RESEARCH PAPER

Second Dose of Scorpion Antivenom in Children with Indian Red Scorpion (*Mesobuthus tamulus*) Sting Envenomation

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ABSTRACT

Objective: To study the effect of the second dose of scorpion antivenom in children with non-resolving or worsening scorpion sting envenomation.

Methods: 72 children aged ≤12 years with scorpion sting envenomation grade 2 and above were enrolled. 61 received the first dose of three vials of antivenom at admission (group A). Children with persistent/worsening envenomation at 6 hours received the second dose (group B). The time required for resolution of autonomic symptoms, myocardial dysfunction, predictors of the second dose and side effects were studied.

Results: The mean time taken for resolution of autonomic symptoms were similar in GroupA and B (4.1 *vs*. 5.3 hours, *P*=0.452), and of myocardial dysfunction was shorter in Group A (10.8 *vs*. 37.6 hours, *P*=0.019). On regression analysis, abnormal echocardiography at admission was found to be a significant predictor of the second dose (OR=27.6, 95% CI, 4.7–162.5; *P*=<0.001). Six of children had allergic reactions (itching and rash), and two developed hypotension.

Conclusion: Children with severe scorpion sting envenomation with abnormal echocardiography may require a higher dose of scorpion antivenom.

Keywords: *Autonomic dysfunction, Myocardial dysfunction ,Poisoning.*
Trial registration: Clinical trial registry of India (CTRI/2015/03/005652)

INTRODUCTION

Scorpion sting envenomation is a commonly encountered emergency and preventable cause of morbidity and mortality [1,2]. Medically important species found in India are *Mesobuthus tamulus* (Indian red scorpion) and *Palamneus Swammer dami* (Indian black scorpion) [3,4]. Symptoms range from local pain to myocardial dysfunction and respiratory failure in *Mesobuthus tamulus* sting envenomation.

In the management of scorpion sting envenomation, the efficacy of Scorpion antivenom (SAV) has been shown in many studies [2,5,6]. The current dose of SAV used in children is primarily based on studies in adult population [2,5]. Even after the use of 30 mL of SAV, few children may deteriorate [5,7]. Antivenom, when injected intravenously, binds to the venom and facilitates its excretion [8-10]. Subsequently, a concentration gradient of venom between the vascular compartment and the

peripheral tissue compartment facilitates the redistribution of venom from peripheral tissues to the vascular compartment from where the antivenom moderates further excretion of venom [8-10]. The dose of SAV seems to be related to the severity of envenomation, but has not been well researched. The purpose of this study was to describe the effect of the second dose of SAV in children with non-resolving envenomation.

METHODS

The prospective pilot study was undertaken in the Pediatric Critical Care Unit in a tertiary healthcare hospital in Puducherry between April 2015 and July 2016. Approval was obtained from the Institute Ethics Committee.

All children ≤12 years presenting with definite scorpion sting (red scorpion was seen by bystanders/brought the killed scorpion or identified it on pictures) or unknown bite with features of grade 2 and above scorpion sting envenomation were included [2,5]. Grading of clinical fetures was done as follows: *Grade-1*: local pain and reaction at the sting site, without systemic involvement; *Grade-2*: Signs and symptoms of autonomic storm characterized by parasympathetic or sympathetic overactivity; *Grade-3*: Evidence of myocardial dysfunction diagnosed when any one of the following were observed. (a) Heart failure or cardiomegaly- Clinically or by echo without previous heart disease (b) Required an inotrope (≥5µg/kg/min of dobutamine or dopamine)/ hypotension with cold peripheries (cold shock); *Grade-4*: Hypotension with warm peripheries (warm shock) /Multiorgan dysfunction involving more than two-organ.

