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Original Article

Biochemical study on cardiotoxic effects of *Mesobuthus eupeus* scorpion venom and the role of antivenom and carvedilol in rats

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Abstract

Mesobuthus eupeus is an indigenous scorpion species in Southwest Iran which is responsible for the majority of scorpion sting cases in Khuzestan province. To conduct this research a total of 75 Wistar male rats were divided into 5 equal groups randomly. Group 1 (control); Group 2: *M. eupeus* venom was administered with a dose of 1 mg/kg IP. Group 3: Venom + 0.5 ml of polyvalent antivenom intramuscularly, 30 minutes after envenomation. Group 4: Venom + 5 mg/kg of carvedilol 30 minutes after envenomation IP. Group 5: Venom + 0.5 ml of polyvalent antivenom + 5 mg/kg of carvedilol 30 minutes after envenomation IP. Blood samples were collected by cardiac puncture at 8, 24, and 48 hours after saline/venom injection from anesthetized rats. Heparinized plasma was isolated to measure cardio-related biochemical parameters, including the activity of CPK, LDH, and AST and troponin-I levels were measured by routine methods. The results showed that the activity of the enzymes of CPK-MB, LDH, AST, and also troponin-I as a specific index of heart damage elevated at different times following venom injection compared with the control group. Even though the administration of anti-venom following venom injection at different times significantly reduced the activity of these enzymes and also troponin-I levels, but the level of these indicators was still higher than the control group. Carvedilol administration had no significant effect on reducing the activity of the above-mentioned factors. Meanwhile, the combined administration of carvedilol and anti-venom following venom injection had similar results with the antivenom group. This result may relate to the dose and its frequency of carvedilol use.

Keywords: Cardiotoxicity, *S*corpion, *Mesobuthus eupeus*, Antivenom, Carvedilol

Introduction

Scorpions are a common arthropod found all over the world, including every continent except Antarctica. If threatened, a scorpion may use its long, flexible tail to sting a potential predator. Frequently, people unknowingly come into contact with these species and experience the painful sensation of envenomation (Murugan and Saini 2019, Cid-Uribe et al. 2019, O Collaço et al. 2019). Scorpion envenomation is an acute life-threatening medical problem especially in children and

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older individuals who suffer from respiratory and/or cardiovascular diseases. More than 1.2 million scorpion stings occur annually worldwide, particularly in tropical and subtropical regions (Ebrahimi et al. 2017). There are 1500 subspecies of scorpions worldwide, with 50 subspecies having venom dangerous for humans with scorpion (Buthidae) families are the most toxic offender (Ali 2015).

Scorpion venom shows variability by subspecies and has a complex structure composed of neurotoxic proteins, salts, acidic proteins, and organic compounds, thereby having neurologic, cardiovascular, hematologic, and renal side effects, in addition to local effects such as redness, pain, burning and swelling (Yılmaz et al. 2013). It carries a potential risk to induce severe and often fatal clinical complications; as scorpion venoms are complex of several toxins and incorporate a mixture of cardiotoxins, nephrotoxins, hemolytic toxins, and neurotoxins. Mortality is due to cardiac dysfunction and pulmonary edema (Bawaskar and Bawaskar 1992, Das et al. 2013).

The *Mesobothus eupeus* scorpion as one of the most dangerous scorpions in Iran. This scorpion is one of the most abundant indigenous scorpions of Khuzestan province and belongs to the buthidae family. This scorpion is the 3rd scorpion that causes envenomation in this province (Radmanesh 1990, Schor and Kliegman 2011, Razi Jalali et al. 2015).

Venom comprises a mixture of a variety of biologically active components: enzymes, peptides, nucleotides, lipids, mucoproteins and biogenic amines that most of which have not been investigated yet (Xu et al. 2014). Symptoms of envenomation may range from local itching and local pain to systemic symptoms, such as cardio-respiratory distress as the main causes of death from scorpion envenomation. Cardio-respiratory disturbances caused by scorpion envenomation include congestive heart failure, pulmonary edema, heart muscle lesions, etc. (Bouaziz et al. 2008, Cupo et al. 2007).

