Can the Addition of Prazosin or Dobutamine to the Antivenom Improve Scorpion Envenomation-induced Cardiotoxicity in Children?

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Abstract

Introduction: Antivenom plays an important role in the management of scorpion envenomation but it may be inefficient especially when used alone in cases of envenomation complicated by cardiotoxicity and hence the need for establishing a new treatment. Objective: Evaluating the efficacy of prazosin or dobutamine besides scorpion antivenom (SAV) in managing patients with the cardiotoxic complications following scorpion sting. Methods: A total of 102 patients who presented with scorpion sting and complicated by myocarditis and hypotension. Cases were divided into three groups. Groups were given SAV, SAV plus prazosin and SAV plus dobutamine, respectively. Results: Clinical improvement without the development of pulmonary edema was noticed in 47.06%, 73.53% and 70.59% in Group I, II and III, respectively. Conclusion: Adding prazosin or dobutamine to SAV was found to improve cardiotoxicity associated with scorpion sting. However, oral prazosin revealed the highly significant improved results.

Keywords: Antivenom, dobutamine, prazosin, scorpion

Introduction

Scorpions are nocturnal eight legged arthropods that have a wide geographic distribution worldwide. Among 1500 known scorpion species only 50 are considered as venomous species. All venomous scorpion species belong to the large family Buthidae.[1] The venom enters the circulation very rapidly and reaches peak tissue concentration within 37 min inducing complications in almost all the organ systems; however, most of the fatal cases are could be referred to cardiopulmonary complications like myocarditis and acute pulmonary edema (APE) that is frequent in children when compared to adults.[2] Symptoms reflect the initial release of acetylcholine neurotransmitter causing (vomiting, bradycardia, sweating, and salivation) followed by release of catecholamines causing (hypertension, tachycardia, pulmonary edema, and arrhythmias).[3] Multiple regimens had been tried in the past like steroids, lytic cocktail of drugs that contains (pethidine, chlorpromazine, and promethazine), chlorpheniramine maleate, largactil, furosemide and insulin with glucose, large boluses of fluid therapy and many other drugs.[4] Although the antivenin is highly beneficial and effective in the management of envenomation, it works only when it is given immediately after the sting and its efficacy declines significantly as the delay time becomes longer when the cardiotoxic effects of the venom become evident, so it is necessary to institute an alternative strategy to treat this condition. The use of prazosin and/or dobutamine in addition to antivenom appears to be promising in managing cardiotoxicity resulting from scorpion envenomation in complicated cases.[5]

Methods

Subjects

This prospective randomized study was conducted in Poison Control Centre (PCC) of Minia University Hospital during the period from June 2014 to December 2015; all cases presented with scorpion sting from the age of 5-18 years were enrolled in the study.

A diagnosis of scorpion envenomation was based on the presence of a positive history of scorpion sting, with the scorpion being seen by patients or bystanders that are then confirmed or denied by clinical presentation. We excluded patients who had no systemic manifestations or cardiotoxicity in the form of myocarditis or hypotension and those who presented with pulmonary edema from the start.

A total of 102 eligible patients (96 females “53.3%:” 84 males “46.7%”) patients with mean age of (9.5 ± 4.5 years) were examined, and baseline data were recorded on standard forms. The patients were divided into three groups on alternate basis 34 per each group. An informed consent was taken from their parents A diagrammatic representation is described in Figure 1.

Inclusion and Exclusion Criteria

Inclusion criteria:

1. All scorpion stung children (males and females) falling at age group between 5 and 18 years that presented to the PCC, Minia University Hospital at the period from June 2014 to December 2015.

2. Systemic envenomation:
   a. Parasympathetic manifestations including vomiting, profuse sweating, salivation, bradycardia, ventricular premature beats, priapism in male, and hypotension
   b. Sympathetic manifestations including cold extremities, hypertension, tachycardia, and shock.[6]
3. Features of myocarditis:
   a. Tachycardia
   b. Muffled heart sounds
   c. Gallop rhythm, hemodynamic compromise that required a vasopressor (≥5 μg/kg/min of dobutamine or dopamine)
   d. Electrocardiogram (ECG) changes (ST segment changes, and the presence of arrhythmias)
   e. Elevated serum creatine phosphokinase-MB (CPK-MB).

