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RESEARCH

Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (*Mesobuthus tamulus*) sting: randomised open label clinical trial

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ABSTRACT

Objective Envenomation by *Mesobuthus tamulus* scorpion sting can result in serious cardiovascular effects. Scorpion antivenom is a specific treatment for scorpion sting. Evidence for the benefit of scorpion antivenom and its efficacy compared with that of commonly used vasodilators, such as prazosin, is scarce. We assessed the efficacy of prazosin combined with scorpion antivenom, compared with prazosin alone, in individuals with autonomic storm caused by scorpion sting.

Design Prospective, open label randomised controlled trial.

Setting General hospital inpatients (Bawaskar Hospital and Research Centre Mahad Dist-Raigad Maharashtra, India).

Participants Seventy patients with grade 2 scorpion envenomation, older than six months, with no cardiorespiratory or central nervous system abnormalities.

Intervention Scorpion antivenom plus prazosin (n=35) or prazosin alone (n=35) assigned by block randomisation. Treatment was not masked. Analysis was by intention to treat.

Main outcome measures The primary end point was the proportion of patients achieving resolution of the clinical syndrome (sweating, salivation, cool extremities, priapism, hypertension or hypotension, tachycardia) 10 hours after administration of study drugs. Secondary end points were time required for complete resolution of clinical syndrome, prevention of deterioration to higher grade, doses of prazosin required overall and within 10 hours, and adverse events. The study protocol was approved by the independent ethics committee of Mumbai.

Results Mean (SD) recovery times in hours for the prazosin plus scorpion antivenom group compared with the prazosin alone groups were: sweating 3 (1.1) *v* 6.6 (2.6); salivation 1.9 (0.9) *v* 3 (1.9); priapism 4.7 (1.5) *v* 9.4 (1.5). Mean (SD) doses of prazosin in the groups were 2 (2.3) and 4 (3.5), respectively. 32 patients (91.4%, 95% confidence interval 76.9% to 97.8%) in the prazosin plus antivenom group showed complete resolution of the clinical syndrome within 10 hours of administration of treatment compared with eight patients in the prazosin group (22.9%, 11.8% to 39.3%). Patients from the antivenom plus prazosin group recovered earlier (mean 8 hours, 95% CI 6.5 to 9.5) than those in the control group (17.7 hours, 15.4 to 19.9; mean difference −9.7 hours, −6.9 to −12.4). The number of patients whose condition deteriorated to a higher grade was similar in both groups (antivenom plus prazosin four of 35, prazosin alone five of 35). Hypotension was reported in fewer patients in the antivenom plus prazosin group (12 of 35, 34.3%) than in the prazosin group (19 of 35, 54.3%), but the difference was not statistically significant. No difference was noted in change in blood pressure and pulse rate over time between two groups.

Conclusion Recovery from scorpion sting is hastened by simultaneous administration of scorpion antivenom plus prazosin compared with prazosin alone.

Trial registration number CTRI/2010/091/000584 (Clinical Trials Registry India).

INTRODUCTION

Scorpion sting can pose a life threatening acute medical emergency and is a neglected public health problem in tropical and sub-tropical countries, especially in North Africa, the Middle East, Latin America, and India. *Mesobuthus tamulus,* an Indian red scorpion, is the tmost lethal species of the *Buthidae* family in India.[1] Its venom delays the closing of neuronal sodium channels, resulting in "autonomic storm" owing to sudden pouring of endogenous catecholamine into the circulation. Autonomic storm is characterised by transient parasympathetic and prolonged sympathetic stimulation.[2-5] Similar cardiovascular manifestations are reported in different species of scorpions.[6] Morbidity and mortality due to scorpion sting result from acute refractory pulmonary oedema, cardiogenic shock, and multiorgan failure.[5] Opinions differ about the correct treatment for scorpion sting. In the past various regimens, including a lytic cocktail,[7] insulin,[8] atropine, β blocker, nifedipine,[9] and captopril[10] have failed

to reduce morbidity and mortality, but since the advent of the α_1 blocker prazosin the fatality rate has been reduced to 1%.[11 12]

