Review Article

Int. J. Chem. and LifeSci.
ISSN: 2234-8638
OPEN ACCESS

Mydriasis in Scorpion Envenoming Syndrome: Insulin administration reverses cardiovascular changes, pulmonary edema and all other clinical manifestations

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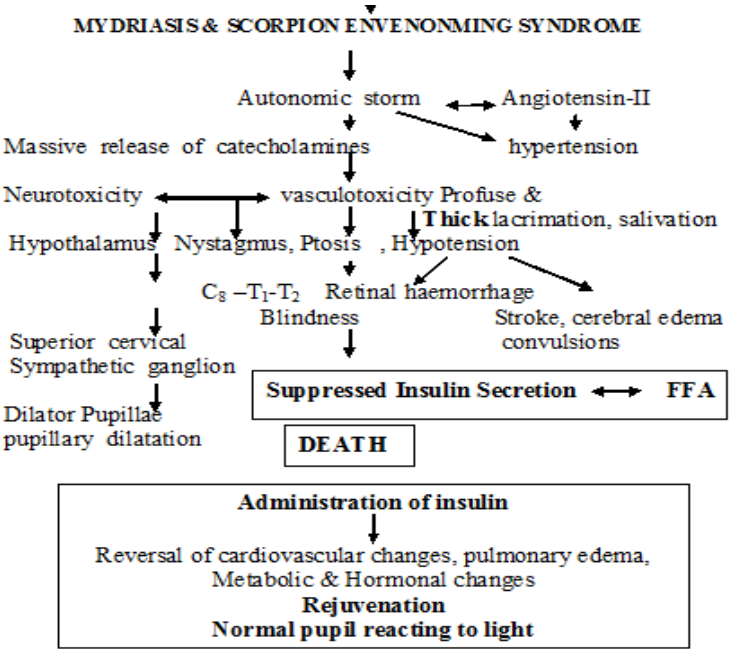
Received for publication: July 17, 2014**; accepted:** August 29, 2014

Abstract: Death due to poisonous scorpion stings of *Buthidae* family is a common event in many of the developing countries located in the tropical and sub-tropical regions of the world. Severe scorpion envenoming causes *an autonomic storm* with massive release of catecholamines, renin-angiotensin II, glucocorticoids, glucagon, growth hormone, simultaneous suppressed insulin secretion, hyperglycemia and a sudden increase in Free Fatty Acid levels (FFA). Sudden increase in FFA is toxic, causes acute myocarditis, cardiogenic shock, disseminated intravascular coagulation, systemic inflammatory response syndrome, multi system organ failure and death. The victims present with mydriasis, papilloedema, nystagmus, squint, miosis, vomiting, profuse sweating, increased salivation, generalized tingling, gangrene, priapism, tachypnoea, hypertension, hypotension, pulmonary oedema, and many other manifestations either singly or in combination. Wide dilated pupils not responding to light is one of the grave signs of scorpion poisoning. Insulin administration reversed all the metabolic and clinical manifestations in our experimental animals and scorpion sting victims. Continuous infusion of regular crystalline insulin at the rate of 0.3 U/g glucose and glucose at the rate of 0.1g/kg body weight/hour, for 48-72 hours, with supplementation of potassium as needed, maintenance of fluid, electrolytes, acid-base balance reverses the metabolic, haemodynamic cardiovascular changes, pulmonary oedema and all other clinical manifestations in scorpion envenoming syndrome. Normal pupil reacting to light is one of the indications of recovery. Insulin is an anabolic hormone, acts against the metabolic and poisonous effects of all the counter regulatory hormones; has a primary metabolic role in preventing; counter-acting, reversing all the deleterious toxic effects of FFA by inducing lipogenesis, increase intra-cellular K^+ and euglycemia. The neurological and patho-physiological basis of mydriasis, nystagmus, and few other manifestations involved in the genesis of scorpion envenoming syndrome and their reversal by administration of insulin is reviewed.

Key Words: Buthidae family, Autonomic storm, increased catecholamine levels, mydriasis, Free Fatty Acids, Insulin administration

Introduction

Death due to scorpion stings is common in many tropical and sub-tropical countries (1-10). Scorpion venom is known to cause an injurious effect simultaneously on the various vital systems of the body on CNS, CVS, respiratory system, endocrine and many more systems and several organs of the body (11-25). The patient is suffering from various emergencies and life threatening medical conditions at the same time. Scorpion stings result in a variety of clinical manifestations (11-55) mydriasis, papilloedema, nystagmus, squint (1-9, 21, 24-27, 37, 44), motor aphasia (28), hemiplegia (9, 24-27, 44), gangrene (34, 52) necessitating amputation, disseminated intravascular coagulation (16, 55), hypertension, hypotension (9, 12-14, 30-33), arrhythmias (49), conduction defects, myocardial ischemia, myocardial infarction (9, 12-15, 17, 21, 49-55), cardiogenic and non-cardiogenic pulmonary oedema (9, 12-14), metabolic changes, many other clinical manifestations and death (1-55).