A convenient sample size of 15 patients for the second dose was considered. All children showing envenomation-Grade 2 and above were administered the first dose of SAV— three vials (30 mg) i.e. a single 30 mL dose of monovalent M. tamulus antivenom (Haffkine Biopharma, Mumbai) in 100 mL of normal saline, which was infused intravenously over one hour. All children received oral prazosin (30 µg/kg/dose), and it was repeated every three hours until the extremities were warm as per the assessment of treating team.

A second dose of three vials (30 mL) of SAV was administered in case of persistence of an autonomic storm or worsening to higher grades of envenomation at the end of 6 hours of the first dose. Children with myocardial dysfunction showing improvement in ejection fraction or on a tapering dose of inotropes were not treated with the second dose. The decision to administer the second dose of SAV was taken by the treating team after documenting the eligibility criteria.. Clinical and biochemical data and investigations (CPK-MB, Troponin-I, 12-lead electrocardiography (ECG) and echocardiography (ECHO)) were performed at admission, and six-hourly till recovery.

The patients were divided into Group-A (received 30 mL SAV) and Group-B (received 60 mL SAV) to determine the predictors of the second dose of SAV. Continuous data, if normally distributed, was compared by Student t test and, if non-normally distributed, was compared by Mann-Whitney U test and proportions with chi-square test (Fisher exact test if cell frequencies were small). Multivariate binary regression analysis (backward: conditional method) with predefined clinical variables was done to find out the predictors of the second dose, and model fit was assessed with Hosmer and Lemeshow test. All tests were two-tailed and *P*-value <0.05 considered as statistically significant. SPSS 20.0 software and Epi Info 7 was used for data analysis.

RESULTS

Seventy-six children with scorpion sting envenomation were assessed for eligibility, and 72 were enrolled (***Fig.* 1**). Baseline characteristics, investigations, and intervention are described in ***Table* I**. Cold peripheries (94.4%) and Sweating (69%) were the most common symptoms observed. One child in Group-A required mechanical ventilation for 6 hours for pulmonary edema at admission due to excessive fluid administration at an outside hospital.

Eleven children with persistent/worsening symptoms at the end of six hours received the second dose of SAV. The time taken for the resolution of autonomic symptoms was similar between the two study groups. Time take for normalization of ECG, ECHO, myocardial dysfunction, and discharge was longer in Group-B as compared to Group-A **(*Table* II)**. No mortality was found in this study. By multivariate logistic regression analysis, among the parameters included (age, gender, time to first dose prazosin and SAV, abnormal ECHO and ECG), abnormal ECHO at admission significantly predicted the need for the second dose (OR 27.6, 95% CI 4.7 to 162.5, R^2 =0.420, *P*=<0.001).

Six (8%) of children had allergic reactions to SAV (itching and rash; 4 during the first dose and 2 during the second dose). In Group-A, two children developed hypotension along with rash and managed by stopping SAV, fluid bolus, adrenaline, hydrocortisone, and antihistamine. The premedication with intravenous chlorpheniramine and H^2 blocker (Ranitidine) were given to all children, which prevented major reactions to SAV in subsequently enrolled children.

DISCUSSION

In this study, we documented efficacy of a second dose of ASV in a subset of children with Indian red scorpion sting envenomation who did not improve after the first dose. Abnormal ECHO at admission predicted the need for the second dose of SAV.

This study was only a pilot interventional trial, and there was no comparison arm to determine the efficacy of the second dose of SAV. Moreover, the SAV used was only against

Mesobuthus tamulus; whether the results can be extrapolated to other scorpion species need to be studied further. The delay in recovery after two dose of SAV could be due to two reasons; one is the severity of envenomation, delay in giving the antivenom or insufficient amount of antivenom. Hence it is important to neutralize the venom in both vascular and the tissue compartment with a higher dose of SAV can be considered with reasonable certainty consistent with findings from other studies [6,9]. This would mean that children with severe envenomation might benefit from 60 mL of SAV as the first dose at admission or an early administration of the second dose of SAV (another 30 mL).

