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Review Article

Scorpion sting envenomation - An Overview.

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Abstract

Scorpion stings are a major public health problem in many underdeveloped tropical countries, especially in rural parts of India. Patients often presents with life threatening complications. Envenomation due to scorpion sting results in various clinical manifestations. They range from mild local pain to diffuse intolerable pain of whole limb and body to systemic manifestation involving almost all systems, predominantly cardiovascular and may sometimes lead to death.

Key words: Envenomation, Management, Pathophysiology, Scorpions.

Introduction

Scorpion venom is a water soluble, antigenic, heterogeneous mixture, as demonstrated on electrophoresis studies. The venom is composed of varying concentration of neurotoxin, cardiotoxin, nephrotoxin, haemolytic toxin, phosphodiesterase, phospholipases, hyaluronidases, glycosaminoglycons, histamine, serotonins, and tryptophan and cytokine releasers [1-4].

The most potent toxin is the neurotoxin of which two classes exists. Both of these are heat stable, have low molecular weight and are responsible for causing cell impairment on nerves, muscles and heart by altering ion channels. Long chain polypeptide neurotoxin: causes stabilization of voltage dependent sodium channels in the open position, leading to continuous, prolonged repetitive firing of somatic, sympathetic and parasympathetic neurons. Short polypeptide neurotoxin: blocks, potassium channels. The binding of neurotoxin to host is reversible but different neurotoxins have different affinities.

The stability of neurotoxin is due to disulfide bridges that fold the neurotoxin into 3 dimensional compact structures thus making it resistant to PH and temperature changes However reagents which can break the disulfide bridges can inactivate this toxin. The antigenicity of the toxin is dependent on length and number of exposed regions that are sticking out of 3 dimensional structures. The understanding of biochemical properties and the clinical effects of the venom, have important implications in designing appropriate therapeutic interventions [5, 6].

Fatal dose of scorpion venom

From various experiments it is found that scorpion venom is more toxic than snake venom on weight basis but scorpions inject very little venom. The median lethal doses of various scorpion venoms in mg/kg when injected in to mice are as follows[7, 8]. In general most lethal scorpions have LD50 below 1.5 mg/kg.

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Sl. No	Scorpion Species	Territory	LD 50
1	Ceiurus quinquestrriatus	Middle East	0.25 mg/kg
2	Androctonus Crassicauda	Middle East	0.08-0.5 mg/kg
3	Centuroids Noxius	Mexico	0.26 mg/kg
4	Androctnous Mauritanicus	North Africa	0.32 mg/kg
5	Centruroids Santa Maria	Central America	0.39 mg/kg
6	Tytus Serrulatus	Brazil	0.43 mg
7	Buthus Occitanus	North Africa	0.9 mg/kg
8	Centruroids Scalp Turatus	USA	1.12 mg/kg
9	Mesobuthus Eupeus	Iran	1.45 mg/kg
10	Heterometrus Bengalensis	India	3.6 mg/kg

Table-1 Showing various scorpion species and lethal doses of their venom

Mechanism of action of venom

The scorpion toxic peptides are broadly classified as alpha and beta toxins. Alpha toxins (Mesobuthus sps.) block voltage - dependent inactivation of sodium channels and toxins shift voltage dependent activation of these channels to a more negative membrane potential. Voltage - gated sodium channels are integral membrane proteins that permit selective permeation of sodium channels across biological membranes, thus causing generations of action potentials in excitable cells [9, 3, 6]. Beta toxin with short chain polypeptide which is main constituent in centruroides species blocks the potassium channels. The stimulation of sodium channels and the inhibition of potassium channels, both lead to intense, persistent stimulation of autonomic nerves, predominantly ± receptors, leading to massive release of neurotransmitters from adrenal medulla, stimulating parasympathetic and sympathetic nerve endings, thus initiating "Autonomic storm" [10].

Clinical features

The signs of the envenomation are determined by the scorpion species, venom composition, and the victim's physiological reaction to the venom. The signs occur within a few minutes after the sting and usually progress to a maximum severity within 5 hours. The signs last for 24-72 hours and do not have an apparent sequence. Thus, predicting the evolution of signs over time is difficult. Furthermore, a false recovery followed by a total relapse is common. In India, Israel, Brazil and Mexico, cardiac manifestations are more 2 common. In Iran, tissue necrosis and hemolysis predominate. Neurological manifestations are prominent in USA and South Africa, while acute pancreatitis is the 2 principal manifestations in Trinidad.[9] The toxicity variation and duration of the symptoms depends on the following factors [9-14].