Exclusion criteria:
1. No systemic envenomation features
2. Pulmonary edema at presentation:
   a. Tachypnea
   b. Pinkish frothy sputum
   c. Bilateral crepitation
   d. Radiological findings, which were emphasized by the arterial blood gas analysis.[7]
3. Patients who developed pulmonary edema after institution of therapy
4. Patients with pre-existing cardiac disease
5. Patients below 5 years because of technical difficulties associated with applying investigations needed for the study at this age group.
6. Patients above 18 years of age when envenomation is not likely to cause cardiotoxicity as in children. Cardiomegaly on chest X-ray and decreased ejection fraction (EF) on 2D echocardiography without previous cardiomyopathy (Kumar et al., 2012).[8]

Sample Size
The study subjects were randomized to one of the three treatment groups. In view of the convenient and multiple advantages of scorpion antivenom (SAV) in scorpion envenomation, it was felt that it would be essential to include it in all treatment groups.

a. Group I: A total number of 34 patients of both sexes who received antivenom alone
b. Group II: A total number of 34 patients of both sexes who received antivenom with oral prazosin
c. Group III: A total number of 34 patients of both sexes who received antivenom with IV dobutamine hydrochloride.

Protocols of Drug Administration

SAV administration protocol
Initial single 1 mL dose of polyvalent antivenom was given intramuscular followed by another ampoule after 1/2 h in the case of persistent symptoms. If no improvement within 1 h, five ampoules were infused intravenously over 30 min irrespective of the patient’s age to be repeated every 2 h up to 20 mL (if the clinical manifestations did not improve). During the intravenous infusion, the patient was closely observed for anaphylactic reactions. Children were observed for a period of 24 h post-SAV administration.

Prazosin
Minipress (prazosin hydrochloride 1 mg tablet, manufactured by Pfizer Egypt S.A.E. - A.R.E. Under Authority of Pfizer Inc., USA) was given orally as 30 μg/kg every 3 h that is immediately followed...
by antivenom IV bolus, as mentioned above. Prazosin was repeated every 3 h until the extremities were warm and EF reached 50% or more.

**Dobutamine**

Dobutamine 250 mg/20 ml, MYLAN 10 A, almasria for drug trading was given by continuous IV infusion at the rate of 10 mg/kg body weight/min, which is then titrated as per the condition of the patient. This infusion was continued for 48 h of hemodynamic stability and till the left ventricular EF (LVEF%) increased to 50% or more and then was tapered downward at the rate of 5 mg/kg body weight every 12 h.

All patients were initially evaluated to classify patients and detect degree of envenomation for:

- **Clinically:**
  - Pulse, blood pressure, and extremities temperature
  - Presence of dyspnea or orthopnea
  - The presence of pinkish froth.

- **Biochemically:**
  - Oxygen saturation (SaO₂)
  - Serum CPK-MB isoenzyme activity using immune-inhibition method (Cat. No 92453. Diagnostics, Italy), (reference range = 0-8.5 ng/mL).

- **Imaging procedures:**
  - Chest X-ray (posteroanterior view) to check for the development of pulmonary infiltrates associated with pulmonary edema
  - ECG: Standard 12 lead ECG was done on admission to detect any abnormalities in rate or rhythm including and if found abnormal, was repeated every 12 h, till abnormality got corrected
  - Echocardiography: A 2D-M mode echocardiography, Doppler and color flow mapping echo were done to the studied patients using a sector scanner with 2.5 and 5 MHZ transducers to find out the cardiac status of the patient including the EF and any regional wall motion abnormality before starting treatment and then every second day (if general condition of the patient allowed) till hospital stay. The examination was performed using Vivid 3 GE Computed Sonographic System.

Follow-up clinical, biochemical, and radiological evaluation were carried out periodically till the time of complete recovery or development of pulmonary edema.

**Main outcome measures**

- **Primary end point** was considered as time taken for complete clinical recovery which was defined as time required for complete normalization of:
  - Pulse
  - Respiratory rate
  - Blood pressure and no deterioration in the next 4-8 h.

