Original Article

Captopril in The Treatment of Cardiovascular Manifestations of Indian Red Scorpion (*Mesobuthus Tamulus Concanesis* Pocock) Envenomation

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Abstract

Objectives : To study outcome of patients with scorpion envenomation treated with oral captopril in the ICU of a Tertiary Care, University Hospital in Mumbai.

Methods : Retrospective analysis of all patients with scorpion sting admitted to Medical Intensive Care Unit of a tertiary care university hospital in Mumbai between 1993 and 2003.

Results : Of 38 patients with cardiovascular manifestations, six had tachycardia alone and 8 had hypertension; these patients received oral captopril 12.5–25 mg thrice daily with no deaths. Pulmonary oedema with normal blood pressure and high central venous pressure (CVP) was seen in 10 patients. Five patients had hypotension, low CVP but no pulmonary oedema; with fluid infusion, these patients had correction of low CVP and hypotension, but developed pulmonary oedema. Pulmonary oedema resolved in all 15 patients with captopril (6.25–25 mg thrice daily); one patient died of ventricular tachycardia. Nine patients had cardiogenic shock; 6 patients, whose blood pressure improved with dopamine received, captopril; 1 of these 6 died. The other three patients did not respond to maximum vasopressor therapy and could not be given captopril; all three died. Four of the 5 deaths occurred in patients weighing < 25 kg suggesting that severity of cardiovascular manifestations also depends on body weight of the victim.

Conclusion : Afterload reduction with oral captopril is safe and effective in scorpion envenomation with cardiovascular manifestations. Results are similar to those with other vasodilators. ©

Introduction

Scorpion stings are common in tropical and subtropical regions of the world. The major components of scorpion venom are short-chain peptides, which affect gating mechanisms of sodium and potassium channels in excitable tissues. α-toxins block voltage-dependent inactivation of sodium channels, resulting in persistent depolarization. β-toxins shift the voltage-dependent activation of these channels to a more negative membrane potential, making tissues more excitable.[1,2] Blockade of potassium channels slows repolarization and prolongs the action potential in neurons and myocytes.[2,3] The resultant intense persistent depolarization of autonomic nerves with massive release of neurotransmitters from the adrenal medulla and parasympathetic and sympathetic nerve endings.[4,5] is largely responsible for the toxic cardiovascular manifestations. The toxin may also directly affect myocardial contractility and excitability.[6] Central nervous system effects include irritability, muscle rigidity, altered consciousness and convulsions.[7]

Unlike snake antivenom, antiserum against scorpion venom does not help in the treatment of systemic manifestation.[8,9] Inotropic drugs like dopamine and dobutamine may produce hemodynamic improvement.[10] However, envenomation results in a catecholamine-excess state and some studies suggest that these drugs alone may not reduce mortality.[11,12] Vasodilators have been used in both hypertensive and hypotensive phases of envenomation. Nifedipine, prazosin, and sodium nitroprusside[11,13,14,15] reduce left ventricular afterload, improving cardiovascular manifestations and reducing mortality. Angiotensin converting enzyme (ACE) inhibitors are used extensively in patients with congestive cardiac failure with improved survival. However, there are only anecdotal reports regarding use of captopril in scorpionism.[11,16] We report here, our experience with use of captopril in scorpion envenomation.

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Material And Methods

All patients with scorpion sting admitted to Medical Intensive Care Unit of a tertiary care university hospital in Mumbai over a 10-year period were studied. On admission, history (including distance of residence from hospital, time between sting and hospitalization, and prior treatment received) and physical examination findings were noted. A 12-lead electrocardiogram (ECG) was recorded in all patients on admission and continuous ECG monitoring was carried out in all patients for at least 24 hours. A central venous catheter was placed in all patients with pulmonary oedema or hypotension. Radial artery pressure was invasively monitored in hypotensive patients.

