RESEARCH PAPER

Predictors of Renal Complications in Children With Hematotoxic Snakebite

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Objective: To study the predictors of renal complications following hematotoxic snakebite in children. **Methods:** This comparative study was conducted in the pediatric ward of a tertiary-care centre among 364 consecutively children admitted with hematotoxic snakebite between January 2016 and December 2017. Clinical and laboratory indicators were compared between children who developed acute kidney injury and those who did not. **Results:** Acute kidney injury was seen in 139 children (38.2%), majority being stage 2 (55, 39.5%). 59 children (16.2%) developed permanent renal damage and 16 (4.4%) died due to envenomation. Acute tubular necrosis was the most common (25, 39.1%) histopathological change. **Conclusion:** Receiving anti-snake venom more than one hour after bite was the most significant adverse prognostic indicator, both for renal complications and mortality.

Keywords: *Acute kidney injury, Anti-snake venom, Envenomation.*

Snakebite is a common problem in tropical countries, affecting nearly 6 million people every year, with nearly 10% of these fatalities occurring in India [1]. Russell's viper (RV) (*Daboia russelii*), the foremost cause of morbidity and mortality [2], and is responsible for both hemato-toxicity and neuro-toxicity. Local tissue damage, venom induced coagulopathy, platelet dysfunction, phospholipase A_2 induced rhabdomyolysis, hyperkalemia, acute kidney injury (AKI) and multi-organ dysfunction, all are effects of RV venom [3]. Direct toxic action of the venom may also be responsible for AKI [4].

Different studies have estimated that the incidence of AKI following hematotoxic bite ranges from 10-32% [4]. Recently, it was reported that there is a geographical variation in the venoms of snake and this variation is responsible for different efficacies of ASV in different parts of country [5]. There is scarcity of data regarding the factors responsible for AKI following hematotoxic envenomation, especially in children. Hence this study was conducted to find out the incidence of renal complications following hematotoxic snake bites and to identify the clinical and laboratory indicators which help in predicting AKI early.

METHODS

A comparative study was conducted in the pediatric emergency ward of a tertiary care centre in between January, 2016 to December, 2017. Prior approval was taken from the institutional ethics committee. Hematotoxic envenomation was identified by identification of snake by the victim/ relatives or witness, and features of intoxication characterized mainly by a positive 20 minute whole blood clotting test (WBCT).

On admission, all the children received 10 vials of ASV diluted with 100 mL/ 200 mL normal saline (0.9% NaCl). Depending on correction of coagulopathy and clinical indication, upto 30 vials of ASV were used. Serum urea and creatinine, electrolytes and an electrocardiogram were obtained at the time of admission. These were repeated once daily or when clinically indicated, till discharge or normalization of the value in three repeated tests. Acute kidney injury was defined according to KDIGO guidelines (Kidney disease: Improving global outcome) [6]. Dialysis (peritoneal dialysis in this institution and hemodialysis in a referral hospital) was used when the patient developed signs of fluid overload, developed oliguria/ anuria (defined as urine output <0.5 mL/kg/h for last 24 hours), hyperkalemia (defined as >5.5 mEq/L with ECG changes or >6 mEq/L). If these values were not normalized even after 6 months of discharge or there was persistent hypertension, it was assumed that there is permanent renal damage. The follow-up period was 6 months or till normalization of renal function, whichever was later.

Statistical analysis: Shapiro-Wilk test was used to check normal distribution. Chi-square test was used to find the

significance of difference between attributes in contingency tables, whereas one-way ANOVA was used to check the significance of difference between means. Kruskal Wallis H test was used for skewed data. Pearson's product moment correlation coefficient (r) was calculated to find the degree and direction of relationship of dependent and independent variables. Significantly correlated variables were considered for a binary logistic regression model taking AKI, permanent renal damage and mortality as dependent /outcome variable to calculate the adjusted odds ratio. $P<0.05$ was taken as statistically significant. Analysis was done by SPSS version 19.0 (Statistical Packages for Social Sciences Inc, Chicago, IL, US).

RESULTS

During the study period, 371 children were admitted with hematotoxic envenomation. Children with known kidney disease, who were severely ill and died immediately, and those with parental refusal of consent were excluded from the study (7 children were excluded; 1 with end stage renal disease due to lupus nephritis, 2 were severely ill and died immediately, and 4 refused consent). Finally, 364 children (69% males) were included. Mean (SD) age of the study population was 8.9 (2.3) years. Majority of them belonged to lower socioeconomic status (60.7%). Out of the 364 children, 139 (38.2%) developed AKI following envenomation. Out of these 48 (34.5%), 55 (39.5%) and 36 (26.0%) children developed stage 1, 2 & 3 AKI, respectively. Sixteen children (4.4%) died and 59 (16.2%) children developed permanent renal damage. Different clinical and laboratory parameters of two groups of children (with AKI and without AKI) are presented in ***Table* I**.

Administration of ASV following 1 hour of bite emerged as the most significant predictor of AKI (adjusted OR=23.4, 95% CI=22.1-24.8), permanent renal injury (adjusted OR=19.7, 95% CI=18.9-20.5) and mortality (adjusted OR=15.2, 95% CI=14.7-15.7) (***Table* II**). Our model can correctly predict 67.2%-78.9% variation of AKI, 62.1-70.3% variation of permanent renal injury and 53.1-61.7% variation of mortality. Renal histopathology was done in 48 (81.4%) children suffering from permanent renal damage and 16 children (100%) who died. Acute tubular necrosis (25, 39.1%) was the most common finding in histopathology, followed by renal cortical necrosis (12.5%).