Scorpion antivenom is a specific antidote capable of neutralising circulating venom toxins if administered soon after sting; it is widely used and believed to be effective by experienced doctors in Mexico, Brazil, Venezuela, Tunisia, and Iran.[13-17] Serotherapy has been a matter of debate and controversy during the past decade.[18-21] Whether the antivenom can reverse the cardiac pathophysiological effects of scorpion venom is uncertain. Several studies have shown that antivenom does not alleviate haemodynamic changes or cardiogenic pulmonary oedema, or prevent death[19 22] and the outcome was the same for victims treated with antivenom and those treated without antivenom.[9 18] De Rezende and colleagues found that although venom antigen in plasma from people who had been stung by a scorpion was not detected one hour after antivenom therapy, and pain and agitation disappeared within a few hours, patients with pulmonary oedema recovered only 48 hours after serotherapy.[23]

Since 2002, monospecific F(ab)2 antivenom serum prepared by immunising horses has been available for clinical use from Haffkine Biopharma Mumbai. *Mesobuthus tamulus* is common in the western Maharashtra, Saurashtra, Kerala, Andra Pradesh, Tamil Naidu, and Karnataka states of India where morbidity and mortality due to stinging have been reported.[7-10 24] Prazosin is widely used for the management of *Mesobuthus tamulus* sting.[11 12 25-30] We did a prospective, randomised trial of scorpion antivenom plus prazosin versus prazosin alone in the treatment of severe *Mesobuthus tamulus* sting.

PATIENTS AND METHODS

Trial design

This study and trial were done without the help of any funding agency. Anti-scorpion antivenom was purchased from Haffkine Biopharma Mumbai and given to participants in this trial. We proposed to include people admitted with scorpion sting over one year, between March 2009 and February 2010. This was a randomised (1:1 allocation ratio), parallel group, open label, controlled trial conducted at Bawaskar Hospital in Mahad, a region of India with a population of 20 000 , situated 180 km south of Mumbai on the Mumbai-Goa highway. An independent data and safety monitoring board monitored the trial and had access to the all data. Statistical analysis was done by a statistician in collaboration with the investigators. The study design was approved by the independent ethics committee of BYL Medical College Mumbai (IEC/08/39) and all participants provided written informed consent.

Sample size

The primary efficacy variable was the time required for recovery after venomous scorpion sting. We estimated that 35 patients in each group would be required to achieve 80% power; α=0.05 to detect a mean difference of four hours in the recovery time between the groups, assuming a mean recovery time of 10 hours (SD 2.5 hours) in the antivenom plus prazosin group and 14 (SD 3) hours for the prazosin alone group.

Randomisation

A statistician generated the sequentially numbered randomisation list with random block sizes of 4 4 2 4 4 6 2 4 6 6 6 8 4 8 2 using www.randomisation.com. This process can be reproduced by using seed 22491 (6 March 2009). This randomisation sequence was concealed by using sequentially numbered, opaque, sealed, and stapled envelopes. Envelopes were opened alternately by HSB or PHB after an eligible patient consented to take part in the trial and patients were allocated according to the randomisation label inside the envelope.

Statistical methods

Demographic factors and clinical characteristics were summarised as counts (percentages) for categorical variables and as mean (standard deviation; SD) for normally distributed continuous variables. All patients who had been randomly assigned to a treatment group were included in the intention-to-treat analyses.

The groups were compared using χ^2 test or Fisher's exact test for categorical variables, unpaired *t* test for normally distributed continuous variables, and Mann-Whitney U test for other continuous variables. We analysed results with SPSS 17 software. Blood pressure and pulse rate were measured at different time points and were repeated factors, and treatment group was included as a between-participant measure. α was set at 0.05. We used the Greenhouse-Geisser P value.

Patients

Between March 2009 and February 2010 we recruited patients who reported to Bawaskar Hospital and Mahad research centre after being stung by *Mesobuthus tamulus* (fig 1).[2 4 6 31]

Inclusion and exclusion criteria

Patients were eligible for enrolment if they reported to hospital with *Mesobuthus tamulus* sting of clinical grade 2 severity, with an interval of less than six hours between sting and hospital admission, and were older than six months. *Mesobuthus tamulus* sting was confirmed if the victim or bystander had seen a red scorpion, had

Fig 1 | Indian red scorpion (*Mesobuthus tamulus*)

Table 1 | Distribution of patients with scorpion sting by month

Month	Prazosin (n=35)	Prazosin plus antivenom (n=35)
January	4	3
February	2	2
March	2	2
April	1	2
May	6	4
June	1	1
August	0	1
September	3	4
October	7	5
November	5	6
December	4	5

brought in the killed specimen, or recognised the hospital's preserved specimen. In this way we made sure that *Mesobuthus tamulus* was not confused with *Palamneus gravimanus*, a larger scorpion that is less lethal and causes only severe local pain without systemic involvement or transient reversible cardiovascular effects.[1 32] Major exclusion criteria were: patient reporting six hours after sting, pregnant women, history of taking prazosin or antivenom, history of bronchial asthma, history of allergic reaction to foreign serum, and refusal to give consent.