The patients were categorized into five groups based on previously described hemodynamic patterns,[17] viz. Group A - those with tachycardia (heart rate > 100/ minute) but normal blood pressure and no pulmonary oedema; Group B - hypertension (BP > 140 systolic or 90 diastolic); Group C - pulmonary oedema (presence of crackles in the lung fields with normal or elevated BP); Group D - fluid-responsive hypotension (systolic arterial pressure (SAP) < 80 mm Hg which is corrected by fluid administration alone without need for inotropes) with or without pulmonary crackles – this group was similar to group C except that they were hypovolemic; and Group E - cardiogenic shock (SAP < 80mm Hg with signs of pulmonary oedema, lack of response to fluid infusion and need for inotropes to improve BP). Pulmonary artery catheterization was done in only a few patients; these have been reported in detail earlier.[17]

Hypertensive patients were treated with 12.5 mg captopril orally, every 8 hours; the dose was increased to 25 mg in those who remained hypertensive. Patients with pulmonary oedema and systolic blood pressure (SBP)≥ 90 mmHg were administered 6.25 to 12.5 mg captopril orally every 8 hours. The dose was increased to 25 mg 8 hourly if pulmonary oedema persisted and SBP was ≥ 90 mmHg. If captopril administration resulted in clearance of pulmonary oedema but caused hypotension, intravenous fluid challenges were given (200 ml of 0.9% saline over 15 minutes) till SBP exceeded 90 mmHg. Patients who failed to respond to fluids were administered dopamine, but captopril was continued. Patients who were hypotensive on admission received prompt intravenous fluid resuscitation and dopamine was added if hypotension persisted after adequate volume repletion. These patients too received captopril once the systolic pressure rose to ≥ 90 mmHg. Captopril was continued for 5 to 7 days after resolution of cardiovascular manifestations. Patients with respiratory failure due to pulmonary oedema were tracheally intubated and mechanically ventilated if necessary.

The Student's t test or Mann-Whitney test were used for statistical comparison of continuous variables and chi-square test or Fisher's exact test were used for proportions.

Results

Thirty-eight patients aged 13 to 59 years were admitted to the ICU following scorpion sting. Most patients were from rural areas in Western India. Fifteen patients resided within 50 km from the hospital, 13 patients stayed between 50-100 km away and 10 patients were from areas that were more than 100 km away. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 11 (range 2-30) and the mean interval between sting and hospital admission was 9.1 hours (range 1 to 45 hours).

Six patients had only tachycardia without changes in arterial pressure or pulmonary oedema (Table 1). Eight patients had systemic arterial hypertension but no pulmonary oedema. All 14 patients showed a prompt response to oral captopril and made an uneventful recovery. Pulmonary oedema and fluid-responsive hypotension were seen in 15 (39.4%) patients; 10 patients had pulmonary oedema without hypotension and 5 had hypotension without pulmonary oedema on admission (Table 1). With fluid resuscitation, the latter five patients had improvement in arterial pressure, but developed signs of pulmonary oedema. All 15 patients showed a good response to oral captopril which was administered only after correction of hypotension with intravenous fluid. There was one death in this group – a thirteen years old boy (weight 20 kg) who had stable haemodynamics after day 1 in the ICU, but developed refractory ventricular tachycardia 4 days after admission.

Nine patients had cardiogenic shock on admission (Table 1). These patients had very high CVP, severe pulmonary edema, metabolic acidosis and peripheral circulatory failure. They were all treated with dopamine, and captopril was administered to six patients, only after hypotension was corrected. The other three patients continued to remain in cardiogenic shock and could not be given captopril; all three died. One of the six patients with cardiogenic shock who had received captopril died.

Other manifestations

Seventeen patients (44.7%) had pain at the site of the bite. Two patients had severe vomiting and three had profuse sweating as major complaints. ECG changes in the form of ST depression, T wave inversion or ventricular premature complexes were seen in 15 patients (39.4%). The incidence of ECG changes increased with increased severity of cardiovascular dysfunction (Table 1).

