

Early Prediction of Acute Kidney Injury by Clinical Features of Snakebite Patients at the Time of Hospital Admission

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Abstract

Background: Snakebite is a major health problem in India. Venomous snakebite, which is an important medical hazard in several tropical countries including India, affects thousands of people per year and some of them develop acute kidney injury (AKI). **Aims:** This study was performed to find out 1) early clinical predictors for acute kidney injury in snakebite patients at the time of hospital admission and 2) incidence of acute kidney injury in snakebite patients. **Materials and Methods:** 171 consecutively admitted non-diabetic, non-hypertensive snakebite patients were examined. Multivariate linear regression analysis with 95 percent confidence interval (CI) was done for statistical analysis. Analyses were performed by software Statistical Package for the Social Sciences (SPSS) (17th version for Windows). **Results:** Incidence of acute kidney injury was 43.27%. Development of acute kidney injury was independently associated with 20 min whole blood clotting test (20 min WBCT) (P value = 0.029; CI 95%), dark or brown color urine (P value = 0.000; CI 95%), and time interval between snakebite and anti-snake venom administration (P value = 0.000; CI 95%). Age (P value = 0.011; CI 95%) and presence of neurological signs (P value = 0.000; CI 95%) were negatively correlated with development of acute kidney injury. **Conclusion:** Incidence of acute kidney injury is slightly higher in our study than previous studies. Early prediction of acute kidney injury development in snakebite patients can be done by presence of black or brown urine, 20 min WBCT > 20 min, and increased time interval between snakebite and administration of anti-snake venom at the time of hospital admission. Young age group of snakebite patients develops acute kidney injury more commonly.

Keywords: Acute kidney injury, age, amount of anti-snake venom, early prediction of acute kidney injury, 20 min WBCT, neurological signs, snakebite, time interval between snakebite and administration of anti-snake venom, urine color

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Introduction


Venomous snakebites are a serious health problem in tropical regions of the world due to their incidence, morbidity, and mortality.^[1] The incidence of acute kidney injury (AKI) due to Russell's viper snakebite is 13–32% in India.^[2] AKI is a serious complication of snakebites by the viperidae family.^[3]

Severely envenomed patients with Russell's viper bite

develop disseminated intravascular coagulation (DIC), resulting in spontaneous bleeding from different sites of body.^[4] Blood can ooze continuously from the bite marks, or severe hemorrhage may manifest as hematemesis, melena, hemoptysis, or bleeding into the muscles, fascial compartments, serous cavities, and the subarachnoid space. Early recognition and appropriate measures can reduce the occurrence of AKI.^[5]

Pain and swelling of the bite sites are generally the earliest symptoms which appear within a few minutes after bite. The swelling may involve the whole limb. Blistering or local necrosis is observed in one-third to one-half of the Russell's viper snakebite patients.

In patients with AKI, oliguria often develops rapidly within the first 24 h, but may be delayed till 2–3 days after the bite. Jaundice and hemoglobinuria resulting from

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intravascular hemolysis are also seen following Russell's viper or *E. carinatus* bites and have been reported from India and Sri Lanka^[6] but not frequently.

The study was done to find out (1) early clinical predictors for AKI in snakebite patients at the time of hospital admission, and (2) incidence of AKI in snakebite patients.

Materials and Methods

One hundred seventy one consecutively admitted non-diabetic, non-hypertensive snakebite patients were included in this prospective observational study. After taking consent, all subjects underwent a careful interview and examination. Snakebite patients were identifying from their history and presence of bite marks. This study was done in a tertiary care hospital in West Bengal, India (Eastern India).

Following clinical features and history were found out:

1. Local swelling at the site of bite and increasing the swelling with time.
2. Bleeding from the bite sites.
3. Black or brown urine. Because black or brown urine suggests generalized intravascular hemolysis.^[7] The black or brown urine which was positive for RBC or Hb, were included.
4. Time in between snakebite and administration of anti-snake venom.
5. Twenty minutes whole blood clotting test (20 min WBCT).
6. Total amount of anti-snake venom serum (AVS) given. AVS was given to the snakebite patients with one or more of the following criteria:
 - 20 min WBCT > 20 min.
 - Presence of ptosis/external ophthalmoplegia/dysphagia/paralysis.
 - Local swelling involving more than half of the bitten limb.
 - Rapid extension of swelling.
 - Spontaneous bleeding from bite site.
7. Presence of neurological signs (glossopharyngeal palsy, ptosis, ophthalmoplegia, and a generalized flaccid paresis, dysphagia).
8. History of diabetes and hypertension.

Criteria for diagnosis of hypertension and diabetes

1. Hypertension was diagnosed when a patient had received medicine for hypertension, or had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after taking 5 min rest.
2. Plasma glucose was measured by a "glucose oxidase-peroxidase" method. Diabetes was diagnosed

according to "American Diabetes Association" when a previous or current 12 h fasting glucose level is 7 mmol/l or greater (≥ 126 mg %).