Written informed consent was obtained in the local language. For illiterate adults, a literate relative of the patient read the statement out loud to them and consent was obtained by thumb impression witnessed by the relative. Parent's consent was obtained for minor children. The study protocol was approved by the independent ethics committee of Mumbai (registration number 1433/1999G.B.B.S.D, IEC/08/39). All people admitted with scorpion sting between March 2009 to February 2010 were insured by the Oriental Insurance Company Limited clinical trial liability cover policy No 111600/48/2009/227.

Evaluation of clinical grade

Cases are graded according to severity of clinical manifestations on arrival at hospital (box). Severity of clinical manifestations, morbidity, and mortality depend on the time lapsed between sting and hospital admission, as well as the grade of a case on arrival.[5 9 18 33 34]

Evaluation of clinical grade of scorpion sting on arrival at hospital

Grade 1: severe, excruciating local pain at the sting site radiating along with corresponding dermatomes, mild local oedema with sweating at the sting site, without systemic involvement

Grade 2: signs and symptoms of autonomic storm characterised by acetylcholine excess or parasympathetic stimulation (vomiting, profuse sweating from all over body, ropey salivation, bradycardia, premature ventricular contraction, hypotension, priapism in men) and sympathetic stimulation (hypertension with blood pressure >140/90, tachycardia with heart rate >120 per minute, cold extremities, transient systolic murmur).

Grade 3: cold extremities, tachycardia, hypotension or hypertension with pulmonary oedema (respiratory rate >24 per minute, basal rales or crackles in lungs).

Grade 4: tachycardia, hypotension with or without pulmonary oedema with warm extremities (warm shock).

Patients with grade 2 signs and symptoms were included in the present study. After giving written consent, all eligible patients were examined by one of the two authors and baseline data were recorded on a standard form. Data included age, sex, time between sting and hospital admission, and history of any medication before admission, vomiting soon after sting, or paraesthesia (tingling and numbness in the perioral region, or sometimes reported by the patient to be felt all over the body).

One of the authors sat by the side of the patients and closely clinically examined them for signs and symptoms of systemic manifestations: presence of profuse sweating all over the body, ropey salivation, priapism in men, heart murmur, coolness of the extremities. Blood pressure, heart rate, cardiac arrhythmias, respiratory rate, and oxygen saturation were monitored on a multipara monitor. These findings were noted on admission at 00.00, at 30 minutes, and at 1, 2, 4, 6, 8, 10, 14, 18, and 24 hours. Subsequent improvement or deteriorations to grade 3 or 4 were closely followed by the author who examined the patient on arrival. Blood was collected from all participants on admission for measurement of haemoglobin, white cell count, and creatine kinase-MB. A 12 lead electrocardiogram (ECG) was done on arrival, after six hours, and before discharge.

Study treatments

Mesobuthus tamulus is not the only venomous scorpion in the state of western Maharashtra, but it may be the only dangerously venomous scorpion in the Mahad area.[24 25] Haffkine Biopharma (Mumbai) has been manufacturing monovalent anti-scorpion venom serum F(ab)2 against *Mesobuthus tamulus* since 1997 and it has been available for clinical use in a rural setting since 2002. Studies conducted at different times show that the antivenom is potent; 1 mL of reconstituted anti-scorpion venom serum neutralised 1.2 mg of Indian red scorpion venom by intravenous route in an in vivo study in mice.[35] The maximum volume of venom injected in one sting by the Indian red scorpion is 1.5 mg, and each mL of antivenom is capable of neutralising 1.2 to 1.5 mg of venom.[36]

A single 30 mL dose of Haffkine Biopharma monovalent antivenom (batch no SS811001, manufacturing date November 2008, expiry date April 2013) was added to 100 mL of normal saline, which was infused intravenously over 30 minutes irrespective of patient's age. During infusion the patient was closely observed for reaction to the serum in the form of sudden onset of vomiting, urticaria, hypotension, tachycardia, bronchospasm, angioneurotic oedema, or anaphylaxis.

