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Medicine

A STUDY ON PROFILE OF AKI IN SNAKE BITE VICTIMS IN A TERTIARY CARE CENTRE IN JHARKHAND.

Rohit Keshav — Junior Resident, Department of Internal Medicine, Rajendra Institute Of Medical Sciences (RIMS), Ranchi

Bindey Kumar — Professor, Department of Internal Medicine, Rajendra Institute Of Medical Sciences (RIMS), Ranchi

Jag Mohan Kumar* — Senior Resident, Department of Cardiology, Rajendra Institute Of Medical Sciences (RIMS), Ranchi *Corresponding Author

ABSTRACT Snake bite is a common occupational hazard and is a common cause of morbidity and mortality in India. Acute kidney injury is a very important and common complication of snake bite and a proper supportive management after the anti-venom administration is of utmost importance for a good patient outcome in these cases. The objectives of this study were to describe the clinical profile of the snake bite patients who develop acute renal failure; assessing the risk and the prognostic factors of snake bite induced AKI; and to identify the predictors of mortality in these patients. This hospital based observational study was carried on 544 snake bite patients admitted in Rajendra Institute of Medical Sciences, Ranchi, Jharkhand. Males are affected significantly more often than the females and the younger population was predominantly involved (20-40 years). Most of the victims who developed AKI were bitten on the lower limbs. 75.47% of the snake bite victims who developed AKI were illiterate. Patients who developed AKI had a significantly longer bite-to-hospital time. Cellulitis, gangrene at the bite area and regional lymphadenopathy were independent risk factors which related to the development of AKI . The patients who visited the traditional healers before arrival to the hospital had a higher incidence of developing AKI. Overall mortality due to venomous snake bites was 12.58%, with a significantly higher mortality in victims who developed AKI. Treatment with dialysis was not associated with improved outcome in patients with snake bite induced AKI. This study highlights the fact that we should be more vigilant in treating snake bite patients with regard to their renal function in order to reduce the mortality and morbidity of such patients.

KEYWORDS : AKI, Snake Bite, Jharkhand.

INTRODUCTION

Snake bite is a common occupational hazard and is a common cause of morbidity and mortality in India, where farming is a major source of employment. It is estimated that more than 2700 species of snakes exist in the world, of which approximately 450 have front fangs making them capable of injecting venom during a bite. India alone harbors more than 250 species and subspecies of these snakes, of which approximately 50 are venomous. However, only 5 venomous species of snakes pose a significant threat to public health in India and these snakes belong to the families, Elapidae, Viperidae, Hydrophidae and Colubridae[1]. Viper bites are far more common than other poisonous snakebites in human beings[2,3]. The WHO has estimated that approximately 1,25,000 deaths occur among 2,50,000 poisonous snake bites worldwide every year[4,5]. In India, approximately 81,000 snake envenomings occur each year, which result in about 11,000 deaths[6].However, these numbers may be a gross underestimation of the true burden of the morbidity and mortality in snake bite victims. The involvement of predominantly young, healthy and the working population particularly in the rural areas which are already compounded by poverty and the lack of access to basic health care services in those areas, signify the social and economic impact of this problem.

Acute kidney injury is commonly observed following bites by snakes which belong to the viperidae species and it is seen less with the sea snake bites and the bites of Colubridae species snakes . Most of the Indians are victims of Russell's viper or echis carinatus bites, which frequently cause AKI[7,8,9]. Acute kidney injury is a very important and common complication of snake bite and a proper supportive management after the anti-venom administration is of utmost importance for a good patient outcome in these cases. Tubular necrosis and cortical necrosis are the main causes that eventually lead to AKI[8,10]. The AKI which occurs after snake bite is frequently reversible, however if acute cortical necrosis occurs, it may lead to an irreversible injury. The main cause of this unacceptable incidence of snake bite mortalities is that people quite often try out all kinds of "bizarre remedies" initially, instead of going to their nearest hospital.

The objectives of this study were to describe the clinical profile of the snake bite patients who develop acute renal failure; assessing the risk and the prognostic factors of snake bite induced AKI; to identify the indications and role of dialysis in these patients; and to identify the predictors of mortality in these patients.