Therefore, rapid diagnosis of disorders and injuries caused in vital organs, especially the heart following bites, as well as envenomation therapy, is important in order to minimize the side effects. In the treatment of scorpion envenomation various drugs and combinations, including antivenom and other supportive therapies include corticosteroids, antihistamines, and antioxidants can be used (Das et al. 2013, Mahmoodi Khatoonabadi et al. 2016, Naserzadeh et al. 2018, Pourkhalili et al. 2015, Razi Jalali et al. 2015).

Based on other studies, one of the antioxidants compounds with a beneficial effect on heart disorders is carvedilol (Antelava et al. 2009, Kumar et al. 2009, Matsui et al. 1999, Tunez et al. 2008, Wawaimuli et al. 2010, Yue et al. 1999). It also has anti-inflammatory and anti-apoptotic effects and blocks alpha-1 and beta receptors. (Kenichi et al. 2011). By blocking beta-adrenergic and alpha-1 adrenergic receptors, carvedilol reduces cardiac output and eliminates exercise-induced tachycardia and isoproterenol. This combination also by eliminating the alpha-1 adrenergic receptor blocker eliminates the effect of phenylephrine vasoconstriction and dilates the vasculature and decreases the resistance of the vascular periphery. Therefore, carvedilol has a beneficial effect on the treatment of heart failure (Dandona 2007). This study aimed to evaluate the changes of biochemical factors concerning heart health and also to investigate the effects of antivenom and carvedilol (Roche China Co. Shanghai, China) after the administration of *Mesobuthus eupeus* scorpion venom.

Materials and Methods

Scorpion venom

The venom of *M. eupeus* scorpion venom used in this study was provided by Razi

Vaccine and Serum Research Institute, Ahvaz which was prepared by electric shock and kept in lyophilized form. The concentration of crude venom protein was 815 mg/g venom. A Solution of 0.05% of venom was prepared in 0.9% sodium chloride solution in suitable volumes proportional to the number of rats in each envenomed group, as described below.

Antivenom

The polyvalent antivenom was produced by Razi Vaccine and Serum Research Institute. It comprises a purified solution with F(ab)2 fractions of equine immunoglobulins specific for venoms of Six scorpion species. It was obtained from hyperimmune plasma of healthy horses that had been immunized with a mixture of venoms from six species of medically important scorpion species in Iran (*Odontobuthus doriae, Mesobuthus eupeus, Androctonus crassicauda, Hottentota saulcyi, Buthotus sach and H. lepturus*). Protein in the plasma mixture precipitated with ammonium sulfate, enzymatically digested with pepsin and thermos denaturated. This followed by dialysis and finally formulated for use (Latifi and Tabatabai 1979). The mean protein content of the antivenom from the used batches was 3.6mg/ml (Zare Mirakabadi et al. 2011).

Laboratory animals

A total of 75 male Wistar rats weighing 200–250 g with the age of 4 to 6 months were housed in groups of five, in plastic cages, in an air-conditioned room maintained at a temperature of 24 ± 2 °C and relative humidity of 55 ±5%, with a 12-h light/12-h dark illumination cycle. They were fed a commercial laboratory pellet diet and tap water ad libitum. All procedures were done following ethical guidelines for care and use of laboratory animals, discarding of dead animals and protection of the researcher against animal bites and were approved by the Experimental Animals Committee of Shahid Chamran University of Ahvaz, Iran.