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Scope of the review article

The treatment of scorpion envenoming syndrome is a difficult problem. It requires extensive knowledge of the clinical manifestations and an understanding of the pathophysiological mechanisms behind the clinical symptomatology. We have been working for the last forty years (both in the experimental envenoming and scorpion sting victims) on scorpion envenoming syndrome (1-8, 15, 36, 38, 42-55).

The neurological basis and patho-physiological mechanisms of mydriasis, papilloedema, nystagmus, squint, and few other manifestations involved in the genesis of scorpion envenoming syndrome and their reversal (in the experimental animals and scorpion sting victims) by administration of insulin is reviewed.

Death due to scorpion envenoming syndrome is common in many countries

Scorpion stings are common in India, Nepal, Bangladesh, Pakistan (1-10), Mexico, Brazil (29), Algeria, Tunisia, West Indies (11, 22), Saudi Arabia (32-35), China, Iraq, Iran, Saudi Arabia, Middle East, and South Africa (17), Central Africa, West Africa (1-55). Many times the scorpion sting victims are brought "dead" and these deaths do not find in the hospital statistics! There is not even a "guesstimate" regarding the number of deaths caused by these "nocturnal visitors" due to inadequate detection and/or data entry of the cases (32-35)!

Death due to scorpion envenoming syndrome in India

Scorpions live in warm dry regions throughout India. They inhabit commonly the crevices of dwellings, underground burrows, under logs or debris, paddy husk, sugarcane fields, groundnut fields, coconut and banana plantations. Their distribution is more in regions with abundant red soil like Rayalaseema region (Kurnool, Kadapa, Anantapur districts) of Andhra Pradesh, Konkan region in Maharashtra, Parts of Rajasthan and Gujarat (1-10). Scorpions retreat in the crevices of dwellings during the day only to emerge at night thus most stings are reported at night. Scorpion stings increase dramatically in summer months and are lowest in winter (21).

Size and age of the victim is of utmost important

The size and age of the victim is of utmost important. Thus, children and babies are more prone to severe intoxication (dose dependent). This is because more venom gets injected in babies and children (per kg body weight) compared to adults. Other factors are possibly differential vulnerability to the venom (74).

Toxicity of scorpion venom is influenced by the age and species of scorpions

Deaths due to Indian red scorpion *(Mesobuthus tamulus concanesis, Pocock)* stings occur in both adults and children, but the mortality is greater in children (74). Besides the age, species of animals is also an important factor for the sensitivity of *Mesobuthus tamulus concanesis, Pocock* venom. The toxic effects of the venom are dissimilar at different doses, e.g. a low dose depleted the liver or ventricular muscle glycogen to a greater extent than did a higher dose in rabbits (1-8).

Young rats required greater concentration of scorpion venom than the adult rats

Young rats required greater concentration of scorpion (*Mesobuthus tamulus concanesis, Pocock*) venom than the adult rats; thus enhanced sensitivity to venom in young animals may not be likely to explain the greater mortality. Tiwari & Deshpande observed dose-dependent fatalities on a weight basis; thus it is possible that the concentration of venom (per kg body weight) per sting will be greater in the young than in the adults, perhaps accounting for the greater casualties in children, even though they may be less sensitive to venom (74).

Scorpion stings are primarily due to accidental contact with scorpion. They use their stings only when they are "molested". It may be the "vibrations" that are made while the humans are at work, walking or sleeping and these "vibrations" that make the scorpion feel "molested". Scorpion does not always inject venom when it stings since it can control its ejaculation; thus the sting is total, partial or non-existent. Scorpions capable of inflicting fatal stings in humans are all members of Buthidae family.

Scorpion sting is a rural emergency occurring in villages where medical facilities are not available. India harbors about 55 most dangerous killer species of scorpions that belong to Buthidae family. Thousands of scorpion sting victims die annually in India! Local governments (Gram Panchayats, Municipalities, Municipal Corporations), State Governments (Andhra Pradesh, Karnataka, Tamil Nadu, West Bengal, Bihar, Gujarat, Rajasthan, Uttar Pradesh, Madhya Pradesh, Maharashtra and many more States in India) and Central Government of India did not take any concrete measures to tackle the problem in India. Many doctors are not even aware that the scorpion stings could result in death! This is because most of the standard textbooks of Physiology (56, 57), Pharmacology (58), and Medicine (10, 59-65) ignore and dismiss "scorpion stings" in few lines! Very little or "no clinical information" useful to the physician to manage and treat a victim of severe scorpion envenoming syndrome is provided in these textbooks (61-65).