Oral prazosin (batch no ML.NH 138 batch no GK 60372 manufactured 04/2006, expiry 03/2011, and ML.NH 138 batch no GK 80282 manufactured 02/

Table 2 | Demographic and baseline clinical data

	Prazosin (n=35)	Prazosin plus antivenom (n=35)
Mean (SD) age in years	32.4 (15.7)	31.1 (21.1)
Sex		
Male	24 (68.6%)	27 (77.1%)
Female	11 (31.4%)	8 (22.9%)
Children <18 years		
Boys	5(26.3%)	9(47.3%)
Girls	2 (10.5%)	3(15.7%)
Mean (SD) time between sting and admission	94.7 (43.9)	115.3 (66)
Vomiting	29 (82.9%)	29 (82.9%)
Paraesthesia	22 (62.9%)	23 (65.7%)
Sweating	34 (97.1%)	35 (100 %)
Salivation	25 (71.4%)	30 (85.7%)
Cold extremities	34 (97.1%)	35 (100%)
Priapism	14 /24 (58.3%)	17/ 27 (62.9%)
Bradycardia	10 (28.6%)	10 (28.6%)
Transient systolic murmur	17 (48.6%)	19 (54.3%)

2008, expiry 01/2013) was given at a dose of 250 µg in children up age 18 years and 500 µg in adults. The same dose was repeated at intervals of 3 hours until the extremities were cold. Similar doses were administered in both randomisation groups.

Dehydration owing to vomiting and sweating was corrected by intravenous crystalloid solution. The prazosin treated group required longer duration and larger volumes of intravenous crystalloid solution than the antivenom plus prazosin group. Patients who developed grade 3 and 4 symptoms were transferred to the intensive care unit. Before discharge all participants were immunised for tetanus.

Outcomes

The primary end point was the proportion of patients achieving resolution of the grade 2 clinical syndrome at the end of 10 hours after administration of the study drugs and prevention of deterioration to grade 3 and 4.[18 21 37] Secondary end points were time required for complete resolution of clinical syndrome, prevention of deterioration to higher grade, doses of prazosin required within 10 hours and overall, and adverse events.

RESULTS

Figure 2 shows the trial profile. We screened 116 patients admitted with scorpion sting for eligibility. Of 72 eligible patients, 70 were enrolled in the study; 35 were randomly allocated to prazosin alone and 35 to prazosin plus antivenom. All patients completed treatment in the group of allocation and none was lost to follow-up. We analysed end points according to group of allocation. Patients were recruited between March 2009 and February 2010 (table 1). We stopped recruiting patients after achieving the required sample size.

The two groups were similar in demographic and clinical characteristics at baseline (table 2). Mean time between scorpion sting and arrival at hospital and presenting symptoms were also similar between the groups.

Table 3 shows recovery time for clinical signs and symptoms in the two groups. The treating doctors actually sat by the side of patients and noted the duration of profuse sweating and flowing of saliva from the corners of the mouth. They repeatedly felt the palm and sole for temperature. Priapism was noted every 15 minutes.

Thirty-two patients (91.4%, 95% confidence interval 76.9% to 97.8%) on prazosin plus antivenom showed complete resolution of the clinical syndrome within 10 hours of administration of treatment, compared with eight patients (22.9%, 11.8% to 39.3%) in the prazosin group; P<0.001 (table 4). The mean time required for clearing of syndrome and recovery in the antivenom plus prazosin group was 8.0 hours (95% confidence interval 6.5 to 9.5), which was significantly shorter (mean difference −9.7 hours, −6.9 to −12.4) than for those treated only with prazosin (17.7 hours, 15.4 to 19.9; P<0.001). The median recovery time for patients treated with antivenom plus prazosin (7 hours) was significantly less than that for patients treated with only prazosin (18 hours; P<.0.001).

Patients in the antivenom plus prazosin group required significantly (P<0.001) fewer doses of prazosin (mean 2.3, 95% confidence interval 2.1 to 2.5) than the prazosin group (mean doses 4.4, 95% CI 4.0 to 4; mean difference −2.0, 95% CI −2.5 to 1.6). Fewer patients in the antivenom plus prazosin group (12/35, 34.3%) developed hypotension than those in the prazosin only group (19/35, 54.3%), but this difference was not statistically significant (P=0.092, tables 3 and 4).

