RESEARCH PAPER

Predictors of Myocardial Dysfunction in Children with Indian Red Scorpion (*Mesobuthus tamulus*) Sting Envenomation

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Objectives: To identify predictive risk factors for myocardial dysfunction in children with scorpion sting envenomation and to evaluate the effects of Scorpion antivenom and prazosin combination therapy on occurrence of myocardial dysfunction.

Design: Observational.

Setting: Tertiary care hospital in Southern India.

Participants: 85 children aged <13 years with scorpion sting envenomation.

Outcome measures: Frequency of myocardial dysfunction; predictors of myocardial dysfunction.

Results: 24 children (28.2%) developed myocardial dysfunction. Hypotension at admission (*P*=0.003) and increased time (>4h) between sting and administration of appropriate therapy (*P*=0.001) were independent predictors of myocardial dysfunction on logistic regression. Scorpion antivenom plus prazosin combination therapy led to an increase in cumulative proportion of children without myocardial dysfunction.

Conclusion: Early (<4 hours) administration of Scorpion antivenom along with prazosin increases the cumulative percentage of children not developing myocardial dysfunction.

Keywords: *Children, Myocardial dysfunction, Scorpion sting envenomation, Scorpion antivenom.*

Scorpion sting envenomation is an acute medical emergency which can be potentially life-threatening in children. Significant reduction in morbidity and mortality due to scorpion sting envenomation has been achieved by use of prazosin [1]. Recently, Scorpion antivenom (SAV) use in children along with prazosin was shown to accelerate recovery times [2,3]. Having achieved significant reduction in mortality in scorpion sting envenomation, the need of the hour is to reduce morbidity due to scorpion sting envenomation, among which myocardial dysfunction is most important [4]. Identification of factors that could potentially predict myocardial dysfunction could be helpful in providing appropriate and timely management, thereby reducing the morbidity due to the condition. We planned this study to identify predictors for myocardial dysfunction in children presenting with Indian red scorpion envenomation, and to study the effect of SAV plus prazosin combination therapy.

Methods

This prospective observational study was conducted in the Department of Pediatrics at a tertiary-care health center in Pondicherry, Southern India, from November 2012 to May 2014. Approval from the Institute Ethics Committee was obtained prior to the conduct of the study, and written informed consent was taken from the parents.

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Children aged less than 13 years presenting to the Emergency medical services or outpatient services of the hospital with features of scorpion sting envenomation or unknown bite with clinical features consistent with scorpion sting envenomation (local pain, sweating, priapism, cold extremities *etc*) were included. The term 'Definite scorpion sting' was used when there was history of sting with features consistent with scorpion sting envenomation, and the bystanders had seen the red scorpion and brought the killed scorpion for identification, or identified the same on pictures shown to them. The term 'Consistent with scorpion sting' was used when there was an unknown bite with features suggestive of Indian red scorpion envenomation. Myocardial dysfunction was diagnosed when the following criteria were met: (*i*) congestive cardiac failure or cardiomegaly, (*ii*) hemodynamic compromise that required a vasopressor (≥5 µg/kg/min of dobutamine or dopamine), (*iii*) left ventricular dysfunction identified by echocardiography without previous cardiomyopathy, (*iv*) elevated CPK-MB levels in the blood and (*v*) abnormal electrocardiogram [5].

Children were managed as per the existing departmental protocol for management of scorpion sting envenomation. Severity of clinical manifestations at the time of arrival to hospital was categorized between grade 1 to 4 [2,3]. Grade 1 envenomation was managed with supportive treatment like local anesthetic injection for acute pain and paracetamol for mild persistent pain. These patients were observed for 24 hours for any deterioration. Children with Grade 2 envenomation were managed with prazosin (30 µg/kg every 3 hourly), and monitored in a high dependency unit till resolution of symptoms. Prazosin was continued until the extremities were warm. Additionally, SAV was administered at admission (subject to availability) according to the protocol followed by Bawaskar, *et al*. [2]. A single 30 mL dose of monovalent antivenom (Haffkine Biopharma) was added to 100 mL of normal saline, and infused intravenously over 30 minutes. During infusions, the patients were closely observed for anaphylaxis or allergic reactions. Patients with Grade 3 and Grade 4 envenomation were managed in the Pediatric intensive care unit (PICU). In addition to prazosin and SAV management was based on other complications. Myocardial dysfunction was managed with oxygen, and intravenous dobutamine infusion at the rate of 6-20 µg/kg/min. Pulmonary edema was managed with oxygen, mechanical ventilation, sodium nitroprusside intravenous infusion (0.3-5 µg/kg/min) or freshly prepared sunlight-protected infusion of intravenous nitroglycerine (2-6 µg/kg/min). Encephalopathy was managed with oxygen, mechanical ventilation, midazolam and/or phenytoin for control of convulsions. Children with complications were discharged only after they were stable without drugs for 24 hours. Children who were administered SAV were observed for a minimum period of 24 hours post-antivenom administration. The selection of patients for SAV therapy was based on the availability of SAV in the hospital at that particular point-of-time.

