Utility of Scorpion Antivenin vs Prazosin in the Management of Severe *Mesobuthus tamulus* (Indian Red Scorpion) Envenoming at Rural Setting

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Abstract

Background: Scorpion antivenom (SAV) is specific antidote to scorpion venom. SAV did not prevent the cardiovascular morbidity and mortality (autonomic storm), hence its utility in the management for severe scorpion envenoming may be limited. Since 1983 the advent of prazosin revolutionized the management of severe scorpion sting. Since 2002 SAV against Indian red scorpion (IRS) for the treatment of scorpion sting cases is available at primary health centers. We compared the effects of SAV Vs Prazosin (PRA) in the management of severe scorpion sting cases at rural setting in a non-randomised open label manner.

Methods: From January 2002 to December 2004, 53 patients accidentally stung by scorpion were admitted in hospital at Mahad. Of these 25 patients received intravenous SAV at primary health centers and were referred to Mahad for further management. 28 patients directly reported to Mahad were treated with oral prazosin (PRA). Time interval between sting and hospitalization, the total dose of SAV and PRA administered was noted. Clinical manifestations were noted in a standard protocol. Details of SAV patients were noted from referred letters or in case of a doubt, details were obtained by direct communication with the medical officer who first saw and examined the case. All 53 cases were evaluated clinically for improvement, deterioration or fatal outcome.

Results: SAV Vs PRA (25 Vs 28) cases reported to hospital within 1½ -3 (1.4) Vs ½-4 (1.3) hours after stung. On arrival 21 (84%) Vs 26 (92%) had hypertension, 2 (8%) Vs 1 (3.5%) had hypotension, 2 (8%) Vs 1 (3.5%) had normal blood pressure. Heart rate 58-102 (82) Vs 48-120 (80.2) respectively. 9 cases received 20 ml, 1 case 30 ml and remaining 15 cases were given 10 ML of SAV on arrival to PHC, while 28 cases received oral prazosin. 20 (80%) Vs 2 (7.5%) had acute pulmonary edema, 5 (20%) Vs 8 (30%) had persistent raised blood pressure. 4 (16%) Vs 0% died. Recovery time was 1½-4 (2.26) Vs 1-2 (1.25) days respectively.

Conclusion: We found that SAV is no more effective to alleviate or reverse the cardiovascular effects of scorpion venom actions in severe case as against prazosin prevents and cures the cardiovascular manifestations in a severe scorpion envenomation. Therefore role of SAV in severe scorpion venomation needs to be relooked and prazosin needs to be a standard of care in such cases to overcome the autonomic storm.

INTRODUCTION

Scorpion envenomation is public health problem in tropical and subtropical countries, especially in north Africa, Middle East, Latin America and India. *Mesobuthus tamulus* an Indian Red Scorpion is most lethal species among *Buthedae* family, flourished all over western Maharashtra. Its venom is sodium channels activator resulting in autonomic storm, characterized by transient cholinergic (vomiting, sweating, salivation, priapism in males, bradycardia, ventricular ectopics) and sustained sympathetic stimulations (hypertension, tachycardia, pulmonary oedema, shock and fatal).1-3 These accidents usually occurred during the night hours because scorpions are nocturnal. For medical help, villagers have to travel 3-5 miles or more. We have been treating victims of scorpion sting since 1976.4 Various pharmacological agents were tried to alleviate the cardiovascular morbidity and mortality.5,6

From January 2002 scorpion antivenin is freely available at primary health centers. PHC is ill-equipped with having untrained staffs. Medical officer may not be aware or treated severe scorpion sting case before. Antivenom is a specific treatment for stings and bites what he was taught and read in text book. Medical officer feels confident regarding recovery of victim
after administering SAV. In India it is standard protocol that any poisonous case to be admitted for 24 hours observations. As admission facilities are not available at PHCs. Hence majority of cases are transferred to higher centers.

Since December 2004 director of health service accepted standard protocol of use of prazosin as a routine treatment of severe scorpion envenomation at government hospitals including PHCs.

The advent of prazosin, an alpha-1 blocker, in recent years has revolutionized the management of severe scorpion sting cases and should be the first line of treatment. It is unethical or irrational to withhold the prazosin therapy simply for scientific trial. Hence we report here the simple non-randomized open trial of SAV Vs prazosin in the management of severe Mesobuthus tamulus envenoming.

