THROMBOCYTOPENIA AND ALBUMINURIA- EARLY PREDICTORS OF ACUTE KIDNEY INJURY IN VENOMOUS SNAKEBITE- A COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

Snakebites and accidents caused by venomous arthropods are important public health problem. Envenomation by snakebite, independently of the species responsible for the bite, enforces medical emergencies since different organs and tissues can be affected at the same time. The hypothesis for pathogenesis of venom-induced AKI includes both a direct cytotoxic action of the venom on different renal structures and a secondary response of the whole organism resulting from systemic envenomation. The aim of the study is to assess the early predictors for acute kidney injury due to snakebite by comparing it with the patients who had not developed acute kidney injury after the snakebite.

MATERIALS AND METHODS

A prospective comparative study was undertaken at the Government Medical College Hospital, Salem, during the period of April 2015-March 2016. A total of 115 patients were included in the study in which 42 patients were having AKI due to snakebite and 73 patients were without AKI after snakebite. Haematological and biochemical investigations were performed in all patients, including haemoglobin, complete and differential leukocyte counts, platelet count, peripheral blood smear, bleeding and clotting times, Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT), blood urea, serum creatinine, serum electrolytes, liver function tests and urine examination.

RESULTS

Thrombocytopenia and albuminuria, which is to be considered as the major early marker for acute kidney injury among snakebite patients was found to be present in 85.7% and 100% in our patients with AKI whereas it was only 1.3% and 4.1% respectively among the patients without AKI and the difference was found to be statistically significant ($p<.05$). The survival rate was higher among the patients without AKI when compared to the patients with AKI and the difference is statistically significant ($p<.05$).

CONCLUSION

Early detection of AKI due to snakebite should be assessed by testing for the platelet count and the urine albumin at the time of admission and appropriate treatment for it would help to reduce the mortality significantly.

KEYWORDS

Acute Kidney Injury, Snakebite, Albuminuria, Thrombocytopenia.

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BACKGROUND

Today, in India, snakebites had become a common public health problem particularly in rural areas. Especially, bites through venomous snakes produces major morbidities and mortalities leaving behind a major impact on the population and public health system.[1] Envenomation by snakebite, independently of the species responsible for the bite, enforces medical emergencies since different organs and tissues can be affected at the same time. In India, most severe cases result from bites by snakes of the family Viperidae (pit vipers and true vipers).[2]

Local effects due to the envenoming by these snakes are characterised by bleeding, swelling, pain and sometimes blister and can be frequently complicated by the development of local abscesses and necrosis. Sometimes, rarely major complication like compartment syndrome, which when developed might lead on to loss of the bitten limb.[3]

Certain clinical manifestations like epistaxis, haemoptysis and haematemesis shows the systemic involvement due to

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snake venom.[4] When thrombocytopenia and disseminated intravascular coagulation had occurred in blood, then death would trigger due to hypovolaemic shock or sepsis.[5]

Renal system is one of the most important organ affected due to snake venom. The commonest pathological manifestation occurring in kidney is acute tubular necrosis, but few studies had shown the occurrence of tubulointerstitial nephritis, renal cortical necrosis, mesangiolysis, vasculitis, glomerulonephritis, proteinuria, haematuria and myoglobinuria. The primary response for the kidney injury is mainly due to the cytotoxic effect of the snake venom and there is also a possibility of secondary response, which is due to the release of inflammatory markers like cytokines and vasoactive substances causing the lesions in the renal system.[6]

Though a few studies had been done in India on acute kidney injury among the snakebite patients in the present study we are assessing the early predictors for AKI due to snakebite, which would have an impact in reducing morbidity and mortality among the snakebite victims due to acute kidney injury.

AIM

To assess the early predictors for acute kidney injury due to snakebite by comparing it with the patients who had not developed acute kidney injury after the snakebite.

MATERIALS AND METHODS

A prospective comparative study was undertaken at the Government Medical College Hospital, Salem, during the period of April 2015-March 2016. The study was approved by the institutional ethical committee. A total of 115 patients were included in the study in which 42 patients were having AKI due to snakebite and 73 patients were without AKI after snakebite. The inclusion and exclusion criteria followed in our study is given below.