MATERIALS AND METHODS

This prospective observational study was conducted from January 2017 to December 2018 in Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi, a tertiary referral government hospital in Jharkhand, India.

Case selection

During above period, 544 patients were admitted with alleged snake bite. Of these, 202 patients did not show any signs of snake envenomation, and were discharged in stable condition after 24 hours of observation. Rest 342 patients with signs and symptoms of local or systemic envenomation were included in this study (n = 342) after obtaining a complete and informed consent from the patients or relatives.

Inclusion Criteria

1. A history of snake bite;
2. The clinical picture was consistent with that of a snake bite, such as the presence of fang marks/ swelling/ cellulitis/ gangrene/ ecchymosis/ blisters, blebs, or bleeding at the site of bite and area proximal to it / coagulopathy/ neurotoxicity (Neurotoxicity was defined as documented ptosis, external ophthalmoplegia, weakness of neck or bulbar muscles, use of neostigmine or ventilatory support.);
3. The presence of an acute kidney injury which is defined as an abrupt (within 48 hours), absolute increase in the serum creatinine concentration of 0.3 mg/dL from the baseline value which was measured at admission, or a percentage increase in the serum creatinine concentration of 50 percent above the baseline, or oliguria of less than 0.5 mL/kg per hour for more than 6 hours, or serum creatinine of more than 1.5 mg/dL or oliguria (urine output of less than 400 mL/day)[8].
4. Presence of at least 1 or more indication for renal replacement therapy.

Exclusion Criteria

1. The patients with a pre-existent renal disease (a serum creatinine of >1.5 mg/dL prior to the snake bite or ultrasonography of the abdomen, suggestive of bilateral small kidneys/loss of the corticomedullary differentiation/ obstructive nephropathy/other renal pathologies);
2. The peripheral blood smear was positive for malaria parasite.

3. Diagnosed cases of hypertension and/or diabetes mellitus;
4. Exposure to nephrotoxic drugs/toxins.

A thorough clinical history taking and a complete physical examination were done in each case. The laboratory investigations included haemoglobin, total and differential leucocyte counts, platelet counts, red cell counts, bleeding and clotting times, the coagulation profile which included PT, aPTT and the international normalised ratio (INR), urine examination, kidney and liver function tests and serum electrolytes. The radiological investigations included X-ray of the chest and USG of the abdomen.

Patients were administered tetanus toxoid injection, if not received previously. We classified all the cases of snake bite as mild, moderate and severe. The Anti-Snake Venom (ASV) was administered in a dose of 5 vials (50ml) in the mild cases, in a dose of 5-10 vials (50-100ml) in the moderate cases and in a dose of 10-20 vials (100-200ml) as an i.v. infusion in a drip for over 30 minutes. Patients showing signs of neuroparalysis were given injection neostigmine with prior atropine. Doses were repeated as needed based on clinical response. Broad spectrum antibiotics and diuretics were also administered, as indicated. Transfusions of blood and blood products were given to the indicated patients. Renal replacement therapy (either peritoneal or haemodialysis, depending on the availability of the resources), was given. Patients were classified into group A and B based upon presence or absence of AKI and various parameters were compared between these 2 groups, which were presence of extensive cellulitis (i.e., cellulitis extending at least 2 joints above the site of bite), mean blood urea, mean serum creatinine, coagulopathy (INR > 1.5), uremic encephalopathy, hyperkalemia (> 5.5 mEq/L), mean bite to hospital time, mean dose of ASV administered, mode of dialysis (i.e., peritoneal Vs. hemodialysis)

For descriptive statistical analysis, mean, standard deviation, and frequencies were calculated. All data were analyzed with statistical software SPSS 22.0 using univariate and bivariate analysis with 95% confidence interval. Bivariate analysis was carried out using Chi-square, Fisher exact, one way ANOVA, Kruskal Wallis test and Pearson coefficient of correlation with significance level set at p<0,05. 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.

