

NT-proBNP in Myocarditis after a Scorpion Sting Envenomation

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ABSTRACT

Objective: This study was to evaluate the levels of NT-proBNP in patients with myocarditis which occurred after a scorpion sting envenomation.

Material and Methods: A total of 30 patients with scorpion sting envenomation and 21 patients with heart failure which was caused by cardiomyopathy, were prospectively studied. The data included the patient demographics, clinical features, echocardiography and the NT-proBNP levels.

Results: An echocardiographic evidence of myocarditis with a left ventricular ejection fraction of less than 50%, was found in 22 patients. In all the 22 patients, NT-proBNP was significantly

elevated. The NT-proBNP levels were very high in the patients with severe LV dysfunction. However, it was in the normal range in the patients without an evidence of myocarditis. The elevated NT-proBNP levels were correlated with the LV dysfunction and myocarditis. When they were compared with the patients with heart failure which was caused by cardiomyopathy, the NT-proBNP levels were found to be significantly more elevated in scorpion sting myocarditis.

Conclusions: The NT-proBNP levels were significantly elevated in myocarditis which occurred after a scorpion sting envenomation.

Key Words: Scorpion, Myocarditis, Envenomation, Echocardiography, NT-pro BNP

INTRODUCTION

The annual number of scorpion sting cases exceeds 1.23 million, of which 32,250 may be fatal [1]. Scorpion sting envenomation is an acute life threatening, time limited, medical emergency, if it is left untreated. It is a frequent event in the tropical, subtropical and the temperate zones of the world. *Mesobuthus tumulus* is the most common and lethal scorpion species which is abundantly found in western Maharashtra, northern Karnataka, Andhra Pradesh, Saurashtra and Tamilnadu in India [2-4]. The deaths which are caused by scorpion sting envenomation are attributed to cardiopulmonary complications like myocarditis and acute pulmonary oedema [5 -7]. The severity of the envenomation is related to the age of the victim, the size of the scorpion, the season of the sting and time which had elapsed between the sting and the hospitalization [8, 9]. A severe scorpion sting envenomation occurs in children with a 3.9-10% fatality, which is irrespective of the intensive care management, in Israel, Turkey and India [10-13]. No clinically useful demographic or epidemiological data to guide the decision making regarding the need for the intensive care unit admission for the paediatric victims of scorpion sting, was noted by Bosnak et al., in Turkey [12]. The decision to transfer and the admission to the intensive care unit is usually based on the development of the systemic findings of envenomation. However, the clinical condition may rapidly deteriorate after the development of the systemic features. There is a need of reliable clinical, biochemical or other investigative parameters to identify the high risk group.

Echocardiography is an ideal tool for assessing various parameters of the cardiac functions non-invasively. It has been used to

document and monitor the myocarditis in scorpion sting envenomation [14-17]. Left ventricular systolic dysfunction is the dominant finding and left ventricular dilatation and regional wall motion abnormalities have been described infrequently [14]. However, its routine use is limited by its non-availability.

Earlier studies have evaluated various biochemical and inflammatory markers. High Creatine Phosphokinase (CPK) levels have been attributed to an increased skeletal muscle activity and signs of cardiac and skeletal muscle injuries [12, 18, 19]. The cardiac troponins (cTnI) have become important diagnostic and prognostic tools in acute coronary syndromes. The cTnI levels rise in certain non coronary conditions also. Meki et al have reported the importance of the cTnI levels in scorpion sting myocarditis. They have also studied interleukin-8 (IL-8), beside the enzymatic activities of CPK, the CPK-MB isoenzyme and lactate dehydrogenase in 41 children with scorpion envenomation. The non-survivor victims showed significant higher mean values of only cTnI on admission and higher mean values of both cTnI and IL-8 on follow-up in comparison to the survivors [19]. We studied 84 patients with scorpion sting and, have reported the significance of cTnI. cTnI was significantly elevated in 60 patients with an echocardiographic evidence of left ventricular dysfunction, and it was correlated with myocarditis [20].