Signs and symptoms following by scorpions stings of Buthidae family, all over the world, is remarkably similar

The highly toxic venomous scorpions of the world belong to *Buthus (Mesobuthus tamulus concanesis, Pocock)* from India (1-8, 15, 16, 24-28, 36-38, 42-54), *Parabuthus* from Africa (17), *Androctonus australis*

hector from Algeria (19), Centruroides, *Leiurus* (29-35, 40, 41, 44), *Tityus* (12-14) genera come under *Buthidae* family. In spite of many zoological differences in the "species" and "genera" of scorpions that belong to *Buthidae* family and differences in their chemical structure of venoms, signs and the symptomatology in humans following scorpion envenoming by all the scorpion stings of *Buthidae* family, throughout the world, is quite similar (1-8, 12-14, 17, 21-28, 30, 31, 37, 39-41).

The clinical presentation of scorpion sting victims stung by scorpions of *Mesobuthus tamulus concanesis*, *Pocock* (1-9, 21, 24-28, 37, 53), *Tityus serrulatus* (11, 22),*Tityus bahiensis* (25), *Leiurus quinquestriatus, Buthus occitanus, Leiurus quinquestriatus* (12-14, 32-35), *Buthus occitanus or Parabuthus* envenomation from India, Brazil, Israel, Saudi Arabia, Tunisia and South Africa, respectively, are similar.

Clinical manifestations following stings by dangerous scorpions of *Buthidae* family may involve the central nervous system (CNS), the autonomic nervous system (the sympathetic as well para-sympathetic systems of the autonomic nervous system), the respiratory system, the pancreas (exocrine as well as endocrine pancreatic systems), and the cardio-vascular system in the experimental animals (1-8, 15, 16, 18-20, 29, 32-36, 38, 44, 45-54, 65, 68, 69) and scorpion sting victims (9, 12-14, 17, 21-28, 30, 31, 37, 39-41) producing scorpion envenoming syndrome.

Cause of death - scorpion venom is neurotoxic and vasculotoxic

The venom releases catecholamine, with firing of alpha receptors, enhances endothelin secretion leading to severe vasoconstriction of the cerebral vessels. This can result low flow infarcts. The venom damages endothelial cells and cause vasculitis. This can initiate thrombosis.

A retrospective study of 951 scorpion sting victims (age: o.6 years to 17 years) over a 13-year period revealed neuromuscular signs in 739 patients, coma (Glasgow Coma Score 12), and convulsions. The other neurological signs were agitation in 709 patients, squint, bilateral miosis, and bilateral mydriasis. The presence of coma, convulsions, bilateral miosis, and bilateral mydriasis correlated with poor outcome (44).

Autonomic storm

Severe scorpion envenoming causes an autonomic storm with massive release of catecholamines, angiotensin II, and the simultaneous suppression of insulin secretion. The symptoms and signs are vomiting, profuse sweating, increased salivation, generalized tingling & numbness, priapism, tachycardia, tachypnoea, hypertension followed by hypotension and pulmonary oedema (9, 12-14, 17, 21-28, 30, 31, 37, 39-41).

Autonomic storm, massive release of catecholamines and rennin angiotensin

Elevated circulating levels of catecholamines and rennin angiotensin had been observed in clinical and experimental envenomation (12-14, 30, 31, 48). Plasma nor-epinephrine levels were elevated on admission (1279 pg/ml) in children (32-35, 40). We have demonstrated massive increase in angiotensin-II in our experimental animal on venom injection. The mean arterial pressure (diastolic pressure) is between 160 mm Hg. to 300 mm Hg. in our experimental animals immediately after scorpion venom injection (48).

Catecholamines and rennin angiotensin facilitate each other's release

Intra venous administration of crude venom of the scorpion (*B. tamulus*) in rats produced a vasopressor response. This pressor response is mediated through an indirect mechanism of catecholamine release from peripheral sites including the adrenal medulla (13-20, 58).

Hypothalamus–Autonomic Nervous System in scorpion envenoming syndrome

The severity of scorpion stings is related to the presence of neurotoxins in the venom that cause a sudden release of neurotransmitters from the autonomic nervous system, predominantly sympathetic. There is also a strong inflammatory response that worsens symptoms. Sharp Pain sensation at the site of sting, no swelling or very minimal local tissue swelling, and ascending hyperesthesia that persists for several weeks (if the victim survives). Pain is the last symptom to resolve while the victim recovers. The site is hypersensitive to touch. Ultimately all the impulses due to "acute sharp pain"/ "burning pain"/ "stinging pain" and "tissue injury" reach hypothalamus and the central nervous system (11-14, 21, 23-28, 37, 44).

Afferent connections of Hypothalamus

Hypothalamus receives nervous connections from the midbrain tegmentum. There is massive projection of catecholamine – and 5-hydroxytryptamine-containing fibers to the Mammillary nuclei and the medial forebrain bundle. It is through this route that the ascending sensory pathways project to the Hypothalamus since they do not establish direct connections with it (56).

Efferent connections of Hypothalamus

Descending fibers (which arise mainly in the lateral hypothalamic nuclei) pass to the reticular formation of the tegmentum and then to the motor nuclei of the bulb and to the spinal motor neurons, thereby contributing to the extrapyramidal facilitatory

pathway. These fibers also constitute a potential route over which the hypothalamus can exert its effects upon the autonomic nervous system since the direct monosynaptic connections to regions containing either sympathetic or parasympathetic neurons have not been demonstrated (56).