METHODS AND MATERIALS

Between January 2002 – December 2004, 53 consecutive cases of severe scorpion sting admitted at hospital in Mahad. Of these 25 cases soon after sting reported to PHCs situated near by village. Medical officer administered SAV by intravenous route, examined the patients and noted the history of stung by scorpion, vomiting, sweating, priapism, blood pressure, heart rate, temperature of extremities with detailed note referred the case for higher center (Mahad) for further observation and management (Table 1). 28 cases from near area reported directly to Mahad were treated with prazosin alone.

Diagnosis of scorpion sting was confirmed by positive history of scorpion sting, or scorpion being seen or killed by patients or bystanders. We excluded patients who received both prazosin and SAV.

Definition

Severe scorpion sting - Victim soon after stung by scorpion suffered an autonomic storm, characterized by vomiting, sweating, priapism, cold extremities. Premonitory signs and symptoms preceded to cardiovascular manifestations.

Pulmonary oedema- Dyspnoea, with respiratory rate >24 per minute, moist rales in the lungs.

Massive pulmonary oedema- Orthopnea, cyanosis, intractable cough with expectorating pinkish froth from mouth and nostrils, bilateral moist rales heard all over chest.

SAV Patients

Detail of 12 cases obtained from the referred note given by medical officer who first examined and administered SAV at PHC, remaining 13 cases details were obtained from medical officers by telephonic communications.

25 (male 18: female 7) reported to primary heath centers within ½ - 3 hours of sting. All had signs suggestive of autonomic storm details of these cases given in Table 3, 21(84%) patient had raised blood pressure on arrival, 2(8%) had hypotension while 2 (8%) had normal blood pressure. These cases took 4-25 (mean 13.3) hours to reach to Mahad. Details on arrival were noted (Table 4).

Electrocardiogram- 5 cases had tented T waves inferio-lateral leads, 19 cases had tachycardia, left anterior hemiblock with marked ST depression, one had left bundle branch block.

<table>
<thead>
<tr>
<th>Character</th>
<th>Scorpion Antivenom</th>
<th>Prazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>25 (M-18 F-7)</td>
<td>28 (M-18 F-10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>3-60</td>
<td>5-70</td>
</tr>
<tr>
<td>Time interval Sting &amp;</td>
<td>½-3</td>
<td>½-4</td>
</tr>
<tr>
<td>hospitalization (hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Sweating</td>
<td>25</td>
<td>100%</td>
</tr>
<tr>
<td>Priapism in males</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>Cold extremities</td>
<td>25</td>
<td>100%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>S-130-170 (149.52)</td>
<td>S-120-180 (148.46)</td>
</tr>
<tr>
<td></td>
<td>D-90-140 (103.9)</td>
<td>D-90-130 (104.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>n-2 70,80 mm Hg</td>
<td>1 (80 mm Hg)</td>
</tr>
<tr>
<td>Normotension</td>
<td>n-2 (110/90, 100/80 mm Hg)</td>
<td>1 (100/90 mm Hg)</td>
</tr>
<tr>
<td>Heart rate (minute)</td>
<td>58-108</td>
<td>48-120</td>
</tr>
</tbody>
</table>

Table 2: Month-wise distribution of cases

<table>
<thead>
<tr>
<th>Month</th>
<th>Scorpion antivenom</th>
<th>Prazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>February</td>
<td>1</td>
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</tr>
<tr>
<td>March</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>April</td>
<td>—</td>
<td>2</td>
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<td>May</td>
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<td>6</td>
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<td>3</td>
</tr>
<tr>
<td>October</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>November</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>December</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1: Demographic data of SAV Vs Prazosin

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Laboratory investigations- 7 cases of SAV and 2 cases of PRA shown in Table 6.

**Prazosin**

28 (male 18 : Female 10) cases soon after stung within $\frac{1}{2}$-4 (mean 1.30) hours reported to Mahad directly without any intervention before. All had signs and symptoms of autonomic storm Table 1. 26 cases (92%) had raised blood pressure, 1 (3.5%) had hypotension remaining 1 (3.5%) had normal blood pressure. Their heart rate was 48-120 (80.8) per minute, sweating persisted from 2-17 (8) hours in 17 patients, while cold extremities 3-21 (12.8) hours and 15 males had priapism persisted for 6-16 (8.6) hours. 10 children below 10 years old were given oral prazosin 250 microgram at three hours interval and oral rehydration solution, rest 18 cases were given 500 microgram prazosin three hourly. Cases were followed till clinically improved or deteriorated.