All snakebite patients were nonhypertensive and nondiabetic.

Snakebite-induced AKI was diagnosed according to the following criteria

- Creatinine clearance (GFR) < 60 mL/min/1.73 m² with in the first 72 h after snakebite was defined as AKI.^[8]
- Glomerular filtration rate (GFR) was estimated with The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula which includes serum creatinine, age, gender, and race as variables, with different versions depending on ethnicity, gender, and creatinine value.^[9]
- Absence of other causes (such as diabetes, hypertension, previous renal diseases) leading to AKI.

Statistical analysis

Multivariate linear regression analysis with 95% confidence interval (CI) was done for statistical analysis. Data were expressed in mean \pm SE (Standard Error). *P* value < 0.05 was taken as statistically significant. All these analysis were performed by using a commercially available software Statistical Package for the Social Sciences (SPSS) (17th version for Windows) on personal computer.

Results

Study subject included 171 consecutively admitted non-hypertensive, non-diabetic snakebite patients, Out of which 44 were female and 127 were male. Mean age of the study population was 40.47 ± 1.19 years. Demographic data of snakebite patients are described in Table 1.

98 (57.30%) patients had local swelling. 82 (47.95%) patients were presented with bleeding from the bite site and 89 (52.04%) had black- or brown-colored urine [Figure 1]. Mean time in between snakebite and administration of AVS was 85.36 ± 4.43 min. 101 (59.06%) snakebite patients were presented with 20 min WBCT > 20 min and of which 55 (54.45%) patients were suffering from AKI. 27 (15.78%) patients had neurological signs [Figure 1]. Total 74 (43.27%) snakebite patients ultimately developed AKI due to snake bite.

Differences of demographic characters between snakebite patients with AKI and without AKI are summarized in Table 2, and incidence of different signs and symptoms in snakebite patients with and without AKI are described in Figure 2.

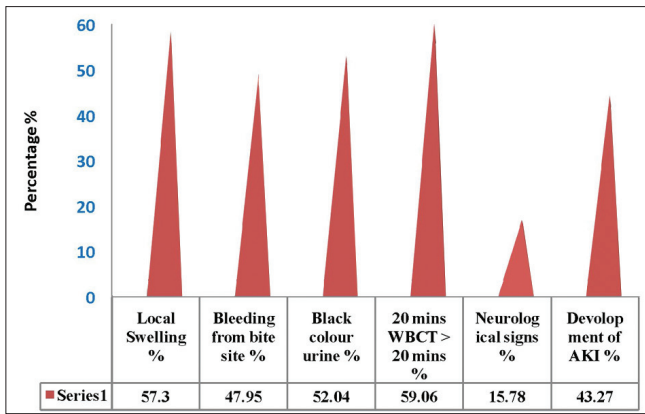


Figure 1: Incidence of different signs and symptoms in snakebite patients

Demographic characters	Snakebite patients
Number	171
Male:Female	127:44
Age (years)	40.47 ± 1.19
Local swelling	98 (57.30%)
Bleeding from the bite site	82 (47.95%)
Black or brown colored urine	89 (52.04%)
Mean time in between snakebite and administration of AVS (minutes)	85.36 ± 4.43
20 min whole blood clotting test > 20 min	101 (59.06%)
Neurological signs	27 (15.78%)
Development of AKI	74 (43.27%)

AVS, Anti-snake venom serum; AKI, Acute kidney injury

In this study, development of AKI was independently associated with 20 min WBCT (P value = 0.029; CI 95%), dark or brown color urine (P value = 0.000; CI 95%), and time in between snakebite and administration of anti-snake venom (P value = 0.000; CI 95%) [Table 3].

Development of AKI was not associated statistically with local swelling (P value = 0.628; CI 95%), bleeding from bite site (P value = 0.120; CI 95%), and amount of AVS given (P value = 0.104; CI 95%) [Table 3].

Age (P value = 0.011; CI 95%) and presence of neurological signs (P value = 0.000; CI 95%) were inversely correlated with development of AKI [Table 3].

Discussion

Some studies^[8,10] showed that incidence of AKI due to snakebite is 29%. In our study, incidence of ARF was 43.27%. This high incidence may be due to (first) treatment delay of snakebite patients in our study area because they attended in hospital after long delay; (second) the use of creatinine clearance (CKD-EPI formula) allowed a higher precision in AKI diagnosis; (third) due to lack

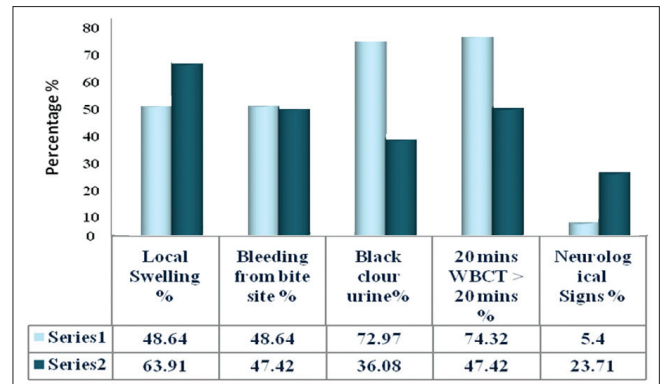


Figure 2: Incidence of different signs and symptoms in snakebite patients with (Series 1) and without acute kidney injury (Series 2)

