RESEARCH PAPER

Russell's Viper Envenomation-associated Acute Kidney Injury in Children in Southern India

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Received; August 12, 2014;
Initial review; October 21, 2014;
Accepted: April 23, 2015.

Objectives: To determine the frequency and risk factors of acute kidney injury in children with Russell's viper envenomation using Acute Kidney Injury Network definition and classification system.

Methods: A prospective observational study recruiting 61 subjects managed as per the National Snakebite Protocol.

Results: 45.9% of envenomed children had acute kidney injury. The median (IQR) of the maximum serum creatinine level during hospitalization was 2 (1.3-4.8) mg/dL. The distribution of stages 1, 2 and 3 of acute kidney injury was 32.1%, 17.9% and 50% respectively. Dialysis was required in 35.7% of the children with acute kidney injury.

Conclusions: Acute kidney injury is common with Russell's viper envenomation. Native treatments and bleeding manifestations were associated with acute kidney injury in our patient population.

Keywords: *Bleeding, Complications, Management, Outcome, Snakebite.*

Acute Kidney injury (AKI) is a common complication of Russell's viper envenomation [1,2]. The quantum of Russell's viper envenomation-associated AKI, using the revised consensus Acute Kidney Injury Network (AKIN) definition and classification system [3] is not well documented in children. We conducted this study to determine the frequency and risk factors of AKI associated with Russell's viper envenomation in children.

Methods

This prospective observational study was conducted at a referral hospital in Southern India from January 2013 to July 2014. Sixty-one children below 13 years of age with systemic features of Russell's viper envenomation were included. The study was approved by the Institutional Ethics Committee. Informed consent was obtained prior to enrolment of subjects. The primary objective of the study was to determine the incidence of AKI using the AKIN definition and classification system in children with Russell's viper envenomation [3], while the secondary objectives were to study the predictors of AKI, and to compare the clinico-biochemical profile in Russell's viper envenomation cases with AKI *versus* those without AKI.

Russell's viper envenomation was diagnosed when [4]: (*i*) the snake was brought to the hospital dead or alive, or (*ii*) the victim or witnesses identified it as a Russell's viper with a matched description in the form of images or photographs; and the victim had a typical clinical presentation (including bleeding manifestations, or limb edema with fang marks); and a positive 20-minute whole blood clotting time (20 WBCT). Patients with known chronic kidney disease were excluded. Indications for renal replacement therapy included fluid overload (e.g pulmonary edema or uncontrolled hypertension), anuria for more than 12 hours, altered sensorium, pericarditis, hyperkalemia (serum potassium >5.5 mEq/L) and refractory metabolic acidosis.

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At admission, serum creatinine was measured in all children by modified Jaffe method [5] using autoanalyzer. Repeat serum creatinine was done every 24 hours after admission for 3 days. Thereafter, serum creatinine was measured at intervals of 48 hours (or whenever clinically indicated, whichever was earlier) till discharge or death. Clinical parameters such as bleeding manifestations, limb edema, duration of hospitalization, number of vials of Anti-snake venom serum (ASV) required, AKI stage,

requirement of mechanical ventilation, blood products or dialysis, and mortality were recorded. ASV was administered as per the National Snake bite Protocol and World Health Organization guidelines for management of snake bites [6,7]. The 20 WBCT was measured every 6 h till normalization. Patients received polyvalent ASV (Bharat Serum and Vaccines, Ltd). The initial dose administered was 10 vials dissolved in 10 mL/kg of normal saline and intravenously infused over 1 hour. If the 20 WBCT did not decrease to less than 20 min after 6 hours, additional 10 vials were administered. This was repeated after 6 hours if the 20 WBCT was still not normal.

Complete renal recovery was defined as normal serum creatinine for age (0.2-0.4 mg/dL for infants, 0.3-0.7 mg/dL for 1-12 years, 0.5-1 mg/dL for >12 years) [8] and normal blood pressure for age [9]. Residual renal injury was defined as elevated serum creatinine for age [8] or persistent hypertension at discharge [9]. The proportion of Russell's viper envenomation-associated AKI was estimated to be 20% [1,2]. Assuming a variability of 10% and 95% confidence, the sample size required was calculated as 61 children.