A decade ago, Brain Natriuretic Peptide (BNP) and N-terminal pro BNP (NT-proBNP) were proposed as potentially valuable diagnostic tests to augment the clinical diagnosis of acute Decompensated Heart Failure (ADHF) [21]. The cardiac natriuretic hormones play an important role in the regulation of the extracellular fluid volume and the blood pressure. BNP is secreted by

the cardiac ventricular myocytes in response to an increase in the ventricular wall tension and it is related to the ventricular filling pressures [22]. The human pro-BNP consists of 108 amino acids; its processing releases the biologically active 32 amino acid peptide and an amino terminal fragment (NT-proBNP). It has been shown that NT-proBNP is a sensitive and specific marker of the ventricular dysfunction. In addition, NT-proBNP is stable in whole blood for >24 hours at 20°C.

The plasma concentrations of the NT-proBNP levels in the control children and in children with heart failure have been previously reported [23,24]. Mir et al., have reported that the NT-proBNP levels in the control children, adolescents, and adults did not show a significant age-related difference. In the control children, the normal range was established between 150 (10th percentile) and 430 fmol/ml (90th percentile). The mean plasma NT-proBNP in the control children was 311 fmol/ml (range 74-654 fmol/ml). In 31 children with heart failure, the plasma NT-proBNP levels were significantly higher (mean 846, range 219-2718 fmol/ml) than in the control children.

The NT-proBNP levels had shown a negative correlation with the LV ejection fraction and a positive correlation with clinical heart failure [23]. Similarly, Rau and Koch have reported that the NT-proBNP levels will be highest during the first few days of life (range 1121-7740 ng/L), with a rapid decrease which is caused by perinatal circulatory changes. They observed no significant difference between male and female children. A negative correlation between the age and concentration was evident for the individuals who were of the age of >1 month. On the basis of the 97.5th percentile curve, the maximum value of 299 ng/L (age 1 year) decreased to 48 ng/L (age 16 years) [24].

The American College of Emergency Physician's clinical policy provides the Level B recommendations that "the addition of a single BNP or NT-proBNP measurement can improve the diagnostic accuracy as compared to the standard clinical judgment alone in the emergency department patients, by using a BNP of <100 pg/dl or an NT-proBNP of <300 pg/dl to rule out ADHF and a BNP of >500 pg/dl or a NT-proBNP of >1000 pg/dl to rule in the diagnosis [25]. The NT-pro BNP levels had not been studied in myocarditis which had occurred after a scorpion sting envenomation, earlier. This study was intended to evaluate the NT-pro BNP levels in cases of scorpion sting myocarditis.

MATERIALS AND METHODS

This prospective study was conducted at the Rajiv Gandhi Super Speciality Hospital, Raichur, which is situated in the northern Karnataka part of India, during the period from June 2010 to January 2012. The departments of Cardiology and Paediatrics monitored the study. The patients who were admitted to the emergency department with a history of scorpion sting envenomation and the presence of a sting mark, with the sting or the scorpion being seen in the vicinity of the victim by a bystander, were included in the study. A total of 30 patients were studied during the study period. An informed consent was taken from the patients and or their relatives. The clinical features and the treatment which was given at the referring centre were noted. All the clinical details which included the blood pressure, heart rate, chest findings and the temperature of the extremities were recorded at the arrival of the patients to the emergency department and at hourly intervals on a pretested standard chart.

The diagnosis of the various systemic involvements was done, based on the clinical manifestations and investigations. Myocarditis was diagnosed if the patient had tachycardia, muffled heart sounds, a gallop rhythm, ECG changes, elevated cTnl levels and a low rejection fraction on echocardiography.

Echocardiography: All the patients underwent echocardiography within 6 hours of their presentation to the emergency department. The echocardiography was done with a Sonosite M-Turbo ultra sound system by using standard views and protocols. A parenteral sedation was used in the paediatric patients to maximize their cooperation during the study. The main parameters which were evaluated were the Left Ventricular Ejection Fraction (LVEF) which was assessed by the M mode (the M-mode measurements, the left ventricular internal dimension in diastole LVIDD and the left ventricular dimension in systole LVIDS were taken in the parasternal long axis view, at the level of the mitral valve chordate), regional or global hypokinesia, the right ventricular function (a subjective assessment of the RV contractility was made in multiple views, and it was supported by a quantitative approach which involved the determination of the RV volume at the end-diastole and the end-systole and the tricuspid annular velocity) and valvular regurgitation (Doppler study).