Species, Size of the scorpion, Number of stings and the quantity of the venom injected, Depth of the sting, Composition of the venom are the factors related to scorpion. However Age, Health, Weight of the victim relative to the amount of the venom, Site of envenomation closer proximity of the sting to the head and torso results in quicker venom absorption into central circulation and quicker onset of symptoms, Presence of co-morbidities, Timing of initiation of treatment and Changes in body temperature are the factors related to victim.

Cardiovascular manifestations dominate the clinical picture in India, especially so with stings by Mesobuthus tamulus (Indian red scorpion). Severe local reactions, acute pancreatitis and CNS manifestation are encountered less frequently in India.[9] The grading of this scorpion envenomation depends on whether or not neurological signs predominate and is as follows: Neurologic predominance [11].

Grade I - Local pain or paresthesia at the sting site
Grade II - Pain or paresthesia that has traveled from the sting site
Grade III - Either cranial nerve or somatic neuromuscular dysfunction
Grade IV - Both cranial nerve and somatic neuromus - cular dysfunction

Severity of manifestations of Scorpion stings are graded as follows, [15]

Grade I : Local pain and paresthesia without any systemic manifestation
Grade II: Patient with pain and paresthesia distant from the site of sting with or without tachycardia and without cardiorespirato - ry signs
Grade III: Patients with peripheral circulatory failure, cardiovascular and respiratory manifestations.
Grade IV: Patient with central nervous system manifestation and multisystem involvement.

Local effects

Pain: This is the commonest clinical feature. A sharp burning, pain sensation at the site of sting which gradually spreads to involve the whole limb within few minutes to hours [9, 11, 16, 17] Pain usually last for 12 - 24 hours but occasionally up to two days. This is followed by a sensation of paresthesia which feels like an electric current, which may persists for weeks and is the last symptom to resolve before the victim recovers[11]. Tap test is administered by tapping at the site.

A positive test result is when the paresthesia worsens with the tap, because the site is hypersensitive to touch and temp, infarct wearing clothing over the area and sudden temp changes exacerbate the symptoms [9, 18].

Autonomic nervous system signs

Mesobuthus tamulus envenoming, evokes a potent autonomic response, characterized by transient cholinergic manifestations, later merging imperceptibly with features of adrenergic stimulation. Early cholinergic over activity, hypotension, hypertension, myocardial dysfunction, pulmonary edema and shock is a spectrum of one process, namely autonomic storm. They may be predominantly sympathetic signs, parasympathetic signs or combination of signs. Hypotension and bradycardia is encountered initially within 1 - 2 hours of sting (cholinergic stimulation), hypotension and tachycardia between 4 - 48 hours due to severe Left Ventricular dysfunction and hypotension alone, with good volume pulse and warm extremities later in the recovery stage. Myocardial dysfunction, pulmonary edema and carcinogenic shock may occur later in the course and are considered part of the "autonomic storm" and not as separate syndromes[9].

Pathophysiology of Scorpion Sting Envenomation

Cardiovascular system Manifestation: Cardiac dysfunction characterized by myocarditis, left ventricular failure and carcinogenic shock, may complicate the clinical picture. Tachycardia: is the commonest finding usually seen with in first 4 hours and may persist for 24 - 72 hours, bradycardia can also be observed. Hypertension: it is secondary to catecholamine and rennin stimulation, seen as early as 4 minutes after envenomation, lasts for 4 - 8 hours, it may be high enough to produce hypertensive encephalopathy, cardiac failure, pulmonary edema. Cardiovascular collapse: Occurs due to biventricular dysfunction due to myocarditis and profuse loss of fluids from sweating, vomiting diarrhea, catecholamine induced cardiac ischemia. However, some case series from south India, report peripheral circulatory failure and hypotension initially, with myocarditis observed only during follow-up[9, 11].

Pathophysiology of Cardiovascular Manifestation
These are mediated via stimulation of both parts of autonomic nervous system with a predominance of sympathetic stimulation and [2,8] release of tissues and medullary catecholamine. Typical effects are initial bradycardia followed by tachycardia and also initial short period of hypotension due to cholinergic effect and a secondary but relatively prolonged hypertension[2].