- **Secondary end point** was the time required for complete resolution of:
  - ECG and echocardiographic abnormalities including EF recovery
  - Normalization of CPK-MB level.

## Statistics

The data were analyzed using a statistical package of social science version 20. The quantitative data expressed as mean ± standard deviation with minimum and maximum of range, whereas qualitative data expressed as number and percentage. Analysis of qualitative data was performed using one-way ANOVA test between the three groups, with post-hoc Tukey’s correction between each 2 groups. Qualitative data were analyzed by Chi-square test between groups. A significant difference is observed at $P < 0.05$.

**Results**

A total of 102 patients were enrolled in this study, the baseline characteristics of the individuals studied, which were similar in all the groups, are summarized in Table 1. The three groups were age and sex-matched.

The patients in the only antivenom group presented (4.79 ± 1.2 h), and those in dobutamine group presented (4.32 ± 1.66 h) after the sting while those in prazosin group presented (4.23 ± 1.61 h) after the sting with no significant statistical difference in between three groups. The majority of cases were from the rural areas, accounting for 84 cases (82.3%).

Patients who developed pulmonary edema after the institution of therapy were excluded from the study. The lower incidence of ECG findings in the form of ST segment changes was found in prazosin group (38.2%) which was significantly lower than that noticed in antivenom and dobutamine groups (64.7% and 41.2% respectively). The proportion of children who
developed pulmonary edema was significantly lower in prazosin group (26.5%, P = 0.026) and dobutamine group (29.4%, P = 0.026) than those in antivenom group (52.9%). Children in prazosin and dobutamine groups demonstrated faster recovery of the vital signs than those in anti-venom group; the time taken for normalization of heart rate was significantly shorter in cases treated with prazosin and dobutamine (20.64 ± 9.49 h and 25.5 ± 11.9 h, respectively) as described in Table 3 than that needed in group treated by antivenom only (46.5 ± 12.29 h), time taken in normalization of blood pressure was significantly shorter in cases treated with prazosin and dobutamine (12.48 ± 2.4 h and 13.6 ± 4.21 h respectively) than that taken in group treated by antivenom only (28.5 ± 8.62 h) and time taken in rewarming of extremities was significantly shorter in cases treated with prazosin and dobutamine (7.2 ± 3.26 h and 8 ± 4.45 h respectively) than that taken in group treated by antivenom only (12.75 ± 5.10 h).

The P value being <0.05, therefore, faster improvement of various parameters was observed in prazosin and dobutamine groups in comparison with the only antivenom group (Table 2). Measurements of (EF%) that were obtained after 48 h showed that addition of prazosin or dobutamine to SAV led to a significant increase in EF% (mean difference: 9.12% ± 2.35% and 8% ± 1.28%) in prazosin and dobutamine groups, respectively. By contrast, children in the SAV-only group showed lesser elevation in LVEF% (5.18% ± 1.19%). No anaphylaxis was noted with the use of SAV. However, two children in SAV alone group developed a mild hypersensitivity reaction during SAV infusion that was successfully managed with antihistaminic without interruption of the SAV infusion. No adverse effects were noted in children with prazosin and dobutamine-treated groups. Laboratory values for CPK-MB were similar between the groups at admission, however, time taken for it to return to a normal level was significantly shorter in prazosin group (123.84 ± 30.73 h) than antivenom and dobutamine groups (152 ± 22.7 and 126 ± 30.7 h), respectively as described in Table 4. Complete recovery of clinical manifestations was found to occur earlier in groups treated with prazosin and dobutamine (34.54 ± 26.95 h and 42.18 ± 28 h, respectively) than the group treated with antivenom only (64.12 ± 21.03 h).

Stay in the intensive care unit was found to be significantly shorter in prazosin and dobutamine groups (26.6 ± 9.49 h and 30.5 ± 11.98 h, respectively) and antivenom alone group (52.6 ± 12.4 h). There were no deaths in any treatment group among cases who did not develop pulmonary edema and no cases required mechanical ventilation.