NT-proBNP: VIDAS NT-proBNP is an automated quantitative test which is used on the VIDAS family instruments for the determination of the N terminal fragment of the B-type natriuretic peptide in human serum or plasma by using the Enzyme Linked Fluorescent Assay technique. The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection. At the end of the assay, the results are automatically calculated by the instrument in relation to two calibration curves which correspond to two detection steps. A fluorescence threshold value determines the calibration curve which has to be used for each sample. The VIDAS NT-proBNP measurement range is 20-25,000 pg/ml. All the patients underwent the NT-proBNP measurement within 6 hrs of their admissions to the emergency department.

The patients with acute worsening of their heart failures, who were admitted to the emergency department due to cardiomyopathy during the study period (below the age of 30 years), who had NT-proBNP levels which were measured within 6 hours of their admissions were compared with patients with scorpion sting myocarditis.

RESULTS

Thirty patients who were admitted to the emergency department were studied during the study period. A majority were below 18 years of age [Table/Fig-1], mean age 11.2 years (20 males and 10 females). Twenty two patients (73.3%) had an evidence of reduced LVEF (mean LVEF 31.9±6.9%, range 44 to 20%) on echocardiography (LVEF less than 50%). In all these patients, cTnl was elevated (mean 2.3µg/l, range 0.4 to 12µg/l). Severe LV dysfunction (LVEF < 30%) was noted in 8 patients (36.3%). RV dysfunction was noted in 8 patients (36.3%). Among the severe LV dysfunction group, one patient required ventilator support and one patient died due to shock. Among the 21 patients who were discharged in a stable state, LVEF had improved pre-discharge in a majority of the patients (19 patients had LVEF of >50%).

The NT-proBNP levels were found to be within the normal range in the patients with normal LVEF on echocardiography (mean 65.6 pg/ml, range 25 to 125 pg/ml). NT-proBNP was markedly elevated

Age (years, mean and range)	11.2 (5 – 32)	
Sex (Male)	20	66.6 %
Sex (Females)	10	33.3%
ECHO findings	LVEF <50%	22 (73.3%)
	LVEF 50-40%	4 (18.1%)
	LVEF 40-30%	10 (45.4%)
	LVEF <30%	8 (36.3%)
	RV dysfunction	8 (36.3%)
Cardiac Troponin	LVEF <50% vs LVEF >50%	2.3 µg/l vs <0.11 (P <0.05)
NT-proBNP (Mean and Range) in relation to LVEF	LVEF >50%	65.6 pg/ml (25 to 125)
	LVEF <50%	7862 pg/ml (1525 to 25,000)
	LVEF <30%	15,200 pg/ml (7880 to 25,000)

[Table/Fig-1]: Clinical and Investigation findings

in the patients with an evidence of LV dysfunction on echocardiography, irrespective of the clinical features (mean 7862 ± 6917 pg/ml, range 1525 to 25,000 pg/ml). One patient who required the ventilator and one patient who died, had the highest values (25,000 pg/ml). The patients with severe LV dysfunction (LVEF <30%) had very high values (mean 15,200 pg/ml, range 7880 to 25,000 pg/ml) of NT-proBNP. The elevated NT-proBNP levels correlated well with the evidence of myocarditis (LVEF <50%, $r = -0.88$, $P < 0.05$). The NT-proBNP levels in the patients with severe LV dysfunction (LVEF <30%) were significantly higher than those in the patients with mild to moderate LV dysfunction (LVEF 50 to 30%, mean 3668.5 pg/ml, range 1525 to 6540 pg/ml vs LVEF <30% mean 15,200 pg/ml, range 7880 to 25,000 pg/ml $P < 0.05$).