Inclusion Criteria

1. A definitive history of snakebite with signs of envenomation.
2. Patients with haemotoxic features with or without neurotoxicity.
3. Age more than 18 years.

Exclusion Criteria

1. The patients with a pre-existent renal disease.
2. Diagnosed cases of hypertension/diabetes.
3. Exposure to nephrotoxic drugs/toxins.
4. Patients with pure neurotoxic features.

The history of snakebite was confirmed by the bite marks and the skin changes like swelling, cellulitis, gangrene or blebs at the bite area. The swelling at the bite site was graded as mild or moderate based on the level of involvement of the limbs and it was considered as severe when changes of necrosis or gangrene is noticed.

When the patients presented with ptosis or weakness in neck muscles, which warranted the use of neostigmine, they were considered as neurotoxic and if required a ventilatory support was provided for them.

In the present study, the acute kidney injury was defined as an increase in serum creatinine levels of more than 0.3 mg/dL or if the urine output is less than 0.5 mL/kg/hr., which approximates to less than 400 mL/day.

A detailed clinical examination was conducted on all the patients. A detailed haematological investigation was done, which includes Hb%, TC, DC, BT, CT, PT and APTT. Urine analysis was done for identifying microalbuminuria. Renal and liver function tests were also done .All the admitted patients were given TT injections if it was not given previously. The anti-snake venom was administered at the rate of 100 mL over 30 minutes for all the patients. For patients with neurological signs, neostigmine was given before administering atropine. Doses were repeated based on the clinical and biochemical response of the patients. Other supportive measures like IV fluids and blood components were given based on their requirements.

In our study, the patients were categorised into two groups. The group A includes patients with snakebite who had developed acute kidney injury and group B includes patients who had not developed acute kidney injury after snakebite. All the parametric variables were analysed and the mean and standard deviation were derived and the student's t-test was used for deriving the statistical inference and for all nonparametric variables. Chi-square test was used to assess the statistical significance between the two groups.

RESULTS

Table 1 shows the age and gender wise distribution of the study population. It is seen from the table that there are almost equal distribution of males and females in all age groups among both the groups and the mean age for the patients with AKI was 43.75 years and patients without AKI it was 46.82 years. Almost, all the patients were from the rural area in which 90% of them are agriculturist and the most common snake bitten them was viper.

The commonest area where the bite mark seen was the legs and cellulitis seems to be the most common manifestation seen among the study subjects in both the groups followed by bleeding manifestations. Whereas oliguria/anuria was present in 100% of the patients with AKI and only 5.4% of patients without AKI had oliguria/anuria. All the clinical manifestations presented by the patients were more with patients with AKI than that of patients without acute kidney injury and the difference was found to be statistically significant ($p<.05$) except for neuroparalysis (Table 2).

Thrombocytopenia and albuminuria, which is to be considered as the major early marker for acute kidney injury among snakebite patients was found to be present in 85.7% and 100% in our patients with AKI, whereas it was only 1.3% and 4.1% respectively among the patients without AKI and the difference was found to be statistically significant ($p<.05$) (Table 3).

The various blood parameters, which were measured among the study subjects like blood urea, creatinine, bleeding time, clotting time and prothrombin time was found to be significantly high among the patients with AKI when compared to the patients without AKI and the difference was found to be statistically significant (p<.05) and the only blood parameter, which did not show any difference between the two groups was HB%. The platelets count was significantly lower among the patients with AKI than that of the patients without AKI and the difference was statistically significant (p<.05) (Table 4).

The survival rate was higher among the patients without AKI when compared to the patients with AKI and the difference is statistically significant (p<.05) (Table 5). The death rate was higher among the AKI group and the major cause of death is respiratory failure, although about 15 patients were put on ventilator for respiratory support, but none of the patients survived.