Experimental design

Animals were randomly divided into 5 equal groups and were treated as follows:

- Group 1: (control group) 0.5 ml normal saline intraperitoneally (IP).
- Group 2: *M. eupeus* venom at a dose of 1 mg/kg body weight IP
- Group 3: *M. eupeus* venom at a dose of 1 mg/kg body weight IP + 0.5 ml of polyvalent antivenom, intramuscularly (IM), 30 minutes after envenomation.
- Group 4: *M. eupeus* venom (1 mg/kg IP) + 5 mg/kg of carvedilol (5 mg/kg, IP) 30 minutes after envenomation.
- Group 5: *M. eupeus* venom (1 mg/kg IP) + polyvalent antivenom (0.5 ml/rat) + carvedilol (5 mg/kg, IP) 30 minutes after envenomation.

Blood collection

Sampling was performed at 8, 24, and 48 hours after venom/ saline injection; five rats from each group were sampled every time. Blood samples were collected with heparin via cardiac puncture following anesthesia with chloroform (Merck, Germany). After centrifugation, the plasma was separated and stored at -20 ºC for subsequent measurements.

Plasma biochemical analysis

The enzymatic activities of cardiac Creatine Phosphokinase (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) in plasma of rats were determined by commercially available kits Pars Azmoon, Iran) according to manufacturer's instructions via biochemical autoanalyzer (BIOTECNICA, BT-1500, Italy). Serum Troponin I (TnI) was determined by ELISA assay (Rat Cardiac Troponin I, ELISA Kit (ab246529) Abcam, USA).

Statistical analysis

Analysis of variance and Tukey post-hoc tests were employed to compare the data between groups using SPSS-24 software (SPSS Inc., Chicago, Illinois, USA). All values were expressed as mean ± standard error, and the value of $P<0.05$ was considered as statistically significant.

Results

Clinical signs

The envenomed rats showed behavioral changes from aggression to depression. Also, hemorrhage and hyperemia in the eyes and mucosal membranes were recorded in intoxicated group.

CK-MB activity

Table 1: Mean±SE changes of CK-MB activities (IU/l) in different groups after injection

Group /Time (after saline/venom injection)	8 hours	24 hours	48 hours
G1(A) (Control)	145.36±21.28 BD	151.48±19.30 BD	147.95±21.79 BD
G2(B) (Venom)	296.24±32.41 ACEbc	368.43±35.12 ACEa	341.32±28.69 ACEa
G3(C) (Venom+Antivenom)	168.19±27.48 BDb	195.14±22.98 BDac	165.25±30.44 BDb
G4(D) (Venom+Carvedilol)	246.08±34.13 ACEb	296.84±28.71 ACEac	251.25±30.69 ACEb
G5(E) (Venom+Antivenom+Carvedilol)	151.22±26.36 BDb	183.32±32.46 BDac	157.34±24.45 BDb

*Different lower case letters (a, b,…) demonstrate significant differences between times ($P<0.05$).
* Different upper case letters (A, B,…) demonstrate significant differences between groups ($P<0.05$).

Following injection of scorpion venom, a significant increase ($P<0.05$) in CK-MB activity was observed at different times after injection (especially at 24 h) (Table 1). The changes were observed after the injection of the antivenom subsequently after envenomation compared to the control group, was not significant ($P<0.05$). Considering the information in Table 1, it seems that the administration of carvedilol did not have a significant effect ($P<0.05$) on the decrease of this enzyme activity compare to control group. However, according to the results, the combination of antivenom and carvedilol similar to antivenom administration alone has been able to prevent a significant increase in CK-MB activity.

LDH activity

Table 2: Mean±SE changes in LDH activities (IU/l) in different groups after injection

Group /Time (after saline/venom injection)	8 hours	24 hours	48 hours
G1(A) (Control)	183.33±22.69 B	179.31±25.08 BD	184.69±30.72 BD
G2(B) (Venom)	295.38±35.89 ACEbc	387.58±32.31 ACEac	425.69±37.58 ACEab
G3(C) (Venom+Antivenom)	221.46±25.28 B	214.34±18.74 B	202.41±27.36 B
G4(D) (Venom+Carvedilol)	282.69±40.88 Bc	336.45±28.39 Aa	354.32±31.72 AEa
G5(E) (Venom+Antivenom+Carvedilol)	228.36±32.12 B	219.85±27.42 B	210.68±25.19 BD

*Different lower case letters (a, b,…) demonstrate significant differences between times ($P<0.05$).
*Different upper case letters (A, B,…) demonstrate significant differences between groups ($P<0.05$).