### Discussion

Scorpion sting represents a medical emergency especially in children; severe morbidity and even mortality are inevitable if not managed properly. Pathogenesis of myocardial dysfunction that represents the worst sequel of scorpion envenomation is related in fact to excessive alpha-receptors stimulation resulting into ventricular impedance due to severe peripheral vasoconstriction. Excessive stimulation of alpha-receptors also suppresses insulin secretion what results in providing free fatty acid in excess as a source for energy which is toxic to the myocardium and causes arrhythmias. Our results showed that addition of prazosin to antivenom induced earlier complete clinical recovery than in cases treated with antivenom only (P < 0.001); these results were in agreement with, clinical recovery time in dobutamine group was also found to be significantly lower than that noticed in antivenom group (P = 0.001), however, it was insignificantly higher than that of prazosin group (P = 0.228). Our results showed that rewarming of extremities occurred in prazosin group after (7.2 ± 3.26 h) which was comparable to results noticed by Bawasker and Bawasker (2010) who found that rewarming with prazosin occurred after (8.5 ± 5.3 h). Both prazosin and dobutamine significantly increased LVEF% in the 1st 48 h after institution of therapy than the antivenin alone did (P < 0.001). However, prazosin showed better results than dobutamine in elevation of LVEF% in the 1st 48 h, but the difference in-between was statistically in significant (P = 0.15). Total time needed for normalization of LVEF% in prazosin and dobutamine groups was significantly shorter than that taken by antivenom alone (P = 0.002 and 0.013, respectively). Again, the statistical difference in between prazosin and dobutamine in time taken for LVEF% to normalize was found to be insignificant (P = 0.423). Above results as regard to the superiority of prazosin over dobutamine in initial elevation of LVEF% and time needed for its normalization without a significant statistical difference in between were in agreement with. Prazosin is a selective alpha-1 adrenergic receptor blocker. Thus, its pharmacological properties can antagonize the hemodynamic, hormonal and metabolic effects of scorpion venom action. It dilates veins and arterioles, thereby reducing pre-load and left without rise in heart rate and renin secretion. It also inhibits sympathetic outflow in central nervous system and enhances insulin secretion which is inhibited by venom action. Dobutamine is a selective β2 agonist that improves the impaired left as well as right ventricular function. It evokes substantial increases in cardiac output and systemic arterial pressure. This study aimed at studying the impact of adding dobutamine or prazosin to scorpion antivenom in the management of scorpion envenomed cases. There is no other study comparing these three protocols in management together. Our study results showed that cases that developed pulmonary edema with prazosin and dobutamine were significantly lower than those who received SAV only. 18 (52.9%) of cases treated with SAV only developed pulmonary edema and this showed that SAV alone is not reliable in protection from cardiotoxic effects of scorpion venom which is concordant with. 1

### Table 4: Comparison of outcome variables in the study groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I n=34</th>
<th>Group II n=34</th>
<th>Group III n=34</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% increase in EF in 1st 48 h</td>
<td>5.18±1.19</td>
<td>9.12±2.35</td>
<td>8±1.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalization of CPK-MB</td>
<td>152±22.7</td>
<td>123±30.7</td>
<td>126±30.7</td>
<td>0.007</td>
</tr>
<tr>
<td>ICU stay</td>
<td>52.0±12.45</td>
<td>9.49±26.6</td>
<td>11.98±30.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPK-MB: Creatine phosphokinase-MB, ICU: Intensive care unit, EF: Ejection fraction

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Conclusion

Although antivenom is essential for the management of scorpion sting and no other drug can represent an effective alternative, but its efficacy declines as the delay time becomes longer when the presenting manifestation in the form of myocardial dysfunction are related to inflammatory cascade induced by the venom rather than the venom itself, as the antivenom acts mainly through neutralization of circulating venom. The use of an adjunctive treatment in the form of prazosin or dobutamine can improve the condition and prevent the development of APE; however, prazosin appears to be better as it is more effective, easily available, fast acting, cheap, and free from any anaphylaxis. Accordingly, in scorpion sting evidenced by myocardial dysfunction combination of immunotherapy and another treatment strategy better prazosin is a must, to neutralize the free circulating venom and ameliorate its hazardous effects on the heart. These treatment strategies potentiate each other and give a satisfactory response.

References


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