**RESULTS**

Twelve hours of treatment, (SAV Vs PRA) 5 (20%) Vs 8 (30%) had raised blood pressure, 20 (80%) Vs 2 (7.1%) had acute pulmonary edema, 19 (76%) Vs 8 (28%) had tachycardia at end of 12 hours of treatment. Of these 20 (80%) Vs 2 (7.1%) required admission to intensive care unit with close monitoring, of these 16 (80%) Vs 2 (100%) recovered within 1.5-4 (2.36) Vs 1-2 (1.25) days. 4 (16%) Vs 0% died (Table 3).

**ILLUSTRATIVE CASES**

Case – 1

Nine years boy while going to toilet in a open ground at 8Am on 4/6/04 stung by red scorpion to his left foot. Scorpion was seen and killed, it was red colored. Soon after sting he vomited 5 times, since then profusely sweated, had priapism, cold extremities, and excessive salivation. He reported to primary health center 1 hour of stung. Medical officer recorded his blood pressure 150/110 mm Hg. Heart rate was 90 per minute. He was given 10Ml of SAV diluted in 200cc of dextrose saline intravenously over one hour. He was referred to Mahad. He reported to Mahad 20 hours of stung. On arrival he was breathless, orthopneic, extremities were...
warm, blood pressure was 70 mm Hg, heart rate 166 per minute, with summation gallop and short systolic murmur heard over precordium. There were bilateral moist rales heard over both lungs. He was admitted in intensive care unit and was given propped up position, nasal oxygen, intravenous dobutamine 10 microgram per/kg/per minute. He was on dobutamine drip for 36 hours. He took 4 days for complete recovery. Laboratory investigations shown in Table 6 case no-1. His ECG showed progressive myocardial injury with development of left bundle branch block which subsequently regressed (Figs. 1, 2). X-ray showed batwing appearance of pulmonary oedema (Fig. 3).

Upon arrival to Mahad, 20 hours of sting- left anterior hemiblock, heart rate 166 per minute, ST depression in II, III, AVF, V4-V6. Small q wave with ST segment elevated, T wave inversion in AVL. 14 hours- heart rate 176 per minute, left bundle branch block (QRS 0.12 seconds). PQRST alternans seen in lead II. 18 hours- heart rate 150 per minute, incomplete left bundle branch block (QRS 0.10 seconds) PQRST alternans seen in lead II. 22 hours- heart rate 150 per minute, incomplete left bundle branch block (QRS 0.8 seconds), small q with ST segment elevated and T inversion in AVL. Heart rate 136 per minute, left anterior hemi-block, ST depression in II, III, AVF, V3-V6. 26 hours-heart rate 136 per minute, left anterior hemi-block, ST depression in II, III, AVF, V3-V6. 50 hours- heart rate 88 per minute, left axis deviation, T inversion in AVL, QTc 0.54 seconds on the 7th day of discharge - T biphasic in AVL. The chest x-ray is shown in Fig. 3 showing bilateral bat-wing pulmonary oedema

Case – 2

A- on arrival shows tented T waves

B- 24 hours of hospitalization. showed regression of acute tented T waves

A 35 years male received accident sting to his right great toe while he was walking on a peddler road at 8.30Am on November 2004. he vomited soon after sting,
since then profusely sweated from all over body. He complained of chest pain. He reported to Mahad at 9.15 AM on arrival to hospital he was anxious, was sweating from all over body, excessive salivating and complained of mild local pain at the site of stung. On examination his blood pressure was 160/100 mmHg. Had priapism, extremities were cold, there was parasternal heave, loud S4 gallop heard over precordium. ECG (Fig. 4) showed tented T waves with heart rate 60 per minute. He was given oral prazosin 500 microgram three hourly sweating priapism, cold extremities persisted for 7, 6 and 9 hours respectively. His blood pressure reduced to 120/80 at the end of 7 hours of hospitalization he was discharged on next day.

