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Role of some vasoactive mediators in scorpion envenomed children: Possible relation to envenoming outcome

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ABSTRACT

Scorpion envenomation causes an autonomic storm resulting in changes in the vasoactive mediators' levels which lead to myocardial damage, cardiovascular disturbances, peripheral circulatory failure, pulmonary edema, multi-system-organ-failure and death. The study aimed to determine the circulating levels of adrenaline, noradrenaline, angiotensin converting enzyme (ACE), Angiotensin II (Ang II), kallikrein enzyme, nitric oxide (NO), aldosterone, and electrolytes Na^+, K^+ and Ca^{+2} in scorpion envenomed children and to evaluate the potential relation between these vasoactive mediators, the severity of scorpion envenoming and the clinical outcome of envenomed children. Forty envenomed children (22 mild and 18 severe cases) along with 10 healthy control children were enrolled in the study. The circulating levels of adrenaline, noradrenaline, Ang II, ACE, kallikrein enzyme, and NO were determined by ELISA, and spectrophotometric assays on admission and 24 h later. On admission, serum aldosterone, and electrolytes; Na^+, K^+ and Ca^{+2} were determined by RIA, Flame photometer and Flame atomic absorption respectively. All envenomed children showed significant surge of adrenaline, noradrenaline, ACE, Ang II, aldosterone, NO and Na^+, that concomitantly faced by significant reduction in kallikrein, K^+ and Ca^{+2} on admission. Twenty four hours later, all envenomed children continued to show significant elevation of ACE, Ang II and NO. The severely envenomed children showed considerable reduction in circulating levels of adrenaline, noradrenaline, ACE and Ang II, while dramatic increase in kallikrein activity was reported in comparison to mildly envenomed children after 24 h of medical care. Also, NO exhibited considerable accumulation in non survivors, on admission, that was persistent for the subsequent 24 h and was accompanied by high kallikrein, low catecholamines and Ang II levels compared to survivors. Finally, the hypertensive cases showed substantial higher levels of catecholamine, ACE and Ang II, 24 h after admission. These findings indicated that, disturbances of the studied vasoactive mediators were common in scorpion envenomed children and may account for several inflammatory manifestations and clinical outcome. ACE inhibitors could be considered as possible therapeutic agent in victims with prominent increase in ACE and Ang II while kallikrein inhibitor and antioxidants may be effective in the treatment of late hypotensive ones.

1. Introduction

Scorpion envenomation is a common health problem in many tropical and subtropical countries, and is an important cause of morbidity and mortality, especially among children (Dehghankhalili et al., 2015; Fukuhara et al., 2004). In Upper Egypt, particularly, Assiut Governorate, scorpion envenomation still represents a medical problem and a life hazard (Mohamad et al., 2014; Mohey-Eldeen and Meki, 1996). Single venom may contain hundreds of different components producing diverse pathological effects. Scorpion venom contains muco-polysaccharides, hyaluronidase, phospholipase, serotonin, histamine, and neurotoxins. Neurotoxins are the most important components of the

Abbreviations: ACE, Angiotensin converting enzyme; Ang II, Angiotensin II; NO, nitric oxide.

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venom. These low-molecular weight polypeptides cause severe adrenergic and cholinergic activities and adversely affect sodium, potassium, and chloride channels of various cells (Bawaskar and Bawaskar, 2003; Utkin, 2015).

Severe scorpion envenoming causes an autonomic storm resulting in massive release of catecholamines, angiotensin converting enzyme (ACE), angiotensin II (Ang II), glucagon, cortisol, bradykinin, prostaglandins and changes in insulin secretion. All these agents cause stimulation of neuro-endocrinal-immunological axis and are proved to induce the release of immunological mediators as IL-6, and RANTES (Abdel-Haleem et al., 2006). As a consequence of these changes in the hormonal milieu, scorpion envenoming results in a syndrome of fuel energy deficits and inability of the vital organs to utilize the existing metabolic substrates, which causes myocardial damage, cardiovascular disturbances, peripheral circulatory failure, pulmonary edema, and many other clinical manifestations alone or in combination, producing multi-system organ failure and death (Chippaux, 2012; Murthy, 2000). The clinical manifestations are characterized by transient cholinergic (vomiting, sweating, bradycardia, ventricular premature contraction, salivation and hypotension) and prolonged sympathetic stimulation (hypertension, tachycardia, pulmonary edema and shock (Bawaskar and Bawaskar, 2003).