We conclude, children with severe scorpion sting envenomation with abnormal ECHO may require a higher dose of SAV, and an initial dose of 60 mL of SAV at admission may be more beneficial. The efficacy and safety of higher and repeated doses need to be confirmed by controlled trials.

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Contributors: RR,SM: conceptualized the study, contributed to review of literature and critically reviewed the manuscript; AA: collected the data, reviewed the literature and drafted the first version of manuscript. PS: contributed to review of literature and performed the echocardiography (ECHO). All authors were involved in the management of the patient, and approved the final version of manuscript.

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Competing interest: None stated.

WHAT THIS STUDY ADDS?

- Abnormal ECHO at admission is a significant predictor of the requirement of the second dose of SAV.

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TABLE I BASELINE CHARACTERISTICS AT THE TIME OF ENROLLMENT INTO THE STUDY.

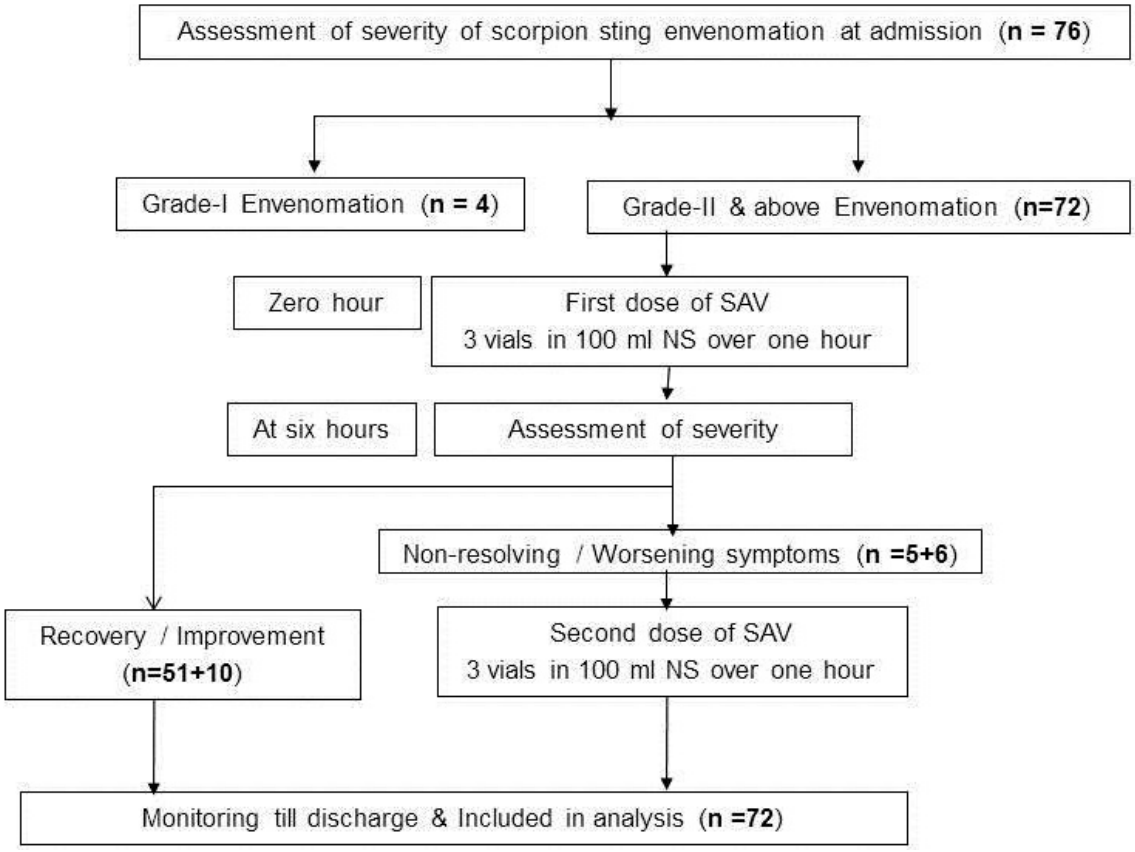
Variables	*Group A (n=61)*	*Group B (n=11)*	*P value*
Age (mo)*	45.8 (23.3, 74.2)	49.0 (24.1, 7)	0.919
Male : Female, n	40 : 21	9 : 2	0.288
Grade at admission, n (%) Grade 2 Grade 3 Grade 4	 49 (80.3) 11 (18) 1 (1.6)	 2 (18.2) 7 (63.6) 2 (18.2)	 < 0.001[c]
Prazosin received outside, n (%)	30 (49.2)	10 (91)	0.010
Vomiting, n (%)	39 (63.9)	6 (54.5)	0.554
Sweating, n (%)	59 (96.7)	10 (90.9)	0.397
Salivation, n (%)	36 (59)	6 (54.5)	0.782
Priapism, n (%)	30 (49.2)	7 (63.6)	0.699
Cold peripheries, n (%)	57 (93.4)	11 (100)	0.382
Myocardial dysfunction, n (%)	12 (19.7)	9 (81.8)	< 0.001
Inotrope,n(%)	10 (16.39)	10 (90.90)	<0.001
Hypertension, n (%) Hypotension, n (%)	26 (42.6) 2 (3.3)	4 (36.4) 2 (18.2)	1.000 0.105
ECG abnormal, n (%)	51 (83.6)	11 (100)	0.148
ECHO abnormal, n (%)	12 (19.6)	9 (81.8)	< 0.001
Elevated CPK-MB, n (%)	42 (68.8)	9 (81.8)	0.384
Elevated Troponin-I, n (%)	12 (19.7)	8 (72.7)	<0.001