DISCUSSION

In this study conducted to detect the incidence and predictors of renal complications due to hematotoxic envenomation, we found that 38.2% children developed AKI following bite and 26% of them developed stage 3 AKI. Acute tubular necrosis was the most common finding in renal histopathology.

Measurement of serum venom level was not possible in our setting. Nearly 20%, 30% and 40% variation of AKI, permanent renal injury and mortality still remained unexplained. Renal histopathology could not be done in all the children due to invasive nature of the investigation and lack of consent.

Table I Characteristics of the Study Population and Acute Kidney Injury (*N*=364)

Variables	*No AKI (n=225)*	*AKI (n=139)*
Age[#], y	9.1 (1.7)	5.8 (1.0)
Males sex	170 (67.7)	81 (32.3)
Rural residence	116 (53.5)	101 (36.5)
Bite on trunk	49 (46.2)	57 (53.8)
Single Bite	221 (73.7)	79 (26.3)
Time b/w bite and ASV[#], min	36.4 (5.9)	74.5 (8.3)
Vials of ASV required*	10 (10-30)	20 (10-30)
Local reaction		
<5 cm	106 (84.1)	20 (15.9)
5-10 cm	72 (66.0)	37 (34.0)
>10 cm	47 (36.4)	82 (63.7)
System involvement		
No	203 (83.2)	41 (16.8)
One system	17 (26.6)	47 (73.4)
>1 system	5 (8.9)	51 (91.1)
Neurotoxicity	24 (20.5)	93 (79.5)
Alteration of K^+		
No	158 (89.8)	18 (11.2)
After 6 h	23 (43.4)	30 (56.6)
2-6 h	32 (42.1)	44 (57.9)
<2 h	12 (20.3)	47 (79.7)
K^+ level[#] (mEq/L)	3.9 (0.3)	5.7 (0.6)
Altered WBCT		
6 h	202 (96.2)	8 (3.8)
12 h	21 (25.3)	62 (74.7)
>12 h	2 (2.8)	69 (97.2)
Bleeding	48 (32.7)	99 (67.3)
Ventilation	7 (8.0)	81 (92.0)
Blood product	55 (34.8)	103 (65.2)
Inotropes	88 (42.5)	119 (57.5)

*All values in no. (%) except [#]mean (SD) and * median (IQR); WBCT –whole blood clotting test, K^+- serum potassium; All comparisons P<0.01 except P<0.001 for rural residence and bite on trunk; b/w – between.*

WHAT THIS STUDY ADDS?

- Administration of ASV following 1 hour of bite is the most significant predictor of acute kidney injury, permanent renal injury and mortality.

Table II Acute Kidney Injury, Permanent Renal Injury and Mortality in Children with Hematotoxic Snakebite (*N*=364)

Variables	*AKI (n=139)*	*Permanent renal injury (n=59)*	*Mortality (n=16)*
Anti-snake venom after 1 h	23.4 (22.1-24.8)	19.7 (18.9-20.5)	15.2 (14.7-15.7)
Need of mechanical ventilation	18.1 (17.4-18.9)	16.2 (15.8-16.6)	13.8 (12.6-15.0)
Bleeding	15.6 (15.3-15.9)	12.9 (12.1-13.7)	9.5 (8.5-10.6)
Blood products	13.2 (12.5-13.9)	8.7 (8.5-9.0)	1.8 (0.3-2.9)
Serum potassium level >6 mEq/L	9.9 (8.2-11.6)	7.5 (6.9-8.1)	1.7 (0.6-2.1)
Alteration of pH in first 2 h	8.7 (8.1-9.3)	5.7 (5.1-6.4)	1.2 (0.7-1.8)
Requirement of inotropes	5.5 (4.7-6.3)	1.1 (0.8-1.3)	1.1 (0.6-1.5)
Rural residence	5.1 (3.8-6.4)	1.2 (0.7-1.5)	0.9 (0.3-1.4)

Values in adjusted odds ratio (95% CI).

Previous studies report 14.6-45.9% children developing AKI after hematotoxic envenomation and 24.5% developing permanent renal injury [7-9]. Mortality was lower in the current study than previous Indian reports of 6.6-22.3% [7-9]. This variability may be due to local variation of venom, heterogeneity of population and availability of resources [5,9]. Similar to the finding of current study, other authors have also noted that the time between administration of ASV and the snakebite was the most significant predictor of AKI [8,9]. Howarth, *et al.* [10] determined that mean periphery to systemic circulation time of venom was 58 (7) minutes. Hence, administration of ASV after 1 hour was less effective in prevention renal impairments. However, Krishnamurthy, *et al.* [7] did not found any significant association between delayed administration of ASV and development of AKI. AKI was more common among the younger children may be due to their ambulatory nature leading to more circulation of toxin [11]. Similar to the findings of current study, multiple researchers have also reported pre-hospital factors, alteration of 20 WBCT for prolonged time, neurotoxic signs and severe illness (characterized by bleeding, requirement of mechanical ventilation, blood products and inotropes) predict adverse outcome [9, 12-15].

To conclude, delay in administration of ASV was the most significant predictor of renal complications and mortality following hematotoxic bite. Prompt hospitalization after bite leads to early initiation of treatment and lesser fatality. As the composition of venom varies according to geographic location [5] and present study includes children from part of Bengal, Bihar and Jharkhand only, further multi-centric research should be undertaken before generalization of findings of this study.

Ethical Clearance: Institution Ethics Committee, Burdwan Medical College, BMC/PG/4456 dated 14/12/2015.
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