A 12-lead electrocardiogram (ECG) was done in all patients at admission, and after six hours. In children who developed myocardial dysfunction, ECG was repeated before discharge. Echocardiography and serum levels of CPK-MB were done within 24 hours in all the patients. In patients with grade 3 or grade 4 envenomation, echocardiography was repeated before discharge.

Clinical and laboratory data that were recorded included age, gender, time between sting and hospital admission, history of any medication before admission, and history of vomiting soon after sting. Blood pressure, heart rate, respiratory rate, and oxygen saturation were monitored at regular intervals (on admission, at 30 minutes, at 1, 2, 4, 6, 8, 10, 14, 18, and 24 hours). Normal values of heart rate, respiratory rate, blood pressure and oxygen saturation were defined based on normative data charts [6]. Children were followed up till discharge or death. Assuming the frequency of myocardial dysfunction as 24% [3], degree of variability at 10%, error of 0.05 and beta error of 0.2, the sample size calculated was 70 children. To allow for a 20% attrition, we decided to recruit 85 children. Chi-square test was used for comparing categorical variables and Student t test for continuous variables between children with or without myocardial dysfunction. Predictive risk factors for myocardial dysfunction were determined by logistic regression. Kaplan Meier survival analysis was used to evaluate the cumulative proportion of children without myocardial dysfunction in scorpion sting envenomation in children receiving SAV plus prazosin therapy *versus*

TABLE I BASELINE CHARACTERISTICS IN CHILDREN WITH SCORPION STING ENVENOMATION (*N*=85)

Characteristic	*No. (%)*
Definite Scorpion sting	65 (76)
Site of sting	
Upper limbs	32 (37.6)
Lower limbs	38 (44.7)
Back	5 (5.8)
Head and neck	2 (2.3)
Unknown	8 (9.4)
Admitted within 4 h of sting	48 (56)
Severity of envenomation at admission	
Grade 1	9 (10.5)
Grade 2	65 (76.4)
Grade 3	9 (10.5)
Grade 4	2 (2.3)
Symptoms and signs	
Local pain	67 (78.8)
Vomiting	59 (69.4)
Sweating	72 (84.7)
Salivation	34 (40)
Cold extremities	76 (89.4)
Priapism	35 (41.2)
Bradycardia	8 (9.4)
Tachycardia	41 (48.2)
Hypotension	9 (10.6)
Hypertension	8 (9.4)
Seizures	3 (3.5)
Echocardiography evidence of LV dysfunction	24 (28.2)
ECG changes	36 (42.4)

those receiving prazosin alone. Analysis was done using SPSS (Statistical Package for the Social Sciences) Version 19.0.

RESULTS

During the study period, 85 children (52 males), aged less than 13 years with scorpion sting envenomation were admitted. The mean (SD) age was 5.4 (3.7) years. Half (*n*=43) of the children were aged less than 5 yrs. Many children received inappropriate pre-referral treatment such as steroids, diuretics and anti-histamines (***Table* I**). Nine children had grade 1 envenomation. Among 76 children with higher grade of envenomation, 40 received SAV plus prazosin therapy while 36 received only prazosin. Ten children (25%) developed myocardial dysfunction in the SAV plus prazosin group, whereas 14 children (48%) developed myocardial dysfunction in the treatment group receiving prazosin alone. All children completed treatment and were followed up until discharge.