On myocardium: Pathogenesis of catecholamine induced myocardial necrosis is multifactorial. Catecholamine induced vasospasm and increased myocardial metabolism leading to hypoxia which is supported by finding that more severe lesions are located near cardiac apex [19, 20, 21].

The effects of alpha receptor stimulation lead to suppression of insulin secretion, hyperglycemia, hyperkalemia, free fatty acid and free radical accumulation, which are injurious to the myocardium. Excess of noradrenalin also induces changes in permeability of the sarcolemma membrane leading to increased calcium influx this increased intracellular calcium has a direct toxic effect giving rise to cellular necrosis[6,22-24]. Animal studies on the effect of Indian red scorpion venom, have demonstrated cardiac sarcolemmal defects, depletion of glycogen content of liver, heart and skeletal [22]muscles in myocarditis.

Hypertension: Hypertension is one of the commonest cardiovascular manifestations of scorpion sting envenomation; this is due to massive outpouring of catecholamine from adrenal medulla and also from postganglionic neurons[10,25].

Hypotension: Probable mechanisms are early cholinergic stimulation, vasodilator effect, increased quantities of potent vasodilators like kinins, prostaglandins, Catecholamine depletion and cardiogenic shock[9,25]. While Cardiac arrhythmias can occur due to either autonomic dysfunction or electrolytic imbalance in particularly hyperkalemia. Other electrolyte abnormalities which are implicated are hyponatremia, hypocalcaemia and hypomagnesaemia) are reported. Scorpion venom increases the membrane permeability to Na+ by stabilizing voltage sensitive Na+ channels in open state, and this effect is associated with Ca+ entry and blockage of Ca+ dependent K+ channels disturbing trans membrane K+ gradient resulting in either absolute or relative hyperkalemia. Other factors like decreased insulin secretion, increased catecholamine also play a role in hyperkalemia[21, 25-28].

Central nervous system Manifestation

Patient may have CNS manifestations in the form of altered sensorium, irritability, restlessness confusion and delirium. Patient may also have an abnormal behavior; thalamus induced systemic paresthesia in all four limbs which is usually seen within 3 - 4 hours of sting. Patient may develop venom induced cerebral thrombosis resulting in strokes, which occurs after

24 - 48 hours after sting. Other less significant manifestation is rigid spastic muscles of limbs and torso, involuntary muscle spasm, twitching, clonus and contractur, alternating episthotonus and opisthotonus, increased tendon reflexes [25, 29].

Cerebrovascular manifestations with neurological deficits were noted in 4 patients in a care series of 50 cases of scorpion sting in Madras[30]. The stroke was secondary to thrombosis in 2 patients and secondary to hemorrhage in 2 patients. Patients sometime presents with seizure. Priapism Bawaskar has noted occurrence of this clinical symptom in as many as 10% of his patients. He noticed subsequent development of cardiac manifestations in all these patients who had priapism. Hence he had considered priapism as one of the premonitory signs of cardiac complications in case of scorpion sting. The priapism is more common in scorpion sting due to Buthus tamulus[30-32].

Pathophysiology of Central Nervous system Manifestation

Cerebrovascular manifestations are uncommon in scorpion stings in the Indian subcontinent[30, 33]. But neurological manifestations are well documented in stings due to Mesobuthus tamulus. The causes of neurological manifestations are multifactorial. The neurotoxin in the venom acts on respiratory center, vasomotor center, nerve terminals and on end-plate of both striated and non-striated muscles[34]. The Neurotoxin may produce convulsions by inducing cortical irritation[35]. Stroke may occur due to thrombosis or hemorrhage, or following intense cerebral 32vasospasm, induced by autonomic storm. Further, hematological changes induced by the effect of the venom, may cause DIC and multiple cerebral 29infarctions. Scorpion envenomation leads to a high arterial blood pressure by a massive catecholamine discharge. When arterial blood pressure is excessive it leads to cerebral damage (edema and ischemia), explaining the observed neurological signs. This hypothesis was advanced in some studies which reported anatomical abnormality in the central nervous system secondary to severe scorpion envenomation, such as hemorrhagic, ischemic, and cerebral infraction[36-38].