Statistical methods: Data were analyzed using Mann Whitney U test. Categorical variables were expressed as proportions and compared using chi-square test or Fisher exact test. Data were evaluated using SPSS version 19. Predictive risk factors for AKI were determined by univariate analysis, followed by stepwise logistic regression analysis.

RESULTS

Sixty-one children (34 males) with Russell's viper envenomation were enrolled. Their mean (SD) age was 7.2 (1.8) years. The median (IQR) time to ASV administration was 4 (2.3, 7) hours, while the mean (SD) number of ASV vials required were 10.9 (7.6). Fourteen children (23%) required mechanical ventilation, 12 (19.7%) required inotropic support, while blood products were administered in 9 (14.8%) children. Bleeding manifestations were encountered in 23 (37.7%) children, including hematuria (24.6%) and hematemesis (9.3%).

Twenty-eight (45.9%) children developed AKI. The characteristics of these 28 children are summarized in ***Table* I**. Fourteen children with AKI (50%) were in stage 3 of AKI. Of these, 10 required renal replacement therapy.

Native treatment, bleeding manifestations and shock were found to be predictors of AKI on univariate analysis. On stepwise logistic regression analysis, bleeding manifestations (OR 3.6; 95% CI 1.21, 10.7; *P*=0.016) and native treatment (OR 6.2; 95% CI 1.19, 32.23; *P*=0.01) were found to be independent predictors of AKI.

TABLE I CLINICAL AND BIOCHEMICAL PROFILE OF CHILDREN WITH RUSSELL'S VIPER ENVENOMATION-ASSOCIATED AKI (*N*=28)

Characteristics	
Age (y), median (IQR)	8 (6.7-10)
Males[#]	15 (53.6)
Oliguria[#]	8 (28.6)
Onset of oliguria after the bite (h), median (IQR)	36 (30-72)
Anuria[#]	9 (14.8)
Time for recovery from oliguria (d), median (IQR)	6 (4.5-5.5)
Hypertension[#]	2 (7.1)
Dialysis requirement[#]*	10 (35.7)
Serum creatinine (mg/dL), median (IQR)	
Maximum	2 (1.3-4.8)
At discharge	0.85 (0.7-1.2)
AKI stage[#]	
Stage 1	9 (32.1)
Stage 2	5 (17.9)
Stage 3	14 (50)
Hyperkalemia[#]	4 (14.3)
Hyponatremia[#]	3 (10.7)
Time to ASV administration (h), median (IQR)	4 (3-8.25)
In children requiring dialysis (*n*=10)	8 (3-10)
In children with AKI stage 3 (*n*=14)	7 (4-9)
Pre-ASV treatment sought (tourniquet /native medications)[#]	27 (96.4)
Length of hospital stay (d), median (IQR)	8 (6-12)
Limb edema[#]	11 (39)
Residual renal injury at discharge[#]	9 (32.1)

[#]Values in No. (%); [*]9 children were managed with peritoneal dialysis, and 1 child underwent hemodialysis.

There were 4 deaths out of 28 children with AKI, whereas there were no deaths in the 33 children without AKI. The frequency of bleeding manifestations and proteinuria was significantly higher with AKI. The median (IQR) values of the highest blood urea and serum creatinine values reached during hospital stay in children with AKI (*n*=28) were 105 (71.3, 205.5) mg/dL and 2 (1.3-4.8) mg/dL respectively, as compared to the corresponding values of 28 (22-34) mg/dL and 0.7 (0.6-0.8) mg/dL in children without AKI (*n*=33) (***Table* II**).

DISCUSSION

In this descriptive study, we observed that AKI occurred in almost half of the children with Russell's viper envenomation. Further, half of the cases of Russell's viper envenomation-associated AKI were in AKI stage 3, while about one-third each required dialysis, mechanical

ventilation and inotropes. Native treatments and bleeding manifestations were independent predictors of AKI. The mechanisms of Russell's viper envenomation-associated AKI include direct nephrotoxic effect of the venom [1,2], hypotension, disseminated intravascular coagulation and intravascular hemolysis [4]. These may lead to acute tubular necrosis, cortical necrosis or immune complex-mediated glomerulonephritis. Though there are multiple studies on snake envenomation in children [10,11], most have included hematotoxic or neurotoxic snake bites.