Symptoms and signs

The symptoms and signs are vomiting, profuse sweating, increased salivation, generalized tingling & numbness, motor aphasia, hemiplegia, ptosis, facial palsy, pri-apism, tachycardia, tachypnoea, transient hypertension followed by hypotension and pulmonary oedema.

Neurological manifestations

Scorpion envenomation can produce neurological manifestations, which are an indicator of the severity of the scorpion sting. Thermoregulatory disturbance is often present after scorpion envenomation. Hypothermia transforms into hyperthermia.

Thermoregulatory abnormalities

The thermoregulatory abnormalities can be explained by a direct action of scorpion venom on the central nervous system or by a massive liberation of cytokines (*IL-1-alpha*, IL-6, IL-10, TNF-alpha, IL-1 beta. [41] In severe cases, the clinical manifestations become more pronounced, reflect a massive liberation of catecholamines secondary to a neurovegetative system disorder leading to a cellular hyper-metabolism manifested as hyper-sweating, myoclonia, agitation and priapism (41, 44).

Anatomical abnormalities in the central nervous system with envenoming

Cerebral damage in the central nervous system secondary to severe scorpion envenomation, such as cerebral hemorrhage, cerebral ischemia and cerebral infarction is common.

Thrombotic stroke with the involvement of the middle cerebral artery

Stroke can occur due to Disseminated Intravascular Coagulation (DIC). We have demonstrated DIC in our experimental animals. This has been confirmed by the demonstration of fibrin deposits in the affected vessels in autopsy studies of victims of scorpion sting. The venom is known to increase platelet aggregation. Thrombotic stroke with the involvement of the middle cerebral artery territory – due to DIC had been reported (16, 55).

Multiple cerebral infarcts, bilateral optic neuropathy

Multiple cerebral infarcts, bilateral optic neuropathy with limb ischemia was observed in a 17 year old subject due to Meso*buthus tamulus* sting. Multiple bilateral triangular watershed cerebral infarcts involving the frontoparietal regions anteriorly and temporo-occipital regions posteriorly in the distribution of the middle cerebral artery especially on the right side were seen. The patient showed improvement slowly over next 2 weeks with deterioration of vision in both eyes. Fundus examination showed bilateral disc pallor with perimacular hemorrhage and pigmentary retinal degeneration on the left. By the tenth week, he was able to walk with residual left hemiparesis. The arterial pulsations in the right arm and the carotid arteries are palpable but blindness of the left eye persisted (46).

Bilateral dilatation of pupils

Large haematoma extending out of necrosed fronto-temporal region of cerebrum was observed in postmortem examination in a 55 year old male with a history of scorpion sting in left ring finger. Severe “burning pain” at the site of sting and the pain radiated to whole of upper limb. His blood pressure was 230/180 mm Hg. bilateral diffuse inspiratory crepts, and clinically hemorrhagic stroke. CT scan revealed massive right fronto parietal intra-parenchymal bleed causing marked mass effect with intraventricular extension. Bilateral dilatation of pupils, pupils dilated to 6 mm and fixed. Fundoscopy revealed papilloedema and exhudates. The victim died 24 hours after the sting (37).

Other neurological manifestations

In very severe cases, neurological manifestations are more pronounced. Generalized or localized convulsions, brain oedema, shock, with or without coma, can be observed. Other neurological manifestations, such as, miosis, mydriasis, nystagmus, squint, and erratic eye movements indicate severe forms of scorpion envenomation (39).

Pain

The experimental rats, rabbits and dogs do not scream in the animal house. But these experimental animals scream within seconds when the venom is injected either sub-cutaneously, intramuscularly or intravenously (1-8, 15, 20, 36, 42, 43, 45, 47-51, 53-55).

Scorpion sting victims scream and cry within seconds to minutes due to pain after the sting, children appear irritable, at times excitable. Random movements of head, eye movements and movements of the neck are often seen (21).

Changes in the eyes in scorpion envenoming syndrome

Pupil: The central opening in the iris is called pupil. The pupillary size varies between 1 and 8 mm. The average diameter of pupil in an adult is 4 mm in ordinary room light. It tends to be smaller in newborn due to Para-sympathetic tone and in elderly persons due to decreased sympathetic activity.

Miosis: Small constricted pupil is called miosis, is one of neurological observations in the eye. This could be because of irritation of the third nerve or parasympathetic over stimulation in scorpion envenoming syndrome.

Dilated pupils: The pupils are dilated in the state of pain and fear due to increased sympathetic tone. Scorpion envenoming syndrome causes unbearable pain at the site of scorpion sting. Poisonous scorpion stings result in severe autonomic storm causing massive release of catecholamines and angiotensin II. Sustained and severe sympathetic discharge results in abnormal dilatation of pupil. Abnormal dilatation of pupil is known as mydriasis (57).