Laboratory values for haemoglobin, white cell count, and creatine kinase-MB were similar between the groups (table 5).

Both groups showed a significant (P<0.001) decline in blood pressure (mean arterial pressure) from the reading on admission (table 3). The pattern of improvement was similar in both groups (P=0.838); the difference between groups was non-significant (P=0.982). Patients with hypotension recovered after treatment with intravenous crystalloid solution.

Table 3 | Recovery time for clinical syndrome

Clinical sign	Prazosin (n=35)	Prazosin plus antivenom (n=35)	P
Sweating, mean (SD) hours	6.6 (2.6)	3 (1.1)	<0.001
Salivation, mean (SD) hours	3.0 (1.9)	1.9 (.9)	0.008
Priapism, mean (SD) hours	9.4 (1.5) (n=24)	4.7 (1.5) (n=27)	<0.001
Cold extremities, mean (SD) hours	17.3 (6.6)	8.5 (5.3)	<0.001
Number (%) with hypotension	19 (54.3)	12 (34.3)	<0.001

Table 4 | Comparison of endpoints between the groups

End point	Prazosin plus antivenom (n=35)	Prazosin (n=35)	Mean difference (95% CI)	P
Clearing of syndrome within 10 hours	32 (91.4%)	8 (22.8%)	68.5% (51.8 to 85.2)	<0.001
Mean recovery time, hours (95% CI)	8 (6.5 to 9.5)	17.7 (15.4 to 19.9)	−9.7 (−6.9 to 12.4)	<0.001
Deterioration to grade 3/4	4 (11.4%)	5 (14.3%)	−2.9% (−18.5 to 12.8)	>0.999
Mean prazosin dose (95% CI)	2.3 (2.1 to 2.5)	4.4 (4.0 to 4.8)	−2.0 (−2.5 to −1.6)	<0.001

Severity of scorpion sting depends on the dose of venom, size of scorpion, season, age of victim, and time between sting and hospital admission. Nine participants (six children and three adults) deteriorated to grade 3 (five from the prazosin group and three from prazosin plus antivenom group) or grade 4 (one from the prazosin plus antivenom group). They all reported more than 130 minutes between sting and admission and had mean systolic and diastolic blood pressure of 159 mm Hg and 105 mm Hg, respectively. Three of these patients had a heart rate of <60 beats per minute and six had a rate of >110 beats per minute. All nine patients had repeated projectile vomiting and vomited their initial dose of oral prazosin (injectable prazosin is not available in India) so that their repeated first dose was received 60 minutes late. All of them had persistently raised blood pressure. The difference between the groups was not statistically significant (P>0.999).

The patients who deteriorated to grade 3 recovered after treatment with nasal oxygen, intravenous aminophylline, and dobutamine drip. The patient whose condition deteriorated to grade 4 was a 13 year girl who was stung on the left foot by a scorpion at 10 pm. A red scorpion was found in her bedding and was killed. Soon after the sting she vomited twice, profusely sweated, salivated, and had paraesthesia around the mouth. She reported to the hospital at 3 am. On arrival her blood pressure was 140/104 and heart rate 128; she had grade 3/6 systolic murmur, cold extremities, sweating, and absent salivation. Total white cell count was 23,thin.000 and creatine kinase-MB was 62. She was given 30 mL antivenom and 500 µg prazosin. She developed marked tachycardia (heart rate 170 beats per minute) and warm extremities with blood pressure 95/70 mm Hg and pulmonary oedema (grade 4). She was given nasal oxygen, dobutamine 15 µg /kg/minute was raised to 20 µg, and oxygen saturation was maintained by non-invasive ventilator for 24 hours in intensive care.

DISCUSSION

We found that in patients treated for scorpion sting with scorpion antivenom and prazosin incidences of improvement and deterioration were similar to those in patients treated with prazosin alone, and the addition of antivenom hastened recovery.