*SAV –Scorpion antivenom; ECG- Electrocardiogram; ECHO- Echocardiography; CPK- Creatine phosphokinase *median (IQR)*

TABLE II TIME (HOURS) TO RESOLUTION OF AUTONOMIC SYMPTOMS, MYOCARDIAL DYSFUNCTIONS AND OUTCOME MEASURES IN THE STUDY SUBJECTS.

Outcome	***All patients (n=72)***	***Group A (n=61)***	***Group B (n=11)***	***Mean difference 95%CI***	***P value***
Sweating	2.3 (1.3)	2.9 (1.1)	3.0 (2.7)	-0.10 (-2.6 to 2.4)	0.924
Salivation	2.3 (1.4)	2.09 (1.0)	4.2 (3.9)	-2.2 (-11.8 to 7.5)	0.442
Priapism	3.5 (1.5)	3.6 (1.2)	2.8 (2.9)	0.8 (-2.8 to 4.4)	0.580
Cold peripheries	4.1 (2.2)	3.9 (1.1)	5.3 (4.9)	-1.4 (-4.9 to 2.1)	0.390
Blood pressure	3.9 (3.3)	3.6 (3.1)	5.7 (4.3)	-2.1 (-5.4 to 1.2)	0.201
Autonomic symptoms	4.2 (2.1)	4.1 (1.1)	5.3 (4.8)	-1.2 (4.8 to -2.3)	0.452
ECG abnormalities	12 (13.9)	8.6 (10.8)	28.5 (16.2)	-19.9 (-31.1 to -8.8)	0.002
ECHO abnormalities	17.4 (23.3)	5.01 (3.4)	31.2 (28)	-32.2 (-52.2 to -12.2)	0.002
Myocardial dysfunction	22.5 (26.2)	10.8 (19)	37.6 (27.5)	-26.7 (-48.4 to -5.1)	0.019
Hospital stay	64.4 (24.1)	57.1 (15.3)	104.7 (24.6)	-47.7 (-58.7 to -36.6)	<0.001

ECG- Electrocardiogram; ECHO- Echocardiography. All values are expressed in mean (SD) in hours unless otherwise indicated. P value by Welch's t-test unless otherwise specified.



SAV- Scorpion antivenom.

Fig. 1 *Study flow chart.*