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UNDERSTANDING THE ASPECTS OF COMMON INDIAN SNAKE ENVENOMATION STRATEGIES –A REVIEW

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Abstract:
Poisoning by venomous snake bite is a common acute life-threatening, time-limiting medical emergency. In the rural area, snake bite poisoning is a leading cause of death of young earning member of the family. More than 2,000,000 snake bites are reported in the country, and it is estimated that more than 50000 people die of snakebite each year. Research is also being carried nowadays to produce the immunity against the specific snake venom by using a targeted drug delivery system. Much emphasis is also given on the correct detection of types of venoms injected in the body of the victim and successful rehabilitation of patients after treatment. One can say that a permanent & suitable protection against any snake bite poisoning will be fulfilled only if the correct identification of the venom injected into the body is possible. Hence, the identification of the snake species becomes the utmost requirement for medical management. In the present paper, an attempt to explain the biology, distribution & pathogenesis of individual species, understanding the structure and functions of venom toxins and species-specific symptoms developed in the victims of snakebites, which may help in the proper identification of the aggressor and in grading the envenomation is discussed.

Keywords: Snake bite, Indian Cobra, Russell's viper, Common krait, saw-scaled viper.

Introduction:

Envenoming by poisonous animals (snakes, scorpions, wasps, ants, and spiders) is an occupational hazard often faced by farmers, farm laborers, hunters, and shepherds of tropical and subtropical countries. Poisoning by venomous snake bite is a common acute life-threatening, time-limiting medical emergency. In the rural area, snake bite poisoning is a leading cause of death of young earning member of the family. More than 2,000,000 snake bites are reported in the country, and it is estimated that more than 50000 people die of snakebite each year. Snakes of more than 3000 known species of snakes, only about 300 are venomous and in India there are about 216 identifiable species of snakes, of which 52 are known to be poisonous. The major families of poisonous snakes in India are Elapid which includes common cobra (Naja naja), king cobra and common krait (Bungarus caerulus, Banded krait, Sind krait), viperidae (Russell's viper), Echis carinatus (saw scaled or carpet viper), and pit viper and hydrophiidae (sea snakes). Recently, venomous viper called hope nosed viper is reported from Cochin region. During monsoon season, fatal snake bites are common to feature in local newspapers. Newly posted or inexperienced doctors and inadequate facilities at primary health center (PHC), ignorance of conventional treatment of snake bite by doctors, further delays appropriate treatment of victims and contribute to increasing morbidity and mortality. It is rather surprising to note that snake bite poisoning is seldom mentioned as a priority for health research in developing country like India. Snake-venom antigen detection Kits should be made available. Mono-specific antivenom producers in India should be encouraged to prepare antivenom from venom obtained from snakes caught from relevant areas of the country. (Bawaskar *et al* 2015)

Biology of Poisonous Snakes: (Vishwapremi 1992**)**
Snakes are the elongated, cylindrical, vormi formed cold blooded animals varying greatly in length & their colour. Abundantly distributed in warmer parts of the world both in aquatic or terrestrial environment belonging to the sub

order ophidian of class reptilia. Snakes are the most awful and dangerous animals which cause terror amongst the people with their simple presence. Apart from the different categories of the snakes found all over the world, poisonous snakes have some distinctive features.1) Triangular shape of the head.2) Head is covered with shield, with 3rd supra labial touching the eye lid (especially in cobras) or the presence of hood mark.3) Presence of the hexagonal vertebrates larger than the rest of scales.4) Presence of 4 infra labials in which 4th is the largest along with enlarged ventral scales.5) Poisonous snake bites are identified with the presence of one or two deep bite marks of the fangs similar with that of an injection. Fangs are the hypodermic needle like hollow teeth having the small openings at their tip for the injection of the venom into the prey. A pair of salivary glands secretes a powerful multipurpose enzyme fluid (venom) that flow at the time of envenoming through fine channeled or grooved teeth called fangs. Venom secretion in all venomous snakes appears to vary in seasons; more in warmer months with high morbidity and fatality. Snake is cold blooded animal. Darker the snake, it secretes more venom as compared to a light colored. Because of the rise in body temperature of dark skin (poor conductor of heat) snake, the venom is in more fluid state and injected rapidly with high speed and maximum quantity in a short time during envenoming. As opposed to light colored skin because of low body temperature, the venom is thick and hence less amount is injected at the time of envenoming. It is quite clear that snake venom is not a substance evolved to attack man or any big vertebrates. Snake can bite and continue to secrete venom a number of times in succession. Most snakes inject 10% of the available venom in a single strike except the Russell's viper which injects 75% of stored venom in one bite due to big long sharp curved fangs. At times snake only, bite without envenoming called as "defence bite or dry bite", while the bite with envenoming is called as the "professional bite". (Bawaskar *et al* 2015)

Fang Orientation & Classification of snakes: (Eric Shull Iful 2008)

Venomous snakes are classified in three types depending on their fang orientation. **Opisthoglyphs:** These are rear fanged snakes. The fangs are enlarged rear teeth with a "groove" through which the venom flows down while the snake swallows its prey. Members of this group are mostly harmless or mildly venomous.

Proteroglyphs: These are the fixed fang snakes which have small non-movable front fangs. Obvious examples of this group are the cobras (*Naja*), sea snakes (*Hydrophiidae*) and mambas (*Dendroaspis*), all of them being venomous and potentially dangerous to man.

Solenoglyphs: These snakes have movable fangs. The fangs fold back into the mouth until they are needed. The poison fangs have enclosed canals within the teeth that transmit the venom out of the body very much like hypodermic needle. Examples of this group are vipers and pit vipers. These are also highly venomous and potentially dangerous to man.

Snake venoms: Properties, functions And Mechanism of Action: (Warrell 2010, Vishwapremi 1992)

Snake venoms are extremely complex mixtures of proteins, carbohydrates, lipids, metal ions, organic compounds, with proteins and peptides accounting for approximately 90% of the dry weight. They are acidic in nature having the pH range between 5.8 to 6.6 and specