SCORPION VENOM BIOLOGY

The scorpion does not always inject the venom when it stings, since it can control its ejaculation to total, partial or nonexistent (dry sting). Telson (venom vesicle gland) is surrounded by striated muscular layer facilitating and regulating venom ejections explains the variation of intensity of symptoms and existence of "dry" sting without envenoming. The scorpion venom is a mixture of various active substances namely polypeptides and enzymes. Venom consists of: (1) neurotoxin, which acts on the respiratory, vasomotor centers, nerve terminals and end plates of both striped and unstriped muscles, (2) hemolysins, agglutinins, hemorrhagins, leukocytolysins, coagulins, lecithin, cholesterol, cardiotoxins, nephrotoxins, hyaluronidases, phosphodiesterases, phospholipases, glycosaminoglycans, histamine, tryptophan and cytokine releasers. Also, a number of free amino acids and serotonin are isolated from the venom. Of the scorpion venom toxins, neurotoxins are the most important and they contain peptides that block the sodium channels (beta-toxins). There is massive release of endogenous catecholamines into the circulation due to delayed activation of sodium neuronal channels by the venom. The main molecular targets of scorpion neurotoxins are the voltage gated sodium channels and potassium channels including calcium activated potassium channels. Iberiotoxin and tamulotoxin content of the scorpion (Mesobuthus tamulus) venom are the only selective inhibitors of potassium channel. Sodium and potassium channel blocking toxins of scorpion venom mediate synergistic effects responsible for intense and persistent depolarization of autonomic nerves with massive release of autonomic neurotransmitters evokes an "autonomic storm" response. The stimulation of nitriergic nerves supplying penile smooth muscles may explain the priapism observed in severe scorpion envenoming (these nerves run from brain to spinal cord in independent pathway to supply penile smooth muscle for vasodilation, i.e. other than sympathetic and parasympathetic tracts pathway).

Scorpion venom contains serotonin, which may cause local pain at the site of sting. Multiple toxins may be present in the venom of a single species of scorpion capable of producing potent synergistic effects in victim. Venom of Tityus trinitatis in Trinidad is pancreotoxic responsible for development of acute pancreatitis, acute edematous and hemorrhagic pancreatitis with development of pancreatic pseudocysts.

EPIDEMIOLOGY

Out of 1,500 scorpion species known to exist, about 30 are of medical importance. Although a variety of different scorpion species exist, majority of them produce similar effects. Most scorpion species produce venom, which causes only minor local reactions in humans, but in certain parts of world including certain parts of India scorpion stings are a serious (sometimes fatal) health hazard. Scorpions capable of inflicting fatal stings are all members of the families Buthidae and Scorpionidae. Except for Hemiscorpius lepturus, all venomous scorpion species belong to the large family Buthidae. Examples of most deadly species are Androctonus australis (North Africa and Middle East), Androctonus crassicauda (Turkey, Middle East and North Africa), Buthus occitanus (countries bordering Mediterranean and Middle East), Leiurus quinquestriatus (North Africa and Middle East), Parabuthus (South Africa), Tityus trinitatis (Trinidad and Venezuela), Tityus bahiensis (Brazil, Argentina), Centruroides sculpturatus (California, New Mexico, Arizona and Baja California) and Mesobuthus tamulus (India). Painful scorpion stings are a common event throughout the tropics; however, fatal envenoming is frequent only in parts of Latin America, North Africa, Middle East and India.

In India, 86 species of scorpions have been identified; two types of poisonous species are important namely the small red Buthus tamulus and the large black Palamneus gravimanus; of the two Buthus tamulus is more toxic. Mesobuthus tamulus (the Indian red scorpion) is the most lethal amongst all poisonous species of scorpions in India with fatalities in adults and children. Mesobuthus
CLINICAL FEATURES
Venom is deposited deep to subcutaneous tissue after sting; almost complete absorption of the venom from sting site would occur in 7–8 hours (70% of maximum concentration of venom in the blood reached within 15 minutes of sting). The severity of envenoming is related to age (high fatality is seen in children and 50% mortality in less than 4 years old in the past), size of scorpion and the season of sting (April to early June and September to October).

Clinical presentation can be divided into local manifestations and systemic manifestations.

Local Manifestations
Severe excruciating local pain is the only clinical manifestation seen in 55% of cases. It is radiating along the corresponding dermatomes. Local signs such as swelling, redness, heat and regional lymph node involvement are never extensive. Stings typically do not produce a visible skin lesion, although on rare occasion a small red mark is noted. Local edema, urticaria, fasciculation and spasm of underlying muscles are rarely seen at the site of sting due to persistent stimulation of pain receptors and the liberated serotonin. Positive tap test is present (on tapping increase in paresthesia occurs) in some patients. Due to pain there is transient bradycardia, transient rise in blood pressure and sweating with warm extremities. Most scorpion stings are minor, producing severe local pain and paresthesias without systemic involvement (benign or dry sting).

Systemic Manifestations
Scorpion venom delays the closing of neuronal sodium channels, resulting in “autonomic storm” owing to sudden outpouring of endogenous catecholamines into the circulation. Systemic symptoms may develop within minutes, but may be delayed as much as 24 hours. Features of autonomic nervous system excitation are transient cholinergic and prolonged adrenergic stimulation. Initial parasympathetic excitation is characterized by vomiting once or twice, profuse sweating (skin diarrhea for 3–17 hours), ice cold extremities, hypersalivation and thick mucus secretion due to stimulation of bronchial mucus glands, lacrimation, pin-point pupils, diarrhea, abdominal distension, priapism, bradycardia and hypotension. Prolonged massive release of catecholamines, as in pheochromocytoma, later produces restlessness, piloerection, marked tachycardia, mydriasis, hyperglycemia, hypertension, toxic myocarditis, cardiac failure and pulmonary edema. All forms of electrocardiogram (ECG) abnormalities are noted and include sinus tachycardia, ventricular premature beats, couplets, transient nonsustained ventricular tachycardia, rarely fatal arrhythmias and ST-T changes closely resemble congenital QT interval syndrome. The outpouring of catecholamines is probably a major factor in the pathogenesis of ST-T changes. The possibility of direct effect of toxin on the myocardium cannot be excluded. The major manifestations include hypertensive crisis and life-threatening pulmonary edema, which may be fatal if not treated timely. Endogenous hypercatecholemia could also explain hyperglycemia and glycosuria in some cases. Hemiplegia and other neurological lesions have been attributed to fibrin deposition resulting from disseminated intravascular coagulation (DIC). On basis of clinical manifestations scorpion envenoming is graded into four grades in India:

- **Grade 1**: Severe excruciating local pain radiating along corresponding dermatomes, mild local edema at the site of sting without systemic involvement.
- **Grade 2**: Signs and symptoms of autonomic storm characterized by parasympathetic and sympathetic stimulation.
- **Grade 3**: Cold extremities, tachycardia, hypotension or hypertension with pulmonary edema.
- **Grade 4**: Tachycardia, hypotension with or without pulmonary edema with warm extremities (warm shock).

MANAGEMENT
No scorpion sting should be taken as benign unless observed for 24 hours irrespective of species involved. On the basis of pathophysiology, therapeutic effort should be directed against the venom, overstimulated autonomic nervous system and correction of hypovolemia.

LOCAL TREATMENT
Mild pain can be abolished by application of ice packs over the site of sting. Severe excruciating local pain can be transiently relieved by lignocaine (without adrenaline) using ring block. However, oral diazepam and nonsteroidal anti-inflammatory drugs (NSAIDs) with lignocaine block can give prolonged relief from pain. Keeping patient calm, applying pressure dressings and ice packs to the sting site decreases the absorption of venom. Incision at the site of sting or tourniquet application is not advisable at all.

Patients suspected of envenomation should be hospitalized for at least 12 hours and observed for cardiovascular and neurological sequelae. Stings of nonlethal species require at most ice packs, analgesics and antihistamines.

TREATMENT OF SHOCK
Treatments of shock are: (1) Foot end of bed to be elevated to maintain cerebral circulation in cases of peripheral circulatory failure; but if left ventricular failure is present back rest is advised, (2) Dehydration, electrolyte imbalance due to vomiting, excessive salivation and profuse sweating should be corrected by oral and parenteral fluids. Intravenous glucose, normal saline given in sufficient volume judiciously as there will be heart failure in some cases and (3) Hydrocortisone 100 mg IV repeated every 4 hours helps to tide over the shock and decreases edema of conductive tissues in toxic myocarditis.

TREATMENT BY PRAZOSIN
Prazosin is pharmacological and physiological antidote to scorpion venom actions; it is a competitive postsynaptic alpha-1 adreno-receptor antagonist. Prazosin has 1,000 fold affinity to alpha receptors (alpha receptors stimulation plays a major role in the evolution of myocardial dysfunction and acute pulmonary edema in scorpion sting). Prazosin inhibits phosphodiesterase, thereby enhancing cyclic guanosine monophosphate (cGMP) level, which is one of the mediators of nitric oxide synthesis. It also enhances insulin secretion that is inhibited by scorpion venom by which it counters hyperglycemia and hyperkalemia. This alpha-1 adrenergic receptor blocker reduces preload, left ventricular impedance without causing...
tachycardia. It totally reverses the metabolic and hormonal effects of alpha receptor stimulation. Thus, its pharmacological properties can antagonize the hemodynamic, hormonal and metabolic effects of scorpion venom. Prazosin (plain tablet not sustained release form) is administered orally as 1 mg in adults (children 30 µg/kg). Prazosin should be given through a nasogastric tube if the patient is vomiting and the patient should be kept in lying posture for about 3 hours (even during examination) in order to prevent the “first dose hypotension phenomenon”. Repeat prazosin in the same dose after 3 hours depending on the clinical response and later every 6 hours (not exceeding 5 mg total in a day) till the extremities are warm, dry and the peripheral veins are visible easily. Prazosin can be given irrespective of blood pressure provided there is no hypovolemia.

Since the advent of prazosin, the fatality due to scorpion sting has been reduced to less than 1%. Prazosin is a cellular and pharmacologic antidote to the actions of scorpion venom and it is also cardioprotective; it should be the first line of treatment for severe scorpion stings. Prazosin is a poor man’s SAV. The time lapse between the sting and administration of prazosin for symptoms of autonomic storm determines the outcome.

ADVANCED SUPPORTIVE MANAGEMENT
Close attention to airway is required. Intubation and mechanical ventilation are sometimes necessary owing to venom effects and respiratory depression from the medications to control symptoms. Pulmonary edema is the most important cause of mortality and should be treated with propped up position, nasal oxygen, intravenous loop diuretics and prazosin. Inotropic support with dopamine and dobutamine 5–15 mg/kg/minute is advocated for 36–48 hours in warm hypotensive shock patients. Cardiac arrhythmias are many times self-limiting. Tachyarrhythmias are treated with intravenous metoprolol or esmolol and bradyarrhythmias can be controlled with atropine. Hypertension and pulmonary edema respond to nifedipine, nitroprusside, hydralazine, or prazosin. Defibrillation syndrome is managed conservatively or with heparin, fresh blood transfusion or fibrinogen infusions. Captopril, glucose-insulin-potassium drip, lytic cocktail (pethidine-chlorpromazine-promethazine) have also been tried to alleviate the venom effects but did not stand the test of time.

SPECIFIC TREATMENT BY ANTIVENOM
Scorpion antivenom as specific treatment has been a matter of debate and controversy during last 5 years; several previous studies have shown that SAV does not alleviate hemodynamic changes or cardiogenic pulmonary edema, or prevent death and the outcome was the same for victims treated with antivenom and without antivenom. But recent randomized controlled trials have overcome the controversy regarding beneficial effects of early administration of SAV. Commercially prepared antivenins are available in several countries for some of the most dangerous species; however, SAV is expensive and always in short supply. In the opinion of most authorities administration of antivenom is the only specific measure for severe scorpion sting poisoning. They were of opinion that polyvalent antivenin, if prepared, will be effective for scorpion sting cases for use anywhere in the world. They advocated 5–25 mL of antivenom diluted in two to three volumes of isotonic saline to be given intravenously over an hour. If there is no significant improvement, further doses of antivenom can be given (total dose of antivenom required is 30–100 mL in severe envenomation).

Scorpion antivenom is effective if a victim is brought at an early stage of scorpion sting (in a stage of acetyl choline excess) ongoing cholinergic phenomenon is suggestive of free circulating scorpion venom, which can be neutralized by SAV. Intravenous administration of antivenom rapidly reverses systemic toxicity features but not pain and paresthesia. No test dose is required as there are high circulating catecholamines and anaphylaxis is very rare. Addition of SAV to prazosin enhances recovery time and shortens hospital stay in patients with grade 2–4 *Mesobuthus tamulus* envenomation in India.

OTHER MEASURES
Administration of oral L-carnitine in a dose 1980 mg/day in three divided doses till the left ventricular function normalized is found beneficial (a study from emergency service of a tertiary care center in Andhra Pradesh showed no mortality and got benefited irrespective of severity of the sting). Prophylactic immunization with scorpion venom toxoid has been considered in Mexico.

BIBLIOGRAPHY