of a tourniquet as primary treatment. A total of 52.

17% of children received initial treatment within an hour and were institutionalized within 6 hours of the bite.

Conclusion

From our study, we concluded that common manifestations of snakebite include cellulitis, coagulation abnormalities, and decreased urine output. The overall mortality rate from snakebite-induced ARI is 6%. Time to hospital admission and abnormal coagulation status are predictors of poor outcome in snakebite-induced acute kidney injury.

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