Dilated pupils with protrusion of eye balls: Wide dilated pupils with protrusion of eye balls are observed in all our experimental animals injected with scorpion (*Mesobuthus tamulus concanesis, Pocock*) venom (1-8, 15, 20, 36, 42, 43, 45, 47-51, 53-55).

Psycho-sensory Reflex: The Psycho-sensory Reflex is complicated and initiated by the stimulation of sensory nerve during pain or emotional states present in scorpion envenoming syndrome.

Sensory excitation leads to rapid dilatation

Sensory excitation initially causes a rapid dilatation of pupil owing to augmentation of the dilator tone via the cervical sympathetic nerve fibers. It is followed by a quick second dilatation which lasts longer due to inhibition of the constrictor tone (Fig. 1) (67, 68).

Adrenergic fibers supply Dilator pupillae

The dilator pupillae is supplied by the adrenergic fibers of the cervical sympathetic nerve.

Sympathetic Pupillary Dilator Reflex

The tract commences in the Hypothalamus and descends downwards through the Medulla Oblongata into the lateral columns of the spinal cord. From here the postganglionic fibers pass along with the carotid plexus into the skull. The fibers run along the ophthalmic division of the Trigeminal nerve (Fifth cranial nerve), follow the naso-ciliary nerve and finally reach the dilator pupillae muscle via the long ciliary nerves.

The pre-ganglionic fibers leave through the ventral roots of C_8, T_1, and T_2 nerves and enter the corresponding cord to reach the superior cervical ganglion (57, 67, 68).

Efferent pathway

Two neural mechanisms are involved for dilatation of the pupil. The active component results from contraction of the radially arranged fibers of the dilator muscle via the cervical sympathetic pathway.

The passive component results from relaxation of the sphincter muscle caused by inhibition of visceral occulo-motor nuclei.

Sympathetic pathway

Sympathetic pathway from the sympathetic centers of the Hypothalamus, the dilator fibers pass downwards with partial decussation in the Midbrain. These nerve fibers then pass through the Medulla Oblongata into the lateral columns of the cord.

Cilio-spinal center

The first order pre-ganglionic neuron: The descending fibers, the first order pre-ganglionic neuron synapses in the intermedio-laterl portion of the spinal cord at the level of C_8 – T_2, known as the **cilio- spinal centre** of budge (Fig. 1) (57, 67, 68).

The second order pre-ganglionic fibers: The second order pre-ganglionic fibers exit the cord primarily with the first ventral thoracic root (T_1) but some pupillo-motor fibers exit along with T_2 or C_8. The fibers then enter the para-vertebral sympathetic chain which is closely related to the pleura of the apex of the lung. Then they ascend up without synapsing through the inferior and middle cervical ganglion to terminate in the superior cervical ganglion.

Nystagmus

Nystagmus is the name given to irregular or jerky eye movements. Nystagmus is frequently observed in the scorpion sting victims. Many parts of the visual system are needed to maintain ocular fixation, and so Nystagmus is complex subject. The condition is almost bilateral. There are many different types of abnormal movements.

Motor Nystagmus could be due to defect in the brain stem, the cerebellum or the vestibular system all of which control the fixation of the eyes. This could be due to ischemia or damage to the brain as discussed. Thrombotic (16, 55) or hemorrhagic accidents are reported in scorpion envenoming syndrome (1-8, 21, 24-28, 37).

Squint

The misalignment of the visual axis of the two eyes is called “Strabismus” or “Squint”.

Paralytic strabismus

“Squint” or “Strabismus” is one of the common observations in the scorpion sting victims. Paralytic strabismus could be due to lesions of the nuclei. The most common cause is a small hemorrhagic thrombotic lesion in the midbrain. The ocular motor nerves (third, fourth and sixth cranial nerves) travel through the cranial and orbital cavities and can be damaged by changes in the microvasculature.

Ptosis

Ptosis means that the upper eyelid droops, usually because the "levator muscle" is weak. Ptosis is also common in scorpion sting victims.

Third cranial (Oculomotor) nerve palsy

If the palsy is complete, it will cause a total ptosis, a dilated pupil and limitation of all eye movements except abduction.

Ocular myopathy

All the extra ocular muscles are weak, but Ptosis is often the first sign of this weakness (67, 68).

Abnormal eye movements

Abnormal eye movements along with wide dilated pupils indicate severity of scorpion poisoning. Involvement of oculomotor, trochlear and abducent nerves could be the cause of abnormal eye movements. [

Actions of epinephrine and norepinephrine in the CNS

The Actions of epinephrine and norepinephrine in the CNS are respiratory stimulation, an increase in wakefulness, psychomotor activity and, Prejunctional action that either inhibit or facilitate the release of neurotransmitters, the inhibitory action being physiologically more important.

Clinical manifestations reflect massive catecholamine liberation

Scorpion envenomation can produce neurological manifestations, which are an indicator of the severity of the scorpion sting. The clinical manifestations reflect a massive liberation of catecholamines.