Twenty-four (28.2%) children had myocardial dysfunction secondary to scorpion sting envenomation; 11 of them had the features at admission. Children who developed myocardial dysfunction (*n*=24) had a longer time gap between sting and admission in comparison to those who did not develop myocardial dysfunction (*n*=61). In children who were admitted late (>4 hours) to the hospital, higher proportion of myocardial dysfunction (79.2%) was detected (***Table* II**).

TABLE II CHARACTERISTICS OF CHILDREN WITH (*N*=24) OR WITHOUT (*N*=61) MYOCARDIAL DYSFUNCTION.

Characteristic	*Myocardial dysfunction (n=24)*	*No myocardial dysfunction (n=61)*
Age <5 years	10 (41.6%)	33 (54.1%)
Male gender	14 (58.3%)	38 (62.3%)
*Admission within 4 h	5 (20.9%)	43 (70.5%)
†$Delay in admission (h)	5.62 (2.74)	2.84 (1.74)
#Antihistamine administration	13 (54.1%)	28 (45.9%)
#Steroid administration	9 (37.5%)	24 (39.3%)
*CPK (Total) (IU/L)	1006 (63)	333 (27)
*CPK MB (IU/L)	105 (59)	40 (30)
*Ventilator requirement	6 (25%)	0
Encephalopathy	1 (4.1%)	0
Death	1 (4.1%)	0

*All continuous variables are depicted as mean (SD) while all categorical variables are depicted as n (%) #Received before admission; $Time between sting and hospital admission; * P = 0.001; † P = 0.012.*

Thirteen of the 65 children, who presented with grade 2 envenomation at admission, deteriorated to grade 3 or grade 4. The proportion of children deteriorating to higher grades was significantly more in children receiving prazosin alone as compared to children who received SAV along with prazosin (11/33 *vs* 2/32, *P*=0.006). In the sub-group where SAV was used (*n*=40), all the 18 children who presented within 4 hours of sting, did not develop myocardial dysfunction after treatment with SAV whereas 10 out of 22 children who presented after 4 hours of sting developed myocardial dysfunction despite treatment with SAV. Kaplan Meier survival analysis showed that usage of SAV plus prazosin therapy led to an increase in cumulative proportion of children without myocardial dysfunction (***Fig.* 1**).

Univariate analysis showed that admission to hospital more than 4 hours after the sting (*P*<0.001), hypotension at admission (*P*<0.001) and not using SAV in grade 2 envenomation (*P*<0.006) were associated with myocardial dysfunction (***Table* III**). The independent predictors of myocardial dysfunction as determined by multivariate logistic regression included longer time between sting and admission, and hypotension (***Table* IV**).

DISCUSSION

The present study demonstrates the beneficial effects of SAV plus prazosin therapy in prevention of myocardial dysfunction. Administration of therapy more than 4 hours after the sting, hypotension at admission and non-usage of SAV for treatment were associated with myocardial dysfunction in the current study. Although SAV usage in grade 2 envenomation was not found to be an independent predictor of myocardial dysfunction, therapy with SAV resulted in an increase in the cumulative proportion of children without myocardial dysfunction.

It has been opined that late administration of SAV may have no beneficial effect as the venom might have already reached the target site of action and may not be accessible to the antivenom for neutralization (due to its short half-life) [7,8]. However, apart from the action on neutralizing circulating unbound venom, the antivenom also creates a concentration gradient between plasma and target tissue. The venom bound to antivenom gets continuously excreted and the toxin in the tissues moves down the concentration gradient into the blood, where the redistributed venom is bound by the antivenom. Thus, even if the venom is not immediately neutralized by antibodies, its removal from tissue may cause rapid regression of symptoms. This has been proven by *in vitro* experimental studies [9-11].