Previous studies

Stimulation of α receptors has an important role in the pathogenesis of venomous scorpion sting.[6 13] In experimental studies, the major physiological abnormality is stimulation of peripheral α_1 adrenergic receptors by venom leading to blood pressure response. For this reason prazosin, an α receptor blocker, has been successfully used to reverse toxicity and improve survival.[3 11 12] By blocking α_1 receptors, prazosin reduces preload and left ventricular impendence without raising heart rate.[9] Prazosin is a simple pharmacological and physiological antidote to venom actions that is easily available in rural settings[9] making it the standard first line management.[11 12] Of 619 patients with severe envenomation by *Mesobuthus tamulus* admitted at Mahad, hypertension was noted in 55%, pulmonary oedema in 27%, tachycardia with hypotension in 18%; all recovered with oral prazosin.[25] Similar beneficial effects of prazosin have been reported from other states of India,[7 26] Saudi Arabia,[12] and Turkey.[27 29] Impressive reductions in mortality from *Mesobuthus tamulus* sting have also been observed with the use of prazosin; from 26% in 1961 to 6% in 1980, and less than 1% at present.[11] In regions where venomous scorpion sting is endemic, prazosin is a "darling" among the drugs kept ready in the outpatient department emergency tray; consultants in these areas even carry two tablets in their bags.[38] Several specific scorpion antivenoms are available but their efficacy is uncertain.[18 19] Ancillary treatment with vasodilators is crucial in severely envenomed patients.[5 39]

Scorpion antivenom has been available for clinical use in India since 2002, but it is always in short supply and not easily available in pharmacies, whereas prazosin is freely available.[33 40] Our experience of severe scorpion sting cases since 1977 shows that mortality can be dramatically reduced even in the absence of anti venom.[11 12 20 26 29] Although the regimen including scorpion antivenom hastens recovery it is not mandatory.[39 40] Species specific antivenom is needed to neutralise the circulating venom; however, prazosin, by antagonising sympathetic overactivity and correcting deranged metabolism, is effective against envenomation by different scorpion species.[7 12 16 17 19] In severe scorpion envenomation the dose of antivenom required is much higher than that noted in an experimental animal study.[35 41] The scorpion stinger by which venom is injected is short and sharp, 3-4 mm

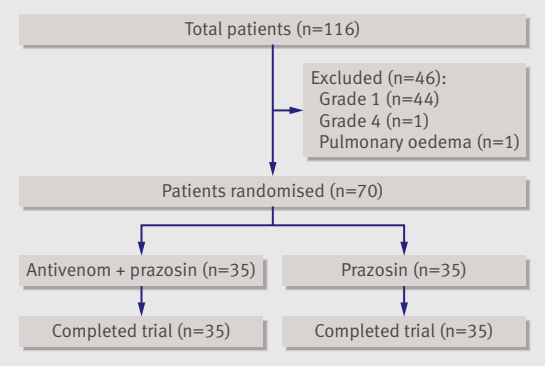

Fig 2 | Trial profile

Table 5 | Laboratory investigations. Data are mean (SD)

Laboratory investigation	Prazosin (n=35)	Prazosin plus antivenom (n=35)	P
White blood cells ($\times 10^9$/L)	16.09 (3.87)	15.48 (4.08)	0.522
Creatine kinase-MB (U/L)	60.1 (23.5)	51.6 (14.9)	0.074
Haemoglobin (g/L)	12.3 (20)	12.4 (20)	0.840

long, enabling it to deposit the venom skin deep (the full thickness of human skin is 1.5-4 mm). Skin circulation is sluggish and normally remains quiescent. Soon after stinging the rapidly absorbed venom evokes autonomic storm owing to sudden pouring of endogenous catecholamine into the circulation. α_1 receptors are stimulated by the circulating catecholamine, causing cold skin as a result of vasoconstriction, which further arrests the absorption of venom from the sting site. Toxicokinetic studies in rabbits showed that scorpion venom was rapidly taken up by organs and tissues, with an estimated half life of two to six minutes after venom injection.[6]

Moreover small doses of scorpion antivenom (such as the 10 mL dose used in a previous report of 25 cases from Mahad) have not been effective in preventing morbidity and mortality caused by *Mesobuthus tamulus* sting. This led us to conclude that the role of antivenom in severe scorpion sting needed to be re-examined and that prazosin is the standard of care to overcome the autonomic storm.[37 38]

Strength and limitations

We are not aware of any previous randomised controlled trials comparing the usefulness of mono-specific F(Ab)2 scorpion antivenom plus prazosin against prazosin alone in severe scorpion sting by *Mesobuthus tamulus*. The number of cases of envenoming peaks in the hot months of the year, May and October (table 1) because of increased agricultural activities. Men are more prone to these accidents owing to greater environmental exposure (table 2). Twenty eight per cent of the study population were younger than 18 years. Our findings in relation to a substantial number of patients with grade 2 envenomation included in this study support a firm conclusion about the efficacy of antivenom plus prazosin in victims reporting within six hours of sting with systemic involvement. Cases of grade 3 and grade 4 envenomation were not included in the present study, as required by the ethics committee. Large randomised trials including victims with grade 3 and 4 envenomation will be needed to demonstrate the effect of antivenom and prazosin on end points such as survival.