Outcome and Prognostic Factors

The overall mortality was 13.1% (5 deaths). Factors associated with poor outcome included increasing cardiovascular dysfunction, younger age, body weight

Table 1 : Various clinical presentations of patients with scorpion envenomation

	Tachycardia	Hypertension	Pulmonary oedema without hypotension	Fluid-responsive hypotension	Cardiogenic shock
Number of patients	6	8	10	5	9
Mean arterial pressure (mm Hg)*	100 ± 9	132 ± 30	84 ± 8	61 ± 2	56 ± 8
Time after sting (hours)*	3.2 ± 3.1	3.0 ± 2.7	7.2 ± 4.7	16.0 ± 19.4	17.4 ± 5.3
Central nervous system affection	0	1	0	0	3
Hypoxia	0	0	7	1	6
Electrocardio-graphic changes	0	0	4 (40%)	2 (40%)	9 (100%)
Died (%)	0	0	1 (10%)	0	4 (44%)

*values are mean ± sd

Table 2 : Differences in clinical and laboratory parameters among survivors and non-survivors in patients with scorpion sting

Parameters	Survived (n = 33)	Died (n = 5)	p value
Age (years)	30 (21 - 39)	14 (13-20)	0.007
Weight (Kg) ≤ 25kg	1	4	
> 25kg	32	1	<0.001
Time after sting (hours)	5.5 (2 - 9.75)	14 (12.5 – 18.0)	0.017
Mean arterial pressure (mmHg)	83.3 (68 – 114)	66.7 (58 – 72)	0.026
APACHE II score	9 (5 –12)	23 (18 –29)	<0.001
Arterial pH	7.42(7.36 – 7.47)	7.25(7.19 – 7.33)	0.007
Arterial pO_2 (mm Hg)	71 (56-84)	45 (44-54)	0.006
Hemoglobin (g/dL)	12.5 (11.6-13.8)	11.6(10.4-13.9)	NS
Total leukocyte count (per mm^3)	12200(8500-16500)	20500(17850-30000)	0.005
Serum AST (units/L)	45 (36 – 57)	146 (65 – 248)	0.01
Serum ALT (units/L)	40 (24 – 48)	63 (43 – 170)	0.033
Serum creatinine (mg/dl)	1.1 (0.9 – 1.2)	1.6 (1.35 – 1.9)	0.004
Serum sodium (mEq/L)	136 (132 –140)	127 (123 –133)	0.012
Serum potassium (mEq/L)	3.6 (3.2 –3.8)	2.8 (2.6 – 3.3)	0.01
Admission blood glucose (mg/dl)	116 (96 – 143)	126 (111 – 160)	NS

All values are median (interquartile range) except weight, where number of patients is mentioned.
Abbreviations: NS, not significant; APACHE, Acute Physiological and Chronic Health Evaluation; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase

of 25 kg or less, longer interval between sting and hospital admission, and presence of hyponatremia, hypokalaemia, elevated transaminases, leukocytosis and metabolic acidosis. Blood glucose levels did not differ in survivors and nonsurvivors (Table 2).

Discussion

Most cases of envenomation in western India are following stings by *Mesobuthus tamulus* (red scorpion).[17] While the species of scorpions differ from region to region, there is considerable similarity in the cardiovascular manifestations produced by them.[7] The mildest form of envenomation produces tachycardia and hypertension; this was seen in 14 (37%) of our patients with no deaths. These patients presented early, and responded promptly to treatment with captopril. Hemodynamics studies in hypertensive patients have shown a predominantly vascular effect with normal cardiac output. The systemic vascular resistance (SVR) may be increased upto four times normal with normal pulmonary artery and pulmonary capillary wedge pressures.[17]

Severe envenomation results in pulmonary oedema, which has been shown to respond well to diuretics. However, while plasma volume contraction by diuresis improves pulmonary oedema, it produces hypotension;[11] fluid replenishment results in the re-appearance of pulmonary oedema.[17] This syndrome can be effectively treated by captopril.[11] Hemodynamic studies have shown that these patients have a depressed myocardial function with normal SVR.[17] It is not clear why the SVR should drop in patients with more severe forms envenomation. Among the mechanisms postulated include cholinergic stimulation, release of histamine, nitric oxide and kinins[7] or a direct effect of toxin on vascular smooth muscle.[7,18] Pulmonary oedema and fluid-responsive hypotension were seen in 15 (39.4%) patients. All patients responded well to treatment with captopril and fluid infusion, with only one death. This patient's pulmonary oedema resolved, but he died of refractory ventricular tachycardia 4 days after envenomation.