**DISCUSSION**

*Mesobuthus tamulus* a lethal scorpion flourished all over western Maharashtra, Pondicherry, Chennai, Saurashtra, Karnnol, Bellary and Mysore districts of Karnataka. Its venom is sodium channel activator resulting in autonomic storm resulting a life-threatening cardiovascular manifestations. 40% fatality due to refractory pulmonary oedema has been reported from Mahad region.\(^9\)\(^{,10}\) Irrespective of various regimes tried lytic cocktail,\(^11\) insulin glucose drip,\(^12\) decongestive, betablocker, isosorbide dinitrate,\(^3\) atropine,\(^13\) steroids,
anti-histamines, diuretics, captopril did not alter the outcome. Venom acts indirectly through the release of auto-pharmacological agents cytokines, catecholamines and platelet activating factors, rather than to the venom itself. Scorpion antivenin is specific treatment for scorpion sting. Antivenin known to cause severe anaphylaxis, hence it should be avoided if possible and it was advocated only in a severe scorpion sting.

Seven of the nine patients received specific antivenin before admission at Mahad, subsequently had heart failure. In comparative study SAV did not show any beneficial effects in severely envenomed children reports from Israel. The beneficial effects of SAV in protecting victims against scorpion sting are still questionable. However systemic administration of SAV irrespective of clinical severity did not alter the clinical course of scorpion sting. Early administration of SAV may help to reduce the circulating venom and symptoms. Highly purified SAV F(ab)2 fraction if administered earlier may have prevented the fatality in Mexico. In a randomized placebo controlled trial no benefit in routine administration of SAV after scorpion sting, irrespective of clinical severity. In India scorpion antivenin against Mesobuthus tamulus became available for routine use at government hospitals since 2002. In our previous cases SAV did not prevent the cardiovascular manifestations of severe scorpion sting.

In present report cardiovascular morbidity (SAV vs PRA) is 100% vs 37%. While intensive care admission is 76% vs 14% and fatality is 16% vs 0% confirmed the inefficacy of SAV. Low molecular weight toxins of venom rapidly enter the blood stream and organs, while the heavy chain antivenin molecules are diffuse slowly in to "shallow" and "deep" compartments, thus heart and circulation are rapidly affected by the toxins or by other substances released by the venom which do not respond to antivenin. In a experimental animal study SAV administered before giving venom did protect the animal but not after the giving venom. Human scorpionism is differing than experimental animals at times victim may manifest in a massive pulmonary oedema. The Mesobuthus tamulus labeled venom injected reach the myocardium within 3-5 minutes, while a SAV took >30 minute to reach the tissue. Maximum venom injected at one sting by Indian red scorpion is 1.5 mg. While each ml of SAV is capable of neutralizing 1.2 to 1.5 mg of scorpion venom. Thus irrespective of early administration with maximum quantity of SAV in present cases did not alter the outcome, more over because of false security and confidence achieved by relatives and treating doctors patients are delayed for hospitalization resulted in deteriorated condition and heavy admission to intensive care and fatality. Irrespective of maximum SAV in present studied cases 19 cases needed adjuvant therapy for recovery (Table 5) similar observation reported from Brazil.

Alpha receptors stimulation plays a vital part in the development of cardiovascular manifestations. Alpha receptors stimulation causes hyperkalaemia and hyperglycemia (inhibition of insulin secretion). Angiotensin II stimulates alpha receptors in the myocardium (increased myocardial contraction) and hypoxia due to coronary spasm. Increased sympathetic activities raised free fatty acids in the circulation which are injurious to myocardium and lethal arrhythmias resulting in sudden deaths.

Prazosin a post-synaptic adrenergic receptors blocker has 1000 fold more affinity to alpha-1 receptors. It is well absorbed by oral administration. 17 cases received oral Prazosin recovered uneventfully except 2 cases had pulmonary oedema and tachycardia necessitated intravenous dobutamine drip for recovery. Prazosin reduces preload and left ventricular impendence without causing tachycardia. As a potent inhibitor of phosphodiesterase, prazosin causes accumulation of cGMP, a second messenger of nitric oxide in vascular endothelium and myocardium, inhibits the liberated interleukins and cytokines. Leucocytosis in SAV treated victims enhanced synthesis of interleukin (IL-6) due to persistent alpha receptors stimulation as against low leucocyte counts in a prazosin treated cases (Table 6). White blood count >10000, raised cardiac enzymes seen in present cases suggestive of activation of cytokines and release of IL-6 abundant in these victims. Myocardiocytolysis and probably by induction of apoptosis due excessive cytokine-related stimulation of inducible NO synthases activity. Since the advent of prazosin the fatality is reduced to <1% in Mahad and similar reports from other part of India. Prazosin enhances insulin secretion resulting in entry of potassium, glucose in the cells, and restore the energy, reduction in free fatty acids, subsequently prevents the development of lethal ventricular arrhythmias and sudden deaths, disseminated intravascular coagulation and stroke. SAV treated two fatal cases had had stroke (Table 3). Hemiplegia due to cerebral thrombosis and DIC have been reported in a cases treated without prazosin. Pulmonary oedema has been considered to be of cardiogenic or non-cardiogenic origin. However echocardiographically and ECG and laboratory study proved majority of cases it is of cardiogenic in origin. Progressive injury to myocardium in form of electrical alternans and conducting system in form of ST-T gamete and left anterior and left bundle branch block seen (Figs. 1, 2).