The level of LDH activity was significantly (P<0.05) higher in the venom group at all three times compared to the control group, especially at 48 hours. In the antivenom and antivenom plus carvedilol treated groups, the activity of this enzyme was significantly lower than the venom group (P<0.05). Administration of carvedilol following venom injection had no significant effect on the activity of this enzyme (Table 2).

AST activity

Table 3: Mean±SE changes of AST activities (iu/l) in different groups after injection

Group /Time (after saline/venom injection)	8 hours	24 hours	48 hours
G1(A) (Control)	30.69±11.36 BCDE	36.59±10.34 BDE	34.56±14.43 BD
G2(B) (Venom)	68.92±17.11 Abc	126.68±14.18 ACEa	134.47±22.57 ACEa
G3(C) (Venom+Antivenom)	53.36±15.78 A	58.67±19.37 BD	64.39±28.18 B
G4(D) (Venom+Carvedilol)	70.79±18.35 Abc	118.44±27.82 ACEa	127.81±26.92 AEa
G5(E) (Venom+Antivenom+Carvedilol)	58.31±17.45 A	60.21±16.28 ABD	73.36±20.75 BD

*Different lower case letters (a, b,…) demonstrate significant differences between times (P<0.05).
*Different upper case letters (A, B,…) demonstrate significant differences between groups (P<0.05).

A significant increase was observed in AST activity following venom injection at different times after envenomation, especially at 48 hours post-injection in the antivenom and antivenom plus carvedilol treated groups, increased the activity of this enzyme at all three times compared to the control group were also observed, but its intensity was significantly lower (P<0.05). Administration of carvedilol following envenomation had no significant effect on the activity of this enzyme (Table 3).

Cardiac Troponin I

Table 4: Mean±SE changes of Cardiac Troponin-I (TnI) (µg/l) in different groups after injection

Group /Time (after saline/venom injection)	8 hours	24 hours	48 hours
G1(A) (Control)	2.68±0.34 BD	2.91±0.36 BD	2.78±0.44 BD
G2(B) (Venom)	17.36±1.24 ACEbc	26.47±1.96 ACEa	33.66±2.16 ACEa
G3(C) (Venom+Antivenom)	6.44±1.04 BD	8.63±1.44 BD	6.58±1.19 BD
G4(D) (Venom+Carvedilol)	13.84±1.19 ACEbc	22.83±2.23 ACEa	19.58±2.06 ACEa
G5(E) (Venom+Antivenom+Carvedilol)	4.83±1.18 BD	7.28±2.54 BD	5.47±2.51 BD

*Different lower case letters (a, b,…) demonstrate significant differences between times (P<0.05).
*Different upper case letters (A, B,…) demonstrate significant differences between groups (P<0.05).

The troponin-I level was significantly increased at different times after envenomation especially at 48 hours post-injection compared to the control group (P<0.05). In the antivenom and antivenom plus carvedilol treated groups, troponin-I levels were significantly lower at different times compared to the venom group (P<0.05). Carvedilol administration had no significant effect on the level of this indicator (Table 4).