During the study period, 21 (13 males and 8 females, mean age 12.2) patients who were below the age of 30 years, who were admitted with acute heart failure, who had NT-proBNP levels within 6 hours of their admissions, were compared with the scorpion sting myocarditis patients. The LV ejection fractions were similar in both the groups (mean LVEF $31.9 \pm 6.9\%$ vs $32.3 \pm 7.1\%$ $p = \text{NS}$). The NT-proBNP levels were significantly high in the patients with scorpion sting myocarditis (7862 ± 6917 pg/ml vs 5862 ± 6222 pg/ml, $p < 0.05$).

DISCUSSION

The lethality of the scorpion venom varies with the species. The clinical effects of the envenomation depend upon the dose of the venom which is injected at the time of the sting. The iberitoxin and the tamulotoxin content of the scorpion *Mesobuthus tumulus* venom are the selective inhibitors of the potassium channel blocking effects, which lead to prolongation of the action potential across the excitable cell membrane. The sodium and potassium channel toxins mediate the synergistic effects which are responsible for an intense and persistent depolarization of the autonomic nerves, with a massive release of autonomic neurotransmitters, thus evoking an autonomic storm. The clinically autonomic storm which is evoked due to the scorpion venom toxins is characterized by transient parasympathetic (vomiting, profuse sweating, ropy salivation, bradycardia, priapism and hypotension), and prolonged sympathetic (cold extremities, hypertension, tachycardia, pulmonary oedema and shock) stimulations [4,8,9,13,26]. The major morbidity and mortality are related to the cardiopulmonary complications.

Pulmonary oedema was noted in 167 (19%) patients among 888 scorpion sting cases which were studied during 19 years at primary health centres over the western coast of Maharashtra, [9]. The pulmonary oedema may develop within 30 minutes with severe hypertension and it may develop after 36 hours of the sting, with hypotension and tachycardia. However, no single clinical marker can predict the development of the cardiovascular complications after a scorpion sting envenomation.

Echocardiography can be used to assess the LV dysfunction, even in an emergency department. It has been used to document and monitor the myocarditis in scorpion sting envenomation. There is good correlation between the clinical improvement and the return of the LV wall motion abnormalities towards normal, which are caused by the *Mesobuthus tumulus* sting [14-17]. Serial echocardiography is useful for following the changes in the LV function and the possibility of the development of cardiomyopathy. However, its routine use is limited by the non-availability of experts.

The estimation of biomarkers is very useful in many cardiovascular diseases. In a study which was done by Meki et al., cTnI showed 100% specificity and sensitivity for the diagnosis of myocardial injuries in relation to echocardiography. They concluded that cTnI and IL-8 may be useful for forecasting the fatal outcome in scorpion envenomation [19]. This was confirmed in our previous study also [20].

NT-proBNP has been used to diagnose heart failures in the emergency department and it is also used to guide the therapy at pre-discharge. It also helps in prognosticating the heart failure patients. However, no study has evaluated its role in scorpion sting related myocarditis. In this study, we estimated the NT-proBNP levels in the patients who presented to the emergency department after scorpion sting envenomation. The patients with no evidence of LV dysfunction on echocardiography had normal levels of NT-proBNP. However, the patients with LV dysfunction had high levels of NT-proBNP and the patients with severe LV dysfunction had very high levels. This appears to be a significant finding, as the patients can be convincingly separated (as with or without LV dysfunction, and as with mild to moderate versus severe LV dysfunction), based on the quantitative estimation alone.

The NT-proBNP levels were significantly more elevated in scorpion sting myocarditis as compared to those in the patients with heart failure which was caused by cardiomyopathy. This may be due to the acuteness, severity and the effect of the scorpion toxins in the scorpion envenomation patients and the underlying chronic heart failure in the patients with cardiomyopathy. Our study results appear very impressive, but our small sample size was a limiting factor. These findings need to be confirmed in a larger cohort of patients. There is also a need to evaluate the importance of serial monitoring, the relative importance of NT-proBNP and cTnI and their timings in relation to scorpion envenomation.

CONCLUSIONS

Severe myocarditis which is caused by scorpion sting envenomation is associated with significant morbidity and mortality. The early use of echocardiography and cTnI, along with a clinical assessment, is very useful for reducing the case fatality. Newer biomarkers like NT-proBNP may be useful and they need further evaluation in this setting.

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