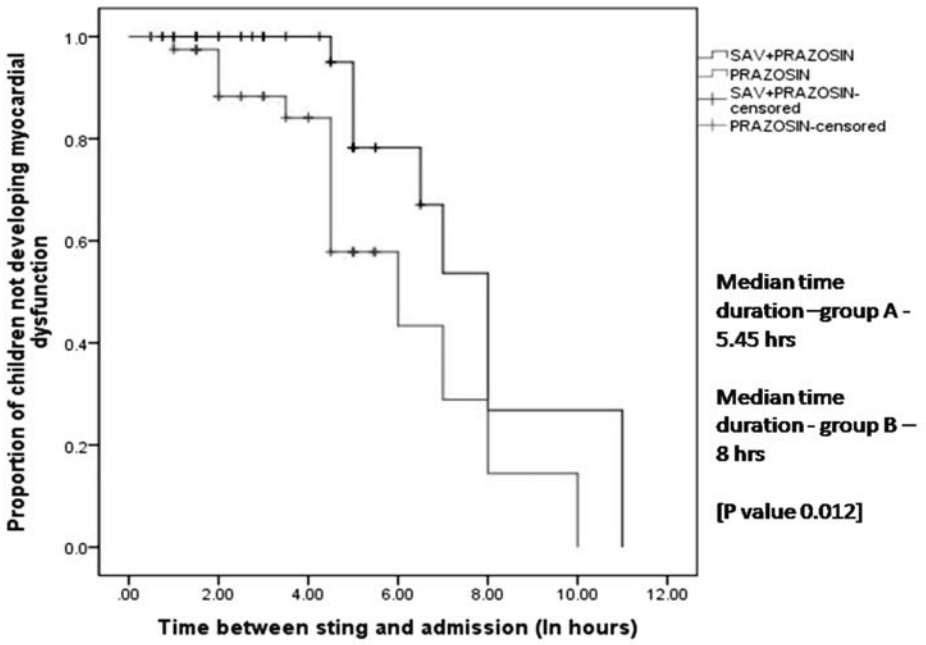

FIG. 1 *Kaplan Meier curve showing cumulative percentage of subjects not developing myocardial dysfunction in the two treatment groups: group A (prazosin therapy alone) and group B (SAV plus prazosin therapy) (P=0.012).*

TABLE III UNIVARIATE ANALYSIS FOR PREDICTORS OF MYOCARDIAL DYSFUNCTION IN CHILDREN WITH SCORPION ENVENOMATION (*N*=85)

	Myocardial dysfunction (n=24)	*OR (95% CI)*	*P value*
Age <5 years	10	1.7 (0.6 – 4.3)	0.342
Male gender	14	2.3 (0.9 – 6.1)	0.736
Time between sting and admission.>4 hours	5	9.1 (2.9 – 28.6)	0.001
Hypotension	8	30 (3.5 – 258)	0.001
Hypertension	0	0.1 (0.01 – 2.4)	0.09
Received antihistamines prior to admission	13	1.4 (0.5 – 3.6)	0.492
Received steroids prior to admission	9	0.9 (0.4 – 2.5)	0.875
Prazosin monotherapy in patients with grade 2 scorpion sting envenomation at admission	11	7.5 (1.3 – 54.8)	0.006

Some other studies have evaluated the risk factors for adverse outcomes after scorpion sting envenomation, but have not specifically focused on predictors of myocardial dysfunction. Bouaziz, *et al*. [15] documented that age less than 5 years, sweating, agitation, leukocyosis and elevated plasma proteins were predictors of pulmonary edema after scorpion sting envenomation. The limitations of our study include fewer patients with higher grades of envenomation, and unavailability of ELISA test for detection of venom antigen and antivenom in the blood. This precluded a correlation between amount of venom and response to treatment in children who were treated with SAV.

TABLE IV PREDICTORS OF MYOCARDIAL DYSFUNCTION IN CHILDREN WITH SCORPION STING ENVENOMATION AS DETERMINED BY MULTIVARIATE LOGISTIC REGRESSION ANALYSIS.

Determinants	*Adjusted OR (95 % CI)*	*P value*
Time between sting and admission > 4 h	13.8 (3.3 – 58.7)	0.001
Hypotension	8.9 (3.4 – 36.8)	0.003
Treatment with Prazosin without SAV	2.0 (0.1 – 14.4)	0.160

WHAT IS ALREADY KNOWN?

- Scorpion antivenom along with prazosin accelerates recovery from autonomia dysfunction associated with scorpion sting envenomation.

WHAT THIS STUDY ADDS?

- Early (<4 hours) administration of Scorpion antivenom along with prazosin prevents myocardial dysfunction in scropion sting envenomation.

The present study suggests that early appropriate therapy and referral of patients with scorpion sting envenomation with autonomic features is vital in preventing myocardial dysfunction, and optimal treatment with SAV and prazosin combination therapy reduces the risk of myocardial dysfunction and prevents clinical deterioration in children presenting with grade 2 envenomations. We recommend similar adequately powered studies for children presenting with higher grades of envenomations.

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