Hence it was thought that CNS manifestations are primarily due to peripheral effect of catecholamine and CNS dysfunction is the result and not the cause of many manifestations of scorpion envenomation[3]. In some cases direct effect of toxin on neurons could contribute to seizures and encephalopathy. However, hemiplegia and other neurological lesions have been attributed to fibrin deposition resulting from DIC[9]. Scorpion venom has both excitatory and inhibitory effect on neuromuscular junction. The venom of Centuroides sculpturatus acts at the pre-synaptic terminals of the neuro-muscular junction, causing depolarization. The depolarization causes increased calcium permeability at pre-synaptic terminals provoking entry of calcium ions and acetylcholine release, resulting in muscle twitching and fasciculation. Further, scorpion venom may produce paralytic or myasthenia like effect on neuromuscular junction, due to persistent depolarization or due to depletion of acetyl 2choline from pre-synaptic terminals[9].

Respiratory system Manifestations

They include cough, breathlessness, wheeze, tachypnea and hyperventilation. Pulmonary edema is a life threatening complication following scorpion sting by Mesobuthus tamulus species. It develops within 30mins to 3 hours following a sting. Pulmonary edema may be due to both cardiogenic and non-cardiogenic causes. Patient presents with cough, dyspnea, pink frothy sputum and cyanosis, usually fatal if unattended. Respiratory failure may occur due to medullary respiratory depression or secondary to diaphragm paralysis[9].

Pathophysiology of Respiratory Manifestations

There are various factors responsible for respiratory manifestations and pulmonary edema. Scorpionism leading to life threatening pulmonary edema has to been well documented in India. A direct toxin induced increase in pulmonary vessel permeability is thought to be a fundamental pathology in acute pulmonary edema[9,11]. Pulmonary edema has also been attributed to be secondary to the catecholamine - induced effects of hypoxia and intracellular calcium accumulation on myocardium, leading to decrease in left ventricular compliance, left ventricular dilatation and diastolic dysfunction[11]. Myocarditis and consequent left ventricular systolic dysfunction also contributes to development of pulmonary edema. It also causes medullary respiratory depression[39].

Hematologic manifestations

There may be catecholamine induced platelet aggregation, resulting in thrombotic episodes and bleeding manifestations due to toxin induced DIC [9,11,25,40].

Pathophysiology of Hematopoietic manifestation

Experimental myocarditis induced by scorpion venom in animals has ++ demonstrated erythrocyte Na - K ATPase activity inhibition and increased red 38 cell fragility (probably secondary to inhibition by FFAs)." Occurrence of an abnormal coagulation

profile, acute DIC and Defibrination Syndrome, probably secondary to action of epinephrine on blood vessels has been demonstrated.

Renal Manifestations

Scorpion sting can produce a syndrome of oliguria, anuria and/or hematuria, associated with puffiness of face. Acute renal failure has also been reported and could be due to toxin-induced acute tubular necrosis, immune complex deposition, disseminated intra vascular coagulation or rhabdomyolysis[31, 41, 42].

Pathophysiology of Renal Manifestation

Pathology may be due to [31, 41, 42] decreased renal plasma flow (hypovolemia) and afferent arteriolar constriction, Toxin induced acute tubular necrosis, Immune complex glomerulonephritis, rhabdomyolysis, renal failure may result from venom induced excessive motor activity

Other systems

Local inflammation is unusual in Indian red scorpion Envenomation. But severe skin reactions, characterized by erythema, edema, lymphangitis and severe necrosis, is well known in Iran, in stings caused by Buthus cosmobuthus and Hemiscorpus species, probably secondary to polypeptide variations of different venoms[33]. The mechanism of pancreatitis has been thought to be due to conversion of trypsinogen to trypsin by scorpion venom, which increases permeability of pancreatic blood vessels leading to edematous and hemorrhagic pancreatitis the other mechanism is perhaps indirect stimulation of release of acetyl choline from pancreatic nerves[1,43].

Scorpion Venom and SIRS

Systemic Inflammatory Response Syndrome (SIRS) is triggered by envenomation following sting by Tityus serrulatus. Increased levels of IL-6, IL-1a and IFN-l and [6] inductions of iNOS were demonstrated in these cases. The levels of cytokines 2correlate with the severity of envenomation [9].

Investigations

The laboratory findings in case of scorpion sting has very limited role to play. No laboratory evaluation is uniformly helpful in the diagnosis and management of scorpion envenomation. The important investigations are ECG, echocardiography, cardiac enzymes, serum electrolytes, random blood sugar estimation.