This study was not blinded and the primary outcome was evaluated by study investigators, albeit investigators with extensive clinical experience with scorpion sting.[1 9 11 20 25 33 34] The determination of the point at which symptoms disappeared was thus subjective, but we think that this was a clinically relevant and pragmatic way of judging the effects of treatment in a trial carried out in challenging circumstances with restricted resources in a rural setting in India.

Scorpion venom evokes transient parasympathetic and prolonged sympathetic stimulation. The presence of clinical signs and symptoms of excess acetylcholine indicate the presence of active free circulating venom in the blood, which can be neutralised by antivenom. The sympathetic signs suggest after effects of venom on the sympathetic system, which are unresponsive to antivenom but reversible with prazosin. Moreover morbidity and mortality due to envenoming are caused by sympathetic overstimulation and not parasympathetic stimulation.[1-4 11] Thus, early administration of antivenom in a stage of acetylcholine excess and prazosin to counteract the sympathetic and metabolic effects may be synergistic in enhancing recovery.[1-4 10 12 15 17] On arrival, absence of sweating and salivation that was present before reporting to the hospital suggests that venom has already reached the target site of action and is not accessible to the administration of antivenom,[22] as in our patient who deteriorated to grade 4.

Total doses of prazosin required were significantly lower in the antivenom plus prazosin group than in the prazosin alone group, suggesting that timely administration of scorpion antivenom leads to rapid neutralisation of circulating venom, resulting in minimum venom available for neuronal sodium channel activation. Amelioration of parasympathetic stimulation (sweating, salivation, arrhythmias) by antivenom may have accounted for the lower incidence of hypotension in the antivenom plus prazosin group. Leucocytosis and raised cardiac enzymes were suggestive of the release of cytokines such as interleukin-6.[22 38]

No participant had a mild or severe reaction to antivenom. High circulating catecholamines induced by venom prevent a reaction to antivenom and act as a prophylaxis against anaphylaxis.[42] Administration of the minimum first dose of prazosin prevented the development of the first dose phenomenon.[43]

Owing to unavailability of an ELISA test for detection of venom antigen and antivenom in blood we could not perform a correlation with clinical manifestations. Facilities for analysis of serum catecholamine levels are not available at Mahad. We could not enrol patients with grade 3 and 4 severe scorpion stings owing to restriction by the ethics committee. Withholding the lifesaving drug prazosin would be unethical in a life threatening situation; hence it was included in both the arms of the trial and no placebo group was included.

Conclusions and policy implications

Early administration of antivenom within six hours of sting in addition to prazosin hastened the recovery and shortened the hospital stay in a rural setting. Although the rapid recovery in patients treated with antivenom is an advantage, the total cost of treatment with antivenom approaches a month's salary for a labourer in the region —10 mL of antivenom costs Rs350 (£4.97, €5.82, $7.77) —while the cost of 10 tablets of 1 mg prazosin is Rs32 (£0.49, €0.58, $0.77). The dose of prazosin administered

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prazosin is a known antidote to *Mesobuthus tamulus* scorpion venom.

Antivenom is also now available but scientific clinical data are scarce.

WHAT THIS STUDY ADDS

Addition of scorpion antivenom to prazosin enhances recovery time and shortens hospital stay in patients with grade 2 *Mesobuthus tamulus* envenomation.

was 250 µg in children up to age 18 and 500 µg in adults. Administration of prazosin at an interval of three hours prevented development of pulmonary oedema and led to rapid recovery as reported previously.[33] The results of the present study would be applicable in settings such as primary health centres, where the majority of the victims first present.[1] Scorpion sting is a potentially life threatening time limiting acute medical emergency, hence it would be unethical to withhold the standard treatment for want of a scientific trial.[33]

Despite much experience of severe scorpion envenomation in endemic regions throughout the world, a standard treatment protocol using drugs and antivenom is lacking.[15 21 37] Randomised controlled trials for treatment of severe scorpion envenomation on which such guidelines can be based are scarce.[18-21]

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