Hypertensive encephalopathy

Scorpion envenomation leads to a high arterial blood pressure. When arterial blood pressure is excessive (exceeding sometimes the cerebral antiregulatory plateau), it leads to cerebral damage (oedema and ischemia). It explains the anatomical abnormalities in the central nervous system secondary to severe scorpion envenomation, such as cerebral hemorrhage, cerebral ischemia, and cerebral infarction (1-9, 21-27, 44).

Brain ischemia - a defect in O_2 transport

Brain ischemia can result from a defect in oxygen transport secondary to pulmonary oedema and cardiogenic shock in scorpion envenomation. We have demonstrated adult respiratory distress syndrome in our scorpion sting victims (9, 54). The effects of scorpion venom on the central nervous system are due to its peripheral action and the observed neurological manifestations are the consequence of other associated peripheral disturbances (12-14, 31-35).

Direct action of venom on central nervous system

Scorpion venom can cross the hemato-encephalic barrier (74) in immature children. CNS lesion can result from excitatory amino acid neurotransmitter liberation and an accumulation of intracellular calcium secondary to the direct action of the venom. Besides the clinical manifestations, CNS lesions are proved by electroencephalographic studies. Impairments of consciousness and coma are common among the children stung by scorpions. Coma is associated with poor outcome. A statistically significant correlation is found between Coma and young age ($p<0.001$), respiratory failure ($p<0.001$), convulsion ($p<0.001$), hyperthermia ($p<0.05$), pulmonary oedema ($p<0.001$), heart failure ($p<0.01$), and liver failure ($p<0.01$) (44).

Behavioral changes

The following behavioral changes were observed in our experimental animals treated with scorpion (Mesobuthus tamulus Concanesis, Pocock) venom procured from Haffkine Institute, Mumbai, India. There was intense lacrimation and profuse thick (ropy) (which cannot be wiped out) salivary secretions dribbling from the mouth, distension of the abdomen, defecation and frequent micturition. The stools were, sometimes, stained with bile and blood. Ejaculation is frequently observed in the experimental animals. The animals had immediate cessation of breathing (laryngeal spasm), apnoea, muscular fasciculations, clonus and tetany like contractions in the skeletal muscles of the body. At the end, **the pupils were widely dilated and there was protrusion of the eye balls which looked glossy** (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Intense thick lacrimation is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Wide dilated pupils are due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Protrusion of the eye balls (in the experimental animals) which looked **glossy** is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Profuse thick (ropy) salivary secretions (which cannot be wiped out) dribbling from the mouth is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Ejaculation (in some of the male experimental animals) is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Defecation is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Frequent micturition is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

General neurotoxicity

General neurotoxicity of an excitatory nature, including the autonomic (parasympathetic and sympathetic) as well as the skeletal neuromuscular system was indicated following envenoming by scorpions of Buthidae family (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Association of CNS and Cardiovascular manifestations

Encephalopathy manifested in ***restlessness****, agitation and* seizure (early) followed by loss of deep reflexes (late). The corresponding cardiovascular effects consisted of tachycardia, hypertension (early) and uncorrectable hypotension and asystole (late) (33-35).

Uncorrectable hypotension is due to hyper-sweating.

Hyper-sweating is due to sympathetic stimulation (1-8, 15, 20, 36, 42, 43, 45, 47-57, 66).

Hyper-sweating due to sympathetic stimulation is not responsible for thermoregulation in scorpion envenoming syndrome (56, 57).

Although either the CNS or the cardiovascular manifestations could occur first in the early phases of the scorpion envenoming syndrome, CNS manifestations always preceded the terminal hypotension and cardiac arrest. This strongly suggests the possible involvement of a central cardiac and / or vasomotor depression in fatal cases of human scorpionism (24-28, 33-35).

Autonomic storm – Endocrine & Metabolic changes
Sudden increase in FFA is toxic

Scorpion envenoming syndrome results in a severe autonomic storm (1-8, 18-22) with a massive release of epinephrine, norepinephrine (26), increased levels of angiotensin II (21, 25), counter-regulatory hormones - glucagon, glucocorticoids, thyroid hormones (28, 30, 32, 38, 39, 40, 45, 47, 49-51, 53-55), changes in insulin secretions (suppressed insulin levels or hyperinsulinemia), hyperglycemia (1-8, 15, 20, 28, 30, 32, 36, 38, 39, 40, 45, 47, 49, 50) and increased circulating free fatty acid levels (FFA) (1-8, 13-21). Sudden increase in FFA increase the myocardial O_2 consumption, aggravate the ischemic injury to myocardium predisposing to arrhythmias, heart failure, increase the susceptibility of the ventricles to the disorganized electrical behavior, inhibit cardiac sarcolemmal (27) and erythrocyte Na^+ - K^+ *ATPase* activity (41), hematological changes (30, 32, 49), increased tendency to intravascular thrombus - Disseminated Intravascular Coagulation (DIC) (39), increased osmotic fragility of erythrocytes (33, 34, 41, 49) and many other abnormalities. These hormonal and metabolic changes could be responsible for the pathogenesis of a variety of clinical manifestations in scorpion envenoming syndrome. Thus scorpion envenoming syndrome with acute myocarditis, myocardial damage, DIC, cardiovascular disturbances, peripheral circulatory failure, Acute Respiratory Distress Syndrome (ARDS) (44, 55), many other clinical manifestations essentially results in **a syndrome of fuel – energy deficits and an inability to use the existing metabolic substrates by vital organs causing MSOF and death** (1-8).