Mesobuthus, Leirus and Androctonus lethal scorpions flourished all over Turkey, where out of 30 children treated with prazosin, one died. This confirmed that irrespective of different species, cardiovascular manifestations are similar so is the treatment.

In the year 2002 SAV became available for treatment of Indian red scorpion. Its efficacy in the management...
of severe scorpion sting was not known. In the view of the advantages of prazosin over the earlier treatments, we believe a placebo-controlled trial to be unethical. Through SAV is specific antidote to scorpion venom actions, in present study we found SAV no more helpful to reverse or to cure the cardiovascular effects of venom and effects of venom-induced liberated pharmacological agents. Thus Prazosin a pharmacological and physiological antidote to venom actions remains main drug of choice.

A study research group was organised under the leadership of Dr Peter Strong at Haffkine Institute for Research and Training which then cam e out recommendations to use prazosin.

SAV is expensive and not free from toxicity, moreover it is no more cardio-protective hence receptor blockers are tried. In experimental animals intravenous lignocaine, a sodium channels blocker, inhibits the release of neurotransmitters.

Cardiovascular morbidity and fatality in the severe scorpion envenoming depends upon time lapsed between sting and hospitalization or administration of prazosin. In present report, patients attended hospital within ½ -4 hours (Table 1). In backward, adiwasi and illiterate populated areas like that of western Maharashtra, total number of PHCs are increased. PHC is situated in vicinity 3-5 kilometers distance from village. Thus instead of wasting time for administration of SAV (test dose, preparation for intravenous line), simple oral administration of oral prazosin, a simple scientific and free from anaphylaxis, should be adopted as a primary line of treatment for severe scorpion envenoming.

India is a developing country and a large amount of raw data is available to an interested physician. However, it is almost impossible to do a randomized trial here, especially in rural areas. Illiteracy is rampant and it is therefore difficult to counsel patients and relatives about entering into a randomized trial. If editors want to give a chance to researchers working in such areas, they should look first originality. Forcing researchers to comply with strict scientific methods can unfortunately result in fraud and fabrication of data.

One ampoule (10ML) SAV cost rupees 350. Dr. Natu in his lecture at Mahad advocated 100 ML of SAV (Rs 3500) bolus to severe scorpion sting. One mg prazosin cost is Rs 2 only, majority of victim required not more than three tablets for recovery. Thus total severe scorpion sting cases admitted in one year allover India can be treated with prazosin in amount required to treat one victim with SAV. 46 species of poisonous scorpion species reported from India it is difficult to prepare a species specific antivenin,

by consultants practicing in endemic areas of severe scorpion sting. Prazosin is poor man scorpion antivenin.

**Acknowledgement**

We are grateful to medical officers at primary health centers Kalanboni, Tisangi and Khed, district Ratnagiri, Cottage Hospital, Mangan, primary health center Poladpur, Birwadi from Raigad district for immediate referring to Mahad the severe scorpion sting cases soon after administrating scorpion antivenin. Dr. SM Sapatnekar for guidance and peerview at Hafkine Institute and manuscript assistance.

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**Announcement**

Bihar Chapter API Conference (BAPICON - 2007) will be held on 17th and 18th March 2007 at Bhagalpur. We welcome speakers for this scientific meet and request articles for the publication in Medicine Update-Bapicon 2007.

For further details contact: **Dr. AK Sinha,** Chairman Scientific Committee and Editor Medicine Update at KK Nursing Home and Research Centre, Raja SN Road, Bhagalpur - 812001.

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