RESULTS

A total of 342 cases of venomous snakebite cases were included in this study, who were admitted to the hospital from January 2017 to December 2018. The mean age of patients who in Group A was 35.68 ± 14.04 years and in Group B was 33.42 ± 13.32 years. This difference was not statistically significant. (P = 0.894). . Out of 342 venomous snake bite patients, 106 (30.99%) developed AKI. In our study, the sex wise distribution of the study subjects was classified, based on whether they had AKI or non-AKI, and among males, it was 58(54.71%) (AKI) and 123(52.11%) (non-AKI) respectively. Among females , it was 48(45.28%) (AKI) and 113(47.88%) (non-AKI) respectively. Illiteracy was more among the patients who suffered from AKI (80(75.47%)). In our study, among all the patients (both AKI and non-AKI patients), viper bite was the commonest and it was seen in 97(91.5%) patients with AKI and in 159 (67.37%) non-AKI patients. In our study, a significant majority of the patients who developed AKI had initially visited traditional healers before visiting our hospital, which was found to be statistically significant.

Table 1 : Demographic profile of snake bite patients

Characteristics	***ARF (n=106)***	***Non-ARF (n=236)***	
Age (years)	35.68 ± 14.04	33.42 ± 13.32	NS
Male	58 (54.71%)	123 (52.11%)	NS
Education status(illiterate)	80(75.47%)	46 (19.49%)	p<0.001
Types of snake Bite			
Elapidae	9 (8.49%)	76 (32.2%)	p<0.001
Viper	97 (91.5%)	160 (67.79%)	p<0.001
Visiti to traditional healer	88(83.01%)	44 (18.64%)	p<0.001

Mean bite to hospital time in Group A was 21.60 ± 42.67 hours and in Group B was5.63 ± 9.45 hours. The difference was statistically significant (P < 0.005). Thus, a prolonged bite to hospital time was associated with a significant increased risk of developing AKI. In our study, we also found that cellulitis and gangrene at the bite site were found to be significantly more in the AKI patients as compared to those in the non-AKI patients, which was statistically significant. In the present study, the DIC and the intravascular haemolysis were also found to be predominant among the AKI group of patients.

In Group A, 82 (77.35%) patients had snake bite in lower limbs and 24 (22.64%) patients had snake bite in upper limbs. Similarly, in Group B, 175 (74.15%) patients had snake bite in lower limbs and 61 (25.84%) patients had snake bite in upper limbs. The difference was not statistically significant (P =0.588), implying that the site of bite has no relation with development of AKI in patients of snake bite.

Table 2 : Clinical Profile of snake bite patients

Characteristics	ARF (n=106)	Non-ARF (n=236)	
Cellulitis	96 (90.56%)	174 (73.72%)	p<0.001
Gangrene at the bite area	87 (82.07%)	67 (27.54%)	p<0.001
Regional Lymphadenopathy	81(76.41%)	71 (30.08%)	NS
Bleeding manifestations	41 (38.67%)	24 (10.16%)	p<0.001
Hypotension	34 (32.07%)	11 (4.66%)	p<0.001
Septicemia	27 (25.47%)	5 (2.11%)	p<0.001
DIC	12 (11.32%)	1 (0.42%)	p<0.01
Intravascular Haemolysis	15 (14.15%)	2 (0.84%)	p<0.001
ARDS	9 (8.49%)	0 (0%)	p<0.01
Time Delay bite to hospital	21.60 ± 42.67 hours	5.63 ± 9.45 hours time)	p<0.001
Amount of ASV units	16.9 (5 – 45 vials)	12.5 (4 -29 vials)	p<0.005
Duration of Hospitalisation	09 (04-20 days)	01 (1-3 days)	p<0.001

Table 3 : Comparison of outcome of patients in the snake bite patients with AKI

Characteristics	Survived (n=82)	Died (n=24)	
Age (years)	35.7 ± 11.2	40.4 ± 11.4	NS
Male	55.2 %	58.6%	NS
Cellulitis	74 (90.24%)	23 (95.83%)	NS
Regional Lymphadnopathy	73 (89.02%)	22 (91.66%)	NS
Bite of lower limbs	66 (80.48%)	21 (87.5%)	NS
Bleeding manifestations	19 (23.17%)	15 (62.5%)	NS
Hypotension	7 (8.53%)	16 (66.66%)	p<0.01
Intravascular haemolysis	14 (17.07%)	13 (54.16%)	p<0.01
Serum Creatinine in mg/dl	2.61 ± 1.3	4.2 ± 2.1	p<0.001
Blood Urea	79.02 ± 27.08	128.24 ± 42.23	p<0.005
Amount of ASV units	15.67 ± 11.4	19.24 ± 10.67	NS
Bite to hospital time (hours)	18.56 ± 15.6	28.32 ± 17.54	p<0.005
ARDS	01	02	NS
DIC	01	04	p<0.01
Septicemia	11	15	p<0.01
Gangrene	70	12	p<0.01

The patients who developed AKI had a greater severity of envenomation and hence they required more number of ASV vials for treatment, in comparison to those patients who did not develop AKI.