Inhibition/ suppression of Insulin secretion and hyperglycemia

We have demonstrated inhibition of insulin secretions in scorpion envenoming (1-8, 15, 38, 42, 45, 50, 51, 55, 69, 70, 71).

Hyperinsulinemia and hyperglycemia in scorpion envenoming

We have also demonstrated increased insulin secretions and hyperglycemia (few hours after venom injection) (insulin resistance) in scorpion envenoming (1-8, 15, 38, 42, 45, 50, 51, 55, 69, 70, 71).

Hyperglycemia-glycogenolysis-insulin resistance in scorpion envenoming

We have demonstrated glycogenolysis in liver, atria, ventricles of the cardiac muscle and skeletal muscles in scorpion envenoming (1-8, 15, 38, 42, 45, 50, 51, 55).

Hyperglycemia-insulin resistance in scorpion envenoming

We have demonstrated hyperglycemia in the experimental scorpion envenoming (1-8, 15, 38, 42, 45, 50, 51, 55).

Hyperglycemia stimulates coagulation in scorpion envenoming

We have demonstrated disseminated intravascular coagulation (16, 55). Scorpion sting patients with hyperglycemia and insulin resistance are especially susceptible to thrombotic events by a concurrent insulin-driven impairment of fibrinolysis and a glucose driven activation of coagulation (28, 30, 32, 36, 38, 39, 40, 45, 47, 50, 73). This could be the reason for motor aphasia (28), hemiplegia (9, 24-28, 44), arrhythmias, conduction defects, myocardial ischemia, myocardial infarction (12-15, 17, 21), disseminated intravascular coagulation (16, 55) and many other clinical manifestations and death in scorpion sting victims.

Lipolysis – sudden increase in Free Fatty Acids

We have demonstrated lipolysis – sudden increase in Free Fatty Acids in scorpion envenoming (28, 30, 32, 36, 38, 39, 40, 45, 47, 55).

Sudden increase in Free Fatty Acids inhibit Na^+- K^+ ATPase activity

Sudden increases in free fatty acids inhibit *Na^+-K^+ ATPase* activity (71). **W**e have demonstrated alterations in cardiac sarcolemmal *Na^+- K^+ ATPase*, *Mg^{++} ATPase* and *Ca^{2+} ATPase* activities (36). We have also demonstrated alterations in erythrocyte *Na^+- K^+ ATPase* activity in a scorpion sting victim as well as in the experimental animals (51).

Insulin resistance-adipose tissue-sympathetic innervations- scorpion envenoming

Adipose tissue is innervated by the sympathetic nervous system, which can regulate lipolysis, fat cell number, and the secretion of adipocytokines, such as ***TNF-a*** and ***Monocyte Chemoattractant Protein 1 (MCP1***). Furthermore, the activity of the sympathetic nervous system increases following envenoming, an effect mediated by catecholamines. In addition, the activity of sympathetic nervous system can contribute to insulin resistance through effects of catecholamines on adipocytes. The pharmacological profiles of molecules acting more selectively on b-adrenergic receptor subtypes suggest that the lipolytic action of *Buthus occitanus tunetanus* venom mainly involves the b_2 / b_1 subtype of adrenergic receptors (19).

Scorpion venom is also a lipolytic agent (in vitro)

Scorpion venom contains a diversity of neurotoxins. The venom of the scorpion *Buthus occitanus tunetanus* contains compounds that activate non-excitable tissues such as adipocytes and causes increased lipolysis (19).

Insulin resistance in scorpion envenoming syndrome

Scorpion venom reduces insulin sensitivity and causes insulin resistance. Scorpion venom induces systemic and local inflammation. Pro-inflammatory cytokines (IL-1b, IL-6, TNF-a) change substantially in adipose tissue. Decreased insulin sensitivity is mainly driven by TNF-a. TNF-a increases Mitogen-activated protein 4 kinase isoform 4 (Map4k4) through a TNFR 1-dependent mechanism to induce insulin resistance in adipose tissue (19). [

Role of insulin on Na (+)-/K(+)-dependent ATPase activity

The *Na^+- K^+-dependent ATPase* (*Na-K-ATPase*) expressed in the basolateral membrane of corneal endothelial cells plays an important role in the pump function of the corneal endothelium. Insulin increases the *Na, K-ATPase* activity and pump function of cultured corneal endothelial cells. The effect of insulin is mediated by protein kinase C (PKC) and presumably results in the activation of protein phosphatases 1 and 2A or both, which are essential for activating *Na-K-ATPase* by alpha(1)-subunit dephosphorylation. Inhibition of insulin secretion will decrease the *Na-K-ATPase* activity and pump function of corneal endothelial cells (72).