Demographic characters	Snakebite patients with AKI	Snakebite patients without AKI
Number	74	97
Male:Female	56:18	71:26
Age (years)	37.45 ± 1.64	42.78 ± 1.67
Local swelling	36 (48.64%)	62 (63.91%)
Bleeding from the bite site	36 (48.64%)	46 (47.42%)
Black- or brown-colored urine	54 (72.97%)	35 (36.08%)
Mean time in between snakebite and administration of AVS (minutes)	110.22 ± 7.60	66.39 ± 4.36
20 min whole blood clotting test > 20 min	55 (74.32%)	46 (47.42%)
Neurological signs	4 (5.40%)	23 (23.71%)
Amount of AVS given (ml)	223.71 ± 7.14	191.95 ± 7.47

AVS, Anti-snake venom serum; AKI, Acute kidney injury.

of awareness regarding the early medical treatment of snakebite patients in people of our study area because patients attained some local non medical treatment before admission in hospital which delay early medical treatment; and (fourth) critically ill snakebite patients were referred to our tertiary health care hospital.

In our study, 44 (43.9%) patients with bleeding from the bite site developed AKI, which was less than that in other reports (60–65%).^[3] Here, this low incidence may be due to comparison of local bleeding from bite side only. In our study, systemic bleeding was identified by measuring 20 min WBCT as a separate criterion.

In our study, we also found that there was independent positive association of AKI with 20 min WBCT, dark or brown urine, and time in between snakebite and

Table 3: Multivariate linear regression analysis of early clinical features correlating with development of AKI in snakebite patients

Independent variables	Standardized coefficients Beta	P value	95% confidence level	
			Lower bound	Upper bound
Age	-0.161	0.011	-.009	-.001
20 min WBCT	0.144	0.029	.015	.274
Mean time in between snakebite and administration of AVS (minutes)	0.278	0.000	.001	.003
Black or brown urine	0.323	0.000	.192	.448
Neurological signs	-0.241	0.000	-.497	-.157
Amount of AVS given	0.106	0.104	.000	.002
Local swelling	-0.485	0.628	-.158	.096
Bleeding from bite site	0.099	0.120	-.026	.223

Dependent Variable: AKI.

AKI, Acute kidney injury; AVS, Anti-snake venom serum; 20 min WBCT; 20 minutes whole blood clotting test. P value <0.05, statistically significant. P value ≥0.05, statistically not significant.

administration of anti-snake venom. So, if a snakebite patient is presented with one or more than one of these symptoms, we can predict that this patient may develop AKI.

Previous several studies^[8,11] have already suggested that there is a correlation between development of AKI and time interval between the snakebite and the administration of anti-snake venom. But there was some controversy. Early administration of antivenom has been demonstrated to completely reverse all clinical manifestations of snake envenomation.^[12] But some studies^[13,14] demonstrated that the early administration of antivenin cannot be too strongly emphasized to prevent development of AKI in snakebite patients.

Athappan *et al.*^[10] showed in their study that presence of bleeding manifestations were identified as independent predictors of poor outcome in snakebite patients. Bleeding manifestations are the manifestation of coagulopathy which was demonstrated in our study as 20 min WBCT > 20 min.

Van holder *et al.*^[15] demonstrated that dark black or brown urine was strongly related to AKI. This result is also supported by our study.

On the other hand, in our study, snakebite patients with neurological signs and symptoms were negatively correlated with AKI development. This result may be due

to (first) low prevalence of mixed type of snakebite which produces both neurological signs and hematological signs; and (second) pure neurotoxic snake does not produce hematological complications and AKI. So, if a snakebite patient is presented with only neurological features, we can hope that this patient will not suffer from AKI.

In our study, AKI was not significantly correlated with local swelling, bleeding from bite site, and amount of AVS given. Some study^[16] showed low-dose AVS regimen is more effective and required dose was 5 vials less than the conventional dose, but another study^[17] showed that patients received initial small doses of antivenom were associated with serious consequences.

This study also showed that snakebite patients with younger age developed AKI most commonly because there was negative correlation between age and development of AKI. This result is similar to other previous studies.^[8,10]

Limitations of our study

(First) regional lymphadenitis, cellulites, hypotension could be not included as predictors in our study, (second) our study population was small, and (third) offending snake species or genus could not be identified.

Conclusion

From our study, we can conclude that early clinical prediction of AKI development in snakebite patients can be detected by presence of black or brown urine, 20 min WBCT > 20 min, and increased time in between snakebite and administration of AVS at the time of hospital admission. Young age group of snakebite patients develops AKI more commonly. Incidence of AKI is slightly higher in our study than previous studies.

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