Age Group	Gender	Patients with AKI	Patients without AKI
20-30	Male	3 (7.1%)	6 (8.2%)
	Female	5 (11.9%)	3 (4.1%)
31-40	Male	4 (9.5%)	11 (15%)
	Female	3 (7.1%)	7 (5.4%)
41-50	Male	6 (14.2%)	4 (5.4%)
	Female	4 (9.5%)	8 (10.9%)
51-60	Male	5 (11.9%)	14 (19.1%)
	Female	4 (9.5%)	7 (9.5%)
>60	Male	4 (9.5%)	6 (8.2%)
	Female	4 (9.5%)	6 (8.2%)
Total		42 (100%)	73 (100%)
Mean Age		43.75±3.25	46.82±4.28

Table 1. Age and Gender wise Distribution

Clinical Signs	Patients with AKI (42)	Patients without AKI (73)	P value
Cellulitis	38 (90.4%)	41 (56.1%)	<.0001
Bleeding Manifestations	36 (85.7%)	28 (38.3%)	<.0001
Oliguria/Anuria	42 (100%)	4 (5.4%)	<.0001
Neuroparalysis	5 (11.9%)	7 (9.5%)	0.7291
Hypotension	29 (69%)	21 (28.7%)	<.0001

Table 2. Distribution of the Study Population Based on the Clinical Signs Presented at the Time of Admission

P value derived by applying chi-square test

Parameter	Patients with AKI (42)	Patients without AKI (73)	P value
Thrombocytopenia	36 (85.7%)	1 (1.3%)	<.0001
Albuminuria	42 (100%)	3 (4.1%)	<.0001

Table 3. Presence of Thrombocytopenia and Albuminuria among the Snakebite Victims

P value derived by applying chi-square test

Laboratory Parameter	Patients with AKI (42) Mean±SD	Patients without AKI (73) Mean±SD	P value
Hb%	9.11±1.21	11.24±2.13	0.0621
Blood urea (mg/dL)	82±9.24	30.24±5.26	<.0001
Blood creatinine (mg/dL)	4.52±0.91	0.81±0.06	<.0001
Platelet count (cells/mm^3)	72,079±208.5	1,28,029±429.6	<.0001
Bleeding time (secs.)	10.24±1.26	7.24±0.89	<.0001
Clotting time (secs.)	14.21±2.10	8.12±1.01	<.0001
Prothrombin time (secs.)	34.28±2.86	16.45±1.14	<.0001

Table 4. Various Laboratory Parameters Measured among the Snakebite Victims

P value derived by applying student's t-test

Outcome	Patients with AKI (42)	Patients without AKI (73)	P value
Patient Survived	32 (76.2%)	67 (91.7%)	0.00281
Patient Dead	10 (23.8%)	6 (8.2%)	

Table 5. Distribution of the Study Population Based on the Patients Survival

P value derived by applying chi-square test

DISCUSSION

Snakebite is a common medical emergency and an occupational hazard, especially in tropical countries like India. The mean age of the patients with and without AKI in our study was 43.5 and 46.5 years respectively, whereas the results quoted by a study done by Athappan et al[7] showed that the age of people with AKI were higher than patients without AKI and the difference was statistically significant. Studies done by Kulkarni et al[8] and Bawaskar et al[9] had shown that males are more commonly affected snakebite

victims than females, whereas in our study, out of 115 patients, 63 were males and 52 were females and the male:female ratio is 1.2:1, which had shown that male and female population are almost equal as both males and females have been exposed in the agriculture as they are all from the rural areas. Snakebite is more common in the rural setting, primarily because farming is a major occupation in villages and farmers are most vulnerable to exposure to snakes during work.

Clinical features like cellulitis, bleeding tendencies and oliguria was found to be more common among the patients with AKI when compared to the patients without AKI and our results are almost in par with the studies done by Mrudul V Dharod et al.[10] He had also quoted that in areas where vipers are predominant, cellulitis and AKI become the major complication following a snakebite.

A study done by Sharma et al[11] on 142 cases of snakebite, he found that 52 had developed haemostatic abnormalities and in that 27 had developed AKI. Various procoagulant enzymes are found in viper venoms, which activate different steps of the clotting cascade resulting in a state of Disseminated Intravascular Coagulopathy (DIC). Thus, bleeding tendencies secondary to DIC are a major factor in the development of AKI in patients of snakebite, especially those involving vipers. In our study, we found that hypotension was more common among patients with AKI and it might cause prerenal insult on the kidneys and may aggravate direct renal insult caused by the venom.