Administration of Insulin

Administration of insulin under these circumstances counter-acts the metabolic effects of catecholamines, stimulate lipogenesis, glycogenesis, reverse the metabolic and electrocardiographic changes in acute myocarditis induced by Indian red scorpion (Buthus tamulus) venom in the experimental dogs (26, 33) and scorpion sting victims (9, 54).

The Dose of Insulin in Scorpion Sting Victims

The dose of insulin is 0.3 Units of regular insulin per gram of glucose, and glucose 0.1 $g{\cdot}Kg^1$ per hour. Blood glucose, serum electrolytes, electrocardiogram, and arterial blood gases should be investigated on admission. In addition to regular clinical observations, estimations of blood glucose should be carried out two hourly and of serum electrolytes 12-hourly. Glucose levels should be maintained between 130 and 180 $mg{\cdot}dl^1$ of blood (9, 54).]

Scorpion envenoming in our hands resulted in a significant reduction in insulin and triglyceride levels (1-8, 38, 42, 45, 50, 53, 54) and an increase in glucose (1-8, 42, 43, 45, 50, 53, 55) and free fatty acid levels (1-8, 15, 42, 43, 45, 50, 53, 55) in animals after venom injection along with depletion of glycogen content in the cardiac and skeletal muscle and more depletion of glycogen content in the liver (19, 42, 43, 45, 50, 53, 55). Insulin administration produced a reduction in FFA, an increase in triglyceride levels and increased tissue glycogen content in cardiac and skeletal muscle and that of liver (19, 42, 43, 45, 50, 53, 55). Catecholamines suppress insulin secretion. This could be the reason for reduction in the circulating insulin levels in the dogs after venom injection. Catecholamines released at sympathetic nerve endings and insulin deficiency thus produced, can activate the hormone sensitive lipase, promote free fatty acid mobilization and produce a sudden increase in free fatty acid levels. This could be the reason for a sudden increase in FFA levels after venom injection.

Medicines either not useful or contra-indicated in scorpion envenoming syndrome

1) Cardiac glycosides,
2) Atropine,
3) Diuretics,
4) Corticosteroids,
5) Emetine hydrochloride (with local xylocaine injection),
6) Adrenaline (with local xylocaine injection),
7) Angiotensin Converting Enzyme (ACE) inhibitors.

Cardiac Glycosides

The cardiac glycosides are not effective in pulmonary oedema in the presence of sinus Tachycardia and normal cardiac size. The cardiac glycosides are

known to act by inhibiting Na^+ - K^+ *ATPase* activity. The scorpion venom produces cardiac sarcolemmal defects displayed as inhibition of Na^+ - K^+ *ATPase* activity.

Atropine

Atropine should not be given routinely. This has been the common practice because of heavy perspiration, increased salivation and lacrimation. Atropine may intensify the tachycardia and sympathetic effects due to the venom after blocking the cholinergic effects.

Atropine potentiates hypertensive effect. Moreover, atropine is a parasympatholytic drug and inhibits insulin secretion from endocrine pancreas. Increase in duration as well as severity of clinical signs, including myocardial injury were observed in scorpion sting victims treated with atropine compared to scorpion sting victims who did not receive atropine.

Atropine increases the severity of pulmonary oedema induced by scorpion toxin.

Diuretics

Administration of diuretics may relieve the pulmonary edema temporarily but diuretics may not relieve pulmonary edema due to adult respiratory distress syndrome.

Corticosteroids

Administration of corticosteroids is contraindicated because corticosteroids will precipitate insulin resistance.

Emetine hydrochloride

Administration of Emetine hydrochloride will cause myocardial toxicity.

Adrenaline (with local xylocaine injection)

Administration of Adrenaline is contraindicated because adrenaline is a sympathomimetic drug and it will worsen the clinical condition.

Angiotensin Converting Enzyme (ACE) inhibitors

Administration of angiotensin converting enzyme (ACE) inhibitors is contraindicated because they will precipitate pulmonary edema (35).

Conclusions

Neurological manifestations like mydriasis are often observed in severe scorpion-envenomed patients and they correlate with poor outcome. Their mechanisms are complex. Prevention is highly warranted. Insulin-glucose infusion along with fluid, electrolyte, acid-base balance should be given at the earliest for preventing; counter-acting and reversing all the deleterious toxic effects due to scorpion envenoming syndrome. Ophthalmologists also should be associated with treatment of scorpion envenoming syndrome (to prevent blindness) in scorpion sting victims stung by scorpions of Buthidae family.

Acknowledgements

The authors would like to thank Dr. Santhiramudu and Dr. Madhavi Latha for their encouragement.

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Source of support: Nil,
Conflict of interest: None Declared