RESEARCH PAPER

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

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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 within 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 comparable in Group A and B (4.1 *vs*. 5.3 h, *P*=0.4), and of myocardial dysfunction was shorter in Group A (10.8 *vs*. 37.6 h, *P*=0.02). 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). **Conclusion:** Children with severe scorpion sting envenomation with abnormal echocardiography may require a higher dose of scorpion antivenom. **Trial registration**: CTRI/2015/03/005652.

Keywords: *Autonomic dysfunction, Myocardial dysfunction, Poisoning.*

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Scorpion sting envenomation is a commonly encountered emergency and preventable cause of morbidity and mortality [1,2]. Symptoms range from local pain to myocardial dysfunction and respiratory failure in *Mesobuthus tamulus* sting envenomation, an important Indian species [3,4].

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 the 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 required 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

This prospective study was undertaken in the Pediatric Critical Care Unit in a tertiary 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 features 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.

All children showing envenomation-Grade 2 and above were administered the first dose of three vials (30 mg) of SAV, *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 within 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.

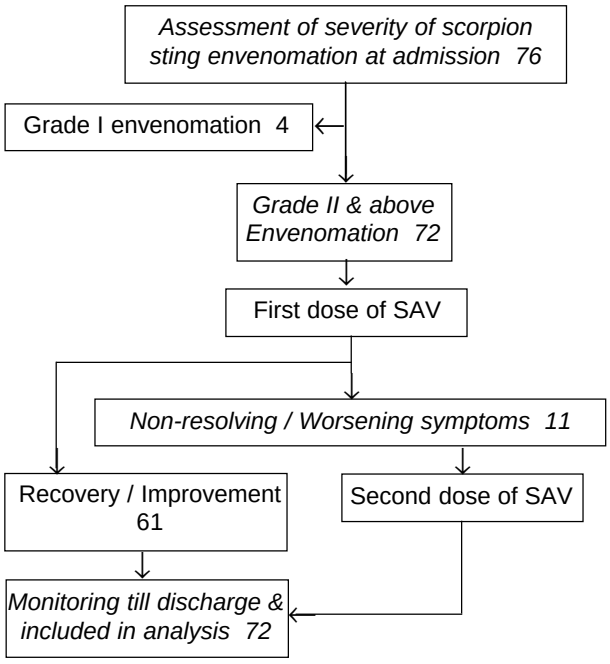

Fig. 1 *Study flow chart.*

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 the 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 SAV in a subset of children with Indian red scorpion sting envenomation who did not improve after the first dose. Abnormal echocardiography at admission predicted the need for the second dose of SAV.

This was only an exploratory study, 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 needs to be studied further. The delay in recovery after two doses of SAV could be due to two reasons; one is the severity of

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)	0.91
Males	40	9	0.29
Grade at admission			
Grade 2	49 (80.3)	2 (18.2)	< 0.001
Grade 3	11 (18)	7 (63.6)	
Grade 4	1 (1.6)	2 (18.2)	
Prazosin received outside	30 (49.2)	10 (91)	0.01
Vomiting	39 (63.9)	6 (54.5)	0.55
Sweating	59 (96.7)	10 (90.9)	0.39
Salivation	36 (59)	6 (54.5)	0.78
Priapism	30 (49.2)	7 (63.6)	0.69
Cold peripheries	57 (93.4)	11 (100)	0.38
Myocardial dysfunction	12 (19.7)	9 (81.8)	< 0.001
Inotrope	10 (16.39)	10 (90.90)	<0.001
Hypertension	26 (42.6)	4 (36.4)	1.00
Hypotension	2 (3.3)	2 (18.2)	0.10
ECG abnormal	51 (83.6)	11 (100)	0.14
ECHO abnormal	12 (19.6)	9 (81.8)	< 0.001
Elevated CPK-MB	42 (68.8)	9 (81.8)	0.38
Elevated Troponin-I	12 (19.7)	8 (72.7)	<0.001

*All values in n (%) except *median (IQR); SAV:Scorpion antivenom; ECG: Electrocardiogram; ECHO: Echocardiography; CPK: Creatine phosphokinase.*

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, this 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 that children with severe scorpion sting envenomation with abnormal echocardiography 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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Competing interest: None stated.

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

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.

WHAT THIS STUDY ADDS?

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

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