The patients who developed AKI were admitted for more days in the in-patients department than the non-AKI patients, which suggested the greater morbidity and mortality which was associated with it.

Out of the 106 patients of AKI, 82 (77.35%) patients survived. Among them, 74 (90.24%) developed cellulitis, 73(89.02%) had regional lymphadenopathy, 19(23.17%) developed bleeding manifestations and 66 (80.48%) had been bitten at the lower limbs.

Out of 106 patients developing AKI, 58 (54.17%) patients having indications for dialysis were treated with Haemodialysis. 38(35.84%) patients needed ventilator support for respiratory failure due to neuroparalyis or pulmonary edema.

Amongst 82 patients with AKI who survived, 47 (57.31%) patients received dialysis while 35 (42.68%) did not receive the same. Similarly, among 24 patients who died, 11 (45.83%) had received dialysis while the rest 13 (54.16%) did not receive the same. The difference was not statistically significant (P = 0.437). Thus, in our study treatment with dialysis was not associated with an improved outcome in patients with AKI.

Among the variables which were entered for the univariate analysis, the following factors were found to predict the development of AKI: age of the patient, his/her educational status, visit to a traditional healer prior to visit to hsopital, cellulitis, gangrene at the area of the bite, bleeding manifestations, hypotension, septicemia, DIC, intravascular haemolysis, ARDS, time delay (bite to hospital time), amount of ASV units and duration of the hospitalization.

Among the variables which were entered for the univariate analysis, the following were found to predict the outcome of AKI: hypotension, DIC, septicaemia, and gangrene, the bite to hospital time (hours), blood urea and serum creatinine mg/dl

DISCUSSION

Snakebites have the highest incidence in Asia and represent an important public health problem. Clinical renal manifestations vary over a wide range and include proteinuria, hematuria, pigmenturia, and renal failure. ARF is mainly observed following bites by the viperidae group, sea snakes, or the colubridae group, but the substantial proportion of these cases mostly result from viper bites. The exact pathogenesis of AKI following snake bites, is not exactly well established. However, a number of factors do contribute to it, like bleeding, hypotension, circulatory collapse, intravascular haemolysis, DIC, microangiopathic haemolytic anaemia and the direct nephrotoxicity of venom .(11)

Males are affected significantly more often than the females, as they constitute the working majority who are actively engaged in farming or other outdoor activities. Our findings were concurrent with those of earlier studies.(12-15) In our study, the younger population was predominantly involved (20-40 years of age), probably due to their more ambulant nature.(16-20) In our study, most of the victims who developed AKI were bitten on the lower limbs (80.48%) consistent with the findings of Viramani et al.(19) We noticed that 75.47% of the snake bite victims who developed AKI were illiterate, which may be because those who are illiterate tend to have more superstitious beliefs, findings comparable to the findings of a study which was done in Nepal.(20) . We found that a delay in administering the adequate dose of ASV units increased the risk of developing AKI in snake bite patients to more than 4 times (odds ratio 4.05), as the venom continues to act until it is neutralized.

The important clinical features in snake bite victims were cellulitis, AKI, neuroparalysis, coagulopathy and hypotension. Snake venom is a mixture of various neurotoxins, digestive enzymes, activators/inactivators of various physiological processes and is responsible for the various complications associated with snake bite. In areas where vipers are predominant species, cellulitis and AKI become the major complication following a snake bite. A significantly higher number of patients with AKI had moderate to severe cellulitis. This extent of cellulitis depends on various factors like the amount of venom injected into the victim's body, the type of snake, the delay in receiving ASV units and the application of any harmful local measures. This moderate to severe cellulitis and swelling of the limb can accommodate many liters of extravasated blood, leading to hypovolemic shock. Also underlying rhamdomyolysis, hyperkalemia and associated sepsis contribute to the AKI.