Nitric oxide (NO) plays a critical role in the regulation of vascular tone, organ blood flow as well as inhibition of platelets and neutrophils aggregation. However, excessive production of NO has been reported in several myocardial disorders involving inflammatory process such as endotoxic shock and heart failure (Lecour et al., 2001). Systemic inflammatory response that is associated with NO overproduction may contribute to vascular hyporeactivity, hypotension and organ failure in scorpion envenomation (Sahan-Firat et al., 2012).

The aim of the present study was to determine circulating levels of adrenaline, noradrenaline, ACE, Ang II, kallikrein enzyme, NO, aldosterone and electrolytes including Na^{+}, K^{+} and Ca^{+2} in scorpion envenomed children on and 24 h after admission. Also, the study was set to evaluate the potential relation between these vasoactive mediators and the severity and outcome of scorpion envenoming in children.

2. Patients and methods

This study was carried out at Pediatrics and Biochemistry Departments, Assiut University, during the summer (May, June and July) of 2015. Written informed consents were taken from the parents of participating children. The study was approved by the ethics committee of Faculty of Medicine, Assiut University, Assiut, Egypt.

2.1. Study population

2.1.1. Pre sampling evaluation

Both cases and control children were subjected to complete medical history taking and clinical examination. The following data: locality, time and site sting, color of scorpion, time laps between sting and initiation of treatment, and history of previous antivenom therapy (at the locality) were collected from cases. The following laboratory routine investigations were carried out for all the studied patients; blood urea, creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), X ray chest, and ECG and blood gases.

2.1.2. Patients

Forty children with scorpion envenomation were admitted to the emergency and intensive care units of Pediatrics Department. They comprised 24 males and 16 females. Their ages ranged from 1 to 13 years. The patients were classified into mild or severe groups according to the degree of severity of envenomation (Meki et al., 2003).

Group I (22 patients, mild cases): Mildly envenomed children were presented with the following manifestations: Pain, flushing, salivation, lacrimation, abdominal pain, tachycardia and mild irritability. They were admitted and treated at the emergency unit of Pediatrics Department.

Group II (18 patients, severe cases): Severely envenomed children were presenting with the following manifestations: Hypotension (blood pressure < 3rd pecentile for age), heart failure (dyspnea, positive hepatojugular reflux and basal crepitation), toxic myocarditis (dyspnea, heart failure, distant heart sound, ECG changes and echocardiography suggestive of myocardial ischemia, myocarditis and cardiomegaly), pulmonary edema (dyspnea, cyanosis and bubbling lung crepitation), convulsions, hallucinations and abnormal movements, disturbed level of consciousness (according to Glasgow coma scale) and renal impairment (oliguria and raised urea and creatinine).

Exclusion criteria: The selected patients had no history of previous liver, renal or heart diseases.

2.1.3. Control group

Ten healthy children of matched age and sex were considered as controls.

2.2. Sample preparation

Two blood samples were collected from each victim, the first was on admission and the second was 24 h later. Only one sample was withdrawn from controls. Two ml of blood were collected on EDTA and 3 ml were collected in plain tubes for plasma and serum preparation respectively. Plasma and serum were aliquoted and

Table 1
Vasoactive mediators in scorpion envenomed children with reference to controls (mean ± SE).

Biochemical parameters	Envenomed children (n = 40)		Healthy controls (n = 10)	P-Values	
	1st sample	2nd sample		P1	P2
Adrenaline (ng/mL)	0.25 ± 0.014	0.20 ± 0.01	0.16 ± 0.015	<0.01	<0.1
Noradrenaline (ng/mL)	0.78 ± 0.05	0.57 ± 0.03	0.47 ± 0.07	<0.01	<0.14
ACE (U/L)	299.40 ± 29.61	257.9 ± 28.26	130.0 ± 15.74	<0.01	<0.05
Ang II (ng/mL)	4.97 ± 0.63	5.138 ± 0.5130	1.78 ± 0.07	<0.01	<0.001
Kallikrein (U/L)	283.0 ± 26.11	339.5 ± 30.20	399.0 ± 35.95	<0.05	<0.33
NO (μM/L)	117.0 ± 13.45	102.8 ± 12.50	50.64 ± 6.13	<0.01	<0.05

Data were expressed as mean ± SE. 1st sample on admission, 2nd: sample 24 h after admission. P1, 1st versus control group; P2, 2nd sample versus control group. P value was considered significant when <0.05.