In the present study, thrombocytopenia found to be independent and early predictor for AKI due to snakebite and similar type of results was also quoted by a study done by Suchitra et al[12] in Kerala and also by certain western studies done by Bucaretchi F et al[13] and Chen JB et al.[14] Platelet count is reduced both due to consumptive coagulopathy and direct toxic effects of snake venom on platelets. Intravascular haemolysis due to phospholipase A_2 is a significant factor in the pathogenesis of snakebite-induced AKI.

The current study had clearly indicated that albuminuria was found to be an early indicator for AKI, as almost all patients with AKI had albuminuria and the similar type of result was also quoted by various studies done by Imitiaz Basha et al,[15] Mittal B Y et al,[16] Sarangi et al[17] and Athappan et al.[7] The other renal parameters like urea and creatinine were also elevated among the patients with AKI. The mortality rate among the patients with AKI was 24% when compared to patients without AKI where it was only 8%, whereas the study done by Mrudul V Dharod,[10] the mortality rate among AKI patients was 40%, which was very high when compared to our study and in another study done by Athappan et al,[7] it was only 23%, which was almost in par with the results of our study.

CONCLUSIONS

From our study, we can conclude that early clinical prediction of AKI development in snakebite patients can be detected by presence of thrombocytopenia and albuminuria and it had also proven that AKI is an important mortality predictor for snakebite victims. So, early detection of AKI by testing for the platelet count and the urine albumin at the time of admission and appropriate treatment for it would help to reduce the mortality significantly.

REFERENCES

1. Warrell DA. Snakebite. Lancet 2010;375(9708):77-88.
2. Williams D, Gutiérrez JM, Harrison R, et al. The global snakebite initiative: an antidote for snakebite. Lancet 2010;375(9708):89-91.
3. Gutiérrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snakebite envenoming: the need for a global partnership. PLoS Med 2006;3(6):e150.
4. Otero R, Gutiérrez J, Beatriz-Mesa M, et al. Complications of bothrops, porthidium, and bothriechis snakebites in Colombia. A clinical and epidemiological study of 39 cases attended in a university hospital. Toxicon 2002;40(8):1107-1114.
5. Santoro ML, Sano-Martins IS. Platelet dysfunction during bothrops jararaca snake envenomation in rabbits. Thromb Haemost 2004;92(2):369-383.
6. Sitprija V. Snakebite nephropathy. Nephrology (Carlton) 2006;11(5):442-448.
7. Athappan G, Balaji MV, Navaneethan U, et al. Acute renal failure in snake envenomation: a large prospective study. Saudi J Kidney Dis Transpl 2008;19(3):404-410.
8. Kulkarni ML, Anees S. Snake venom poisoning: experience with 633 cases. Indian Pediatr 1994;31(10):1239-1243.
9. Bawaskar HS, Bawaskar PH, Punde DP, et al. Profile of snakebite envenoming in rural Maharashtra, India. J Assoc Physicians India 2008;56:88-95.
10. Dharod MV, Patil TB, Deshpande AS, et al. Clinical predictors of acute kidney injury following snakebite envenomation. N Am J Med Sci 2013;5(10):594-599.
11. Sharma N, Chauhan S, Faruqi S, et al. Snake envenomation in a north Indian hospital. Emerg Med J 2005;22(2):118-120.
12. Suchithra N, Pappachan JM, Sujathan P. Snakebite envenoming in Kerala, South India: clinical profile and factors involved in adverse outcomes. Emerg Med J 2008;25(4):200-204.
13. Bucaretchi F, Herrera SR, Hyslop S, et al. Snakebites by crotalus durissus ssp in children in Campinas, São Paulo, Brazil. Rev Inst Med Trop Sao Paulo 2002;44(3):133-138.
14. Chen JB, Leung J, Hsu KT. Acute renal failure after snakebite: a report of four cases. Zhonghus Yi Xue Za Zhi (Taipei) 1997;59(1):65-69.
15. Pasha I, Prabhu SNC, Vardhana HHS et al. Renal parameters as predictors of morbidity and mortality in snakebite patients in a tertiary care hospital in southern India. Global Journal of Medical Research (B) 2014;14(2):21-26.

16. Mittal BV, Kinare SG, Acharya VN. Renal lesions following viper bites --a study of 14 years. Indian J Med Res 1986;83:642-651.

17. Sarangi A, Patnaik BC, Das GC, et al. Renal involvement in viper snakebite. Indian J Med Res 1980;71:918-923.