It was noted that patients who developed AKI had a significantly longer bite-to-hospital time, compared to those who did not develop AKI similar to the findings of Athappan et al.,(21)) and Kalantri et al.,(22) The patients who had recovered from AKI had a shorter bite to needle time, as was observed by Sharma et al.(17).The bite to hospital time often varies depending on the availability of medical facilities and the settings in which the study has been done. The snake venom, which is responsible for almost all the complications of snake bite, must be neutralized as soon as possible with ASV. This fact is now well supported by various studies which show a direct relation between increased rates of complications or mortality with a late arrival to hospital.

Cellulitis was one of the independent risk factors which related to the development of AKI in our study. The earliest symptoms which are seen in the patients of viper bite are pain and swelling at the region of bite. Regional lymphadenopathy was another significant independent risk factor which contributed to the development of AKI. Like cellulitis, gangrene at the bite area and regional lymphadenopathy can be used as bedside indicators of the amount of toxin which is released by the snake bite.

In our study, 38.67% patients who suffered from AKI, developed bleeding manifestations, which was less than the number in the study which was conducted by Chugh K.S (60-65%).(5)

Overall mortality due to venomous snake bites was 12.58%, with a significantly higher mortality in victims who developed AKI. In studies done by Kularatne et al, Kulkarni et al and Athappan et al.,(21,23,24) mortality rate varies from 2.5% to 25%. This mortality rate is significantly higher in studies involving vipers, with higher proportion of patients developing complications. It was also interesting to observe that treatment with dialysis was not associated with improved outcome in patients with snake bite induced AKI, but infact mortality was more among the patients who had required and had undergone dialysis; findings similar to as in study done by Athappan et al (21),which showed higher mortality in patients receiving dialysis.

The patients who visited the traditional healers before arrival to the hospital had a higher incidence of developing AKI, which may be because of two reasons. Firstly, in this context, significant time had elapsed and the second being, the tying of tourniquets or other treatments which could have affected the patients.

The following factors were found to predict the development of AKI: age of the patient, his/her educational status, visit to a traditional healer prior to visit to hsopital, cellulitis, gangrene at the area of the bite, bleeding manifestations, hypotension, septicemia, DIC, intravascular haemolysis, ARDS, time delay (bite to hospital time), amount of ASV units and duration of the hospitalization similar to the findings of Athappan et al.(21). KI. Paul and Dasgupta(25) found that black or brown urine, a 20 minute whole blood clotting time > 20 minutes, and longer bite to hospital time were predictors of AKI development in snake bite victims. The marked association of bite to hospital time with development of AKI highlights the importance of early treatment in snake bite patients. Earlier the patient of snake bite receives ASV, lesser is the chance of developing any of the above complications mentioned above and hence ASV should be made available at all peripheral centers.

CONCLUSION

This study concludes that acute kidney injury occurs in 19.48% victims of snake bite. The common manifestations include cellulitis, bleeding manifestations, neuroparalysis, hypotension. and gangrene at the bite site. The type of snakebite is an important factor in the development of AKI and the Russell viper's bite is more commonly associated with it. The ASV treatment time, bite to renal insufficiency time and the coagulation abnormalities were the major prognostic factors predicting the final outcomes.

Dialysis and appropiate supportive treatment appear to be the mainstay of the therapy in cases which are complicated by renal failure. The indications for dialysis in AKI include anuria of >48 hours, severe hyperkalaemia not responding to medical therapy, pulmonary oedema, severe acidosis and rising blood urea and serum creatinine.

STUDY LIMITATIONS

The limitations of our study were a small sample size, lack of investigations like a renal biopsy and ELISA for the snake venom. In

the developing countries, most of the patients still consult traditional healers first, instead of seeking treatment at the health centres. Also, many snakebite cases are treated at the primary healthcare centres and they are not referred to the higher centres, thus leading to an underestimation of the morbidity status in the studies which are being done at the tertiary health care centres like ours.

CONFLICT: No conflict of interest

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