Cardiogenic shock represents the most severe stage of scorpionism. Gueron *et al* have demonstrated interstitial oedema, cellular infiltration and myocarditis with focal areas of myocardial degeneration and necrosis in

patients dying of scorpion envenomation.[18] Increased myocardial oxygen consumption due to intense catecholamines and angiotensin surge,[4,5,20] alterations in myocardial blood flow[7, 21] and a direct toxic effect cause the "myocarditis," depressed left ventricular function as well as life-threatening cardiac arrhythmias. Hemodynamically, this phase is characterized by low cardiac output, elevated pulmonary wedge pressure, signs of pulmonary congestion and refractoriness to inotropic drugs. This was seen in 9 (23.7%) of our patients with four deaths (44.4%). All patients received dopamine infusions. Captopril could be administered to only six patients after correcting hypotension. In the other three patients hypotension could not be corrected; all three died. Das et al have found that ECG changes are a sensitive marker of myocardial injury;[22] all our 9 patients in this group had ECG changes.

Unlike the present study, previous authors have classified patients not according to hemodynamics, but by the presence of pulmonary oedema. Bawaskar et al have reported 121 patients with scorpion envenomation treated with prazosin, with an overall mortality of only 8%. However, a majority of these patients had mild hemodynamic disturbances; in the 31 patients who had pulmonary oedema there were 9 deaths (mortality 29%) in this series.[23,24] Similarly, two studies from Tunisia have reported 11% mortality in comparable patients treated with dobutamine.[25,10] In the present study, 5 deaths (21% mortality) occurred in 24 patients with pulmonary oedema treated with captopril. Mortality was 44.4% in patients with cardiogenic shock. Only 2 previous studies have described patients with shock as a separate subgroup. Seventy five percent mortality was reported by Bawaskar and Bawaskar in patients with shock treated with prazosin[23] and 100% mortality in a Brazilian study where vasodilators were not used.[26]

In patients with left ventricular dysfunction, ACE inhibitors help by afterload reduction, decreasing sympathetic activity, improving endothelial function and preventing myocardial apoptosis.[27,28] The present study clearly shows that captopril may be effective in treating cardiovascular manifestations following scorpion sting with mortality comparable to that using other vasodilators, including prazosin. Previous reports on the hemodynamics of scorpion envenomation and the effects of captopril support the physiological rationale of its use. Bawaskar et al have extensively studied the clinical benefits of using prazosin as a vasodilator in treatment of scorpion envenomation.[12,13,30,31] Although clinically very useful in the management of the cardiovascular manifestations, hemodynamic studies of the effect of prazosin are lacking. Some authors had expressed reservations about their use because these drugs also inhibit kininase II, which could result in increased bradykinin levels. Experiments in rats suggest that bradykinin may increase pulmonary capillary permeability and contribute to venom-induced pulmonary oedema.[32] However, several hemodynamic studies in humans have convincingly demonstrated that pulmonary oedema is mainly cardiogenic.[25, 33] and that vasodilators including captopril relieve pulmonary oedema and enhance cardiac output. Moreover, ACE inhibitors may also help by their direct action of opening calcium-activated potassium channels, which are blocked by scorpion toxins.[3]

The proportion of patients with severe cardiovascular manifestations in our study is high, mainly due to the referral pattern. Most of these patients resided in remote rural areas with inadequate medical facilities and presented significantly later after the sting. Many patients had been treated in rural hospital and referred after conventional therapy had failed. It is not clear whether the severity of manifestations is due to more severe envenomation, or due to prolonged hypotension and hypoxia resulting from delay in transport to an urban tertiary hospital. However, in a large series from rural India, Bawaskar et al have also found that patients who present later have more severe manifestations with high mortality.[23] Notably, 4 of the 5 deaths in our study occurred in patients who weighed less than 25 kg, suggesting that severity of cardiovascular effects may also depend on body weight of the victim.

In conclusion, captopril appears to be safe and effective in scorpion envenomation. This study also shows that it is possible to administer captopril in over 90% of patients after correction of hypotension with fluid resuscitation and inotropic drugs. Overall mortality in the present series was 13.1% despite the fact that a large proportion of patients had severe envenomation and presented after a considerable delay after scorpion sting. A major limitation of our study is that cardiovascular hemodynamics were not studied by pulmonary artery catheterization in all patients. Nevertheless, the protocol used is simple and can easily be implemented in even primary healthcare facilities in rural areas.

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