Blood analysis

Erythrocyte sedimentation rate (ESR): ESR is likely to be abnormal in significant number of cases, it was found to be raised in 20% cases. However its clinical significance was not noted.

Leukocyte count: polymorphonuclear leukocytosis was noted in few cases of scorpion sting but not found to be pathologically significant.

Urine analysis

Urine color may be smoky / cola colored in nephritis. Proteinuria and hematuria - rarely noted with nephritis. Glycosuria. - Glycosuria has been documented in scorpion stings, Vanylmandelic acid (VMA) levels may be raised in urine and reflects increased metabolism of catecholamine [43].

Blood sugar

Hyperglycemia has been well documented following scorpion stings. Causes for hyperglycemia include: Catecholamine surge, reduced insulin secretion and rarely pancreatitis with beta - cell destruction [22,33]

Serum electrolytes

Hyponatremia and hypokalemia has been noted due to diaphoresis, vomiting and diarrhea. Hyperkalemia is a frequently observed finding in severe envenomation and could contribute to development of arrthymias[22]. Hypocalcaemia has also been noted following scorpion stings [11].

Serum enzymes

Levels of SGOT, SGPT may be increased due to venom induced - liver cell damage and myocarditis[11,45]. Serum amylase level may be elevated, and unless proved otherwise, is taken as a feature of pancreatitis.

Renal functions

Renal functions may be altered with elevation of blood urea and serum creatinine levels in cases with acute renal failure following scorpion sting [42, 46].

Electrocardiography

ECG is an important investigation which helps in diagnosis of fatal conduction disturbance, ischemia and very importantly myocarditis [9].

Chest radiography

Radiographic changes suggestive of pulmonary edema may be seen even within 3 hours of sting, even when asymptomatic. Radiographic changes noted in pulmonary edema include pulmonary vascular congestion, straight non-branching lines in the upper lung fields that run diagonally towards the hilum and inter-lobular septal edema[9].

Echo Cardiograph

Echocardiography is done to detect left ventricular systolic dysfunction. The following findings may be noted[9]. Left ventricular dilatation, Regional wall motion abnormalities, Decreased left ventricular ejection fraction.

Treatment of Scorpion sting

Treatment of scorpion sting was in its primitive stages till recently which primarily constituted application of various herbal medicines like tobacco leaves, tamarind juice, turmeric acid and mixture of calcium carbonate and jaggery and also placing areca nuts, particular stone, and roots of some plants at the site of sting which is believed to absorb the toxin. Antitoxin serum was first prepared in Egypt by Todd in 1909 and has been used since 1930s in some parts of the world with reasonable success. In 1970s and 1980s,' Lytic cocktail' was the mainstay of treatment of pulmonary edema and myocarditis[47]. The use of prazosin in the late 1980's, has revolutionized the management of cardiovascular complications of scorpion sting[48].

First aid

Reassurance of the patient, use of ice bags if available to reduce pain and to slow absorption of venom via vasoconstriction, Immobilize the affected part in a functional position below the level of heart to delay venom absorption, Application of tourniquet or pressure dressing, 1 inch proximal to the sting can be done to produce venous occlusion and delay the absorption of the venom. The tourniquet must be removed in 5 - 10 mins, but the limb is kept cool for alteast 2 hours [9,11].

General Measures

First and foremost is establishment of airway breathing and circulation as in other emergencies, Monitor vital signs frequently administer oxygen, Administer intravenous fluids to help prevent hypovolemia from sweating, vomiting, diarrhea, hyper salivation and and insensible water loss[11]. Tetanus prophylaxis should be administered, Local wound at the site of sting should be managed appropriately and topical or systemic antibiotics should be considered [11].

Management of Pain

Pain relief is essential as it allays anxiety, avoids myocardial stress and delays the absorption of the toxin[9, 49]. Relief of local pain following local injections of lignocaine and streptomycin has been documented. Streptomycin acts by its neuromuscular blockade effect on painful nerve endings[50]. Emetine hydrochloride injected locally has been found to be effective due to its counter irritant action, but is not recommended in children, for its adverse effects on myocardium. Local Ice packs reduce pain and also slow the absorption of toxin, due to vasoconstriction [50].

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