The incidence of snake bite-associated AKI in an adult population from Karnataka using the AKIN definition was 14.6% [12]. This study included adults with snake envenomations irrespective of species of snake. A study from Kolkata [4] studied the profile of Russell's viper envenomation-associated AKI in 61 children, but incidence of AKI could not be determined as cases without AKI were not recruited. Before the advent of the AKIN definition, 'acute renal failure' was documented to occur in 13-22% of snake envenomation [1,2].

We could not demonstrate any association between delayed administration of ASV and development of AKI. ASV administration as soon as four hours after Russell's viper envenomation did not prevent renal failure in one earlier study. The authors had hypothesized that once significant obstruction of renal micro-vessels with fibrin occurs, ASV would not prevent AKI [13]. On the

TABLE II COMPARISON OF CLINICAL FEATURES AND LABORATORY PARAMETERS IN RUSSELL'S VIPER ENVENOMATION CASES WITH AND WITHOUT AKI

Characteristics	*Children without AKI (N=33)*	*Children with AKI (N=28)*	*P*
Age, y*	7 (3-10)	8 (6.7-10)	0.336
Males[#]	19 (57.6)	15 (53.6)	0.754
Length of hospital stay, d*	3 (2-5)	8 (6-12)	0.004
Activity at the time of bite[#]			
Playing	12 (36.4)	10 (35.7)	
Sleeping	6 (18.2)	10 (35.7)	0.232
Walking	15 (45.5)	8 (28.6)	
Site of bite[#]			
Leg	25 (75.8)	23 (82.1)	
Hand	5 (15.2)	4 (14.3)	0.674
Trunk	3 (9.1)	1 (3.6)	
Pre ASV treatment sought[#]			
Tourniquet	7 (21.2)	10 (35.7)	0.266
Native medications	2 (6.1)	8 (28.6)	0.018
Immobilization[#]	1 (3)	3 (10.7)	0.253
No. of ASV vials*	10 (0-11)	10 (8-19)	0.083
ASV reaction[#]	9 (27.3)	13 (46.4)	0.121
Requirement of mechanical ventilation[#]	5 (15.2)	9 (32.1)	0.116
Requirement of inotropes[#]	3 (9.1)	9 (32.1)	0.024
Requirement of blood products[#]	1 (3)	8 (28.6)	0.005
Bleeding manifestations[#$]	8 (24.2)	15 (53.6)	0.019
Hematuria[#]	2 (6.1)	13 (46.6)	0.001
Urine protein: Urinary creatinine (g/g of creatinine)[#]			
0.2 - 2	1 (3)	6 (21.4)	
>2	1 (3)	10 (35.7)	0.001
Mortality	0 (0)	4 (14.3)	0.039

**Values depicted as median (IQR); [#]values depicted as n (%); [$]included hematemesis in 4, hematuria in 13, subconjunctival hemorrhage in 2, epistaxis in 2, melena in 2, and bleeding from bite site in 2 children.*

WHAT IS ALREADY KNOWN

- Acute kidney injury (AKI) is a common complication of Russell's viper envenomation.

WHAT THIS STUDY ADDS

- The incidence of AKI (using AKIN definition) in Russell's viper envenomation is 45.9%.
- Envenomed children with bleeding manifestations and native treatments are at risk for AKI.

contrary, another study observed the time to ASV initiation to be negatively correlated with requirement for dialysis [4]. Variability in these results could be related to heterogeneity in patient populations.

This is the first study from Southern India to analyze the incidence of AKI in Russell's viper envenomation using the consensus AKIN definition in a cohort of exclusively pediatric patients. The profile of patients in our study could have been limited by a referral bias. The model for prediction of AKI explains only 25.1% of all determinants. We also could not assess long term residual renal injury in Russell's viper envenomation; although this is being increasingly recognized [14].

We conclude that AKI is common in Russell's viper envenomation, and children with bleeding manifestations and native treatments are at risk for AKI. There is a need for prompt referral of such patients to higher centres, in order to initiate timely interventions.

Contributors: SK, KG, SM: were involved in management of the patients; SK, KG: collected the data; SK: reviewed the literature and drafted the manuscript; SK, SM: conceptualized the study and reviewed the literature; SM: critically reviewed the manuscript and shall act as guarantor of the paper; ZB: supervised the laboratory tests; APK: performed the statistical analysis. All authors approved the final version of the manuscript.

Funding: None; *Competing interests*: *None stated.*

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