Discussion

In different studies, the changes in the mentioned biochemical factors due to various scorpion venoms have been investigated. For example, Ribeiro et al. (2010) reported the increase in plasma level of CK and AST enzymes and no change in plasma level of LDH and cTnI in the study of *Tityus serrulatus* effects venom on dog biochemistry profile. Chakroun-Walhha et al. (2018), by examining the level of troponin serum of 132 patients with mild scorpion envenomation observed that troponin level increased only in 28 patients with mild cardiac signs. Also, Meki et al. (2002), in a study on 41 children envenomated by different species of scorpion, observed that LDH and CK-MB enzymes activity was significantly increased in all children ($P<0.05$), but the increase in cardiac troponin was mild in these children. In a study by Zare Mirakabadi et al. (2011), on the changes in serum levels of CK-MB, LDH, and AST enzymes with the injection of different doses of *Hemiscorpius lepturus* venom in rabbit, it was shown that no significant changes occurred at hours of 1 and 3 after injection 50 µg /kg of the venom, while serum level of enzymes increased 3 hours after injection 500 mg/kg. Eventually, at the hour of 1 after injection dose of 1500 µg /kg, only the activity of CK-MB enzyme increased significantly, and all of the mentioned enzymes increased at the 3rd hour after injection 1500 µg /kg of the venom. These researchers concluded from their findings that the way to increase the activity of the CK-MB implies a delayed occurrence of cardiac damage caused by the injected venom. In other studies, the *Hemiscorpius lepturus* venom increased the activity of CK-MB, LDH and AST enzymes due to cytotoxic effects (Pipelzadeh et al. 2006).

Costal-Oliveira (2012) examined the cardiotoxic effects of *hadruroides lunatus* venom in the mouse. During this examination, the increase in activity of the CK-MB enzyme in the serum was evident. Also, with the injection of a sublethal dose of *Androctonus australis hector* venom into the mouse, LDH and CPK enzymes activity increased significantly ($P<0.05$) (Adi-Bessalem et al. 2008). Zayerzadeh et al. (2012) in the study of cardiovascular disorders caused by the injection of *Mesobuthus eupeus* venom into the rabbit reported the increase in activity of LDH and TnI, 60 minutes after injection and no change in CK-MB enzyme activity. The results of this study showed that antivenom administration prevented a significant increase of the mentioned factors compared to the venom group, half an hour after venom injection. Other studies showed the therapeutic effects of anti-venom in scorpion envenomation.

Razi Jalali et al. (2017) showed that antivenom administration after *Hemiscourpius lepturus* venom injection in rat prevented the significant changes in the hemogram parameters and osmotic fragility of red blood cells caused by the venom.

Zare Mirakabadi et al. (2011) observed that the CK-MB enzyme activity increased significantly at 3rd hour after administration of antivenom in rabbits receiving venom with a dose of 1500 µg /kg. This observation implies the delayed effect of the *Hemiscorpius lepturus* venom. Also, Razi Jalali et al. (2015) concluded that the use of polyvalent antivenom shortly after envenomation reduces inflammatory reactions and systemic changes due to increased cytokines, by studying some of cytokines changes such as IL-1, IL-6 and TNF- α after injection of *Mesobuthus eupeus* venom.

Mahmoodi Khatoonabadi et al. (2016) studied the *Hemiscourpius lepturus* venom effects in rabbit and the effects of antivenom. Antivenom neutralized bradycardia caused by the *Hemiscourpius lepturus* venom. In the study of cardiotoxic and arrhythmogenic effects of the *Hemiscurpius lepturus* venom in rat, Pour Khalili et al. (2015) reported the

neutralization of cardiotropic complications (negative inotropic and chronotropic) caused by scorpion venom, after the antivenom administration and before the venom injection. In the mentioned study, antivenom injection did not show the mentioned therapeutic effect, 15 minutes after venom injection.

According to the obtained results, administration of carvedilol, 30 minutes after venom injection, could not control the significant increase of cardiac creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase enzymes and the level of troponin I created by the venom. In other words, administration of carvedilol could not act alone as an effective treatment and could not prevent a significant increase in these factors. Antioxidant effects of carvedilol have been proved in different studies. Due to this effect, carvedilol used during a study of the cardiac failure treatment and caused to the reduction in mortality level (Yue et al. 1999). Also, Kumar et al. (2009) found that carvedilol, due to the antioxidant effect, can improve the long-term D-galactose injection damaging effect, which causes aging and decrement of the learning and memory ability. Wawaimuli et al. (2010) showed that PO administration of carvedilol at a dose of 30 mg/kg, has a beneficial effect in preventing cardiac and kidney toxicity caused by donorobucine. In the study of carvedilol protective effect on oxidative stress caused by okadaic acid, Tunez et al. (2008) found that carvedilol prevents the changes made by okadaic acid as a result of induction of oxidative acid. Antelava et al. (2009), in the study of carvedilol, losartan and trimetazidine effects on rat functional parameters caused by oxidative stress of the hydrogen peroxide, found that carvedilol has a very good protective effect on the oxidative stress. Matsui et al. (1999) showed that PO administration of carvedilol with a dose of 30 mg/kg due to its antioxidant effect against cardiomyopathy caused by doxorubicin has a protective role in the rat.

In other studies, positive results have been achieved from using similar drugs to carvedilol with antioxidant effects. During a study about the management of cardiovascular signs due to Indian red scorpion *Mesobuthus tamulus* venom, Bawskar and Bawskar (1992) found that nifedipine and prazosin in combination or each alone are effective in the management of cardiovascular signs. Naserzadeh et al. (2018) studied the curcumin protective effects on cardiac cells and mitochondrion against oxidative damage and apoptosis induced by *Hemiscorpius lepturus* venom. The researchers concluded that curcumin can restrain the mitochondrial respiratory chain disorder due to *Hemiscorpius lepturus* venom and therefore decreases the ATP required for the cardiac cells and apoptosis of these cells.

Based on this findings, due to the changes in the cardiac creatine phosphokinase activity and troponin I (as specific biomarkers of cardiac damages) and also lactate dehydrogenase and aspartate aminotransferase, the appearance of some of the cardiac damages after *Mesobuthus eupeus* venom injection is derived. Changes in these enzymes and biomarkers activity at different hours in the venom group indicate on happening of cardiac damage. Generally, due to the venom effects on different tissues, scorpion venom damages caused functional disorders in many cases through the disrupting of calcium and potassium pumps and change in the cell membranes permeability The resultant of these effects cause intracellular fluids leakage, including electrolytes and some cytosolic enzymes into extracellular fluids and finally into the blood plasma (Abdel-Rahman et al. 2015).

It seems that carvedilol as a beta antagonist receptor and also as an antioxidant has been unable to prevent cardiac parameters significant changes. This result may be due to the dose or protocol used for the drug administration.

However, it cannot opine about the ineffectiveness of this drug with certainty, because it may obtain different results by changing the dose or number of times of the carvedilol administration but in the same conditions, it is observed that antivenom is an effective drug against the cardiotoxicity. Polyvalent antivenom as a high usage drug in scorpion envenomation field has been effective on all measured biochemical parameters. A remarkable point in this study was the beneficial effect of polyvalent antivenom and this point may be due to the quick application of this antivenom after venom injection. Perhaps the reason for the inappropriate efficiency of polyvalent antivenom on some victims is a long distance between the bite location and the antivenom administration. In general, the combined use of antivenom and carvedilol did not differ significantly from the group that received antivenom alone. This was also predictable because carvedilol, on its own, did not has many effect on the cardiac biochemical parameters changes caused by venom injection. Also, these study findings were based on the type of used treatments and it is possible to obtain other results by changing the dose, repeat administration, administration time, etc.

The results of this study showed that heart can be as a target organ for the *Mesobuthus eupeus* scorpion venom and can make disorders at cardiac cells functions, increase the cardiac serum enzymes with troponin-I in plasma could be a reason to that. It is obvious that in the natural biting of the scorpion, these findings will change more severely due to the higher dose of venom injected into the body. Also, the reason for not seeing the therapeutic effects of carvedilol may be related to the dose of the drug or the frequency of its use. Clarifying the other aspects of this study needs more study and research.

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Conflict of interest

Authors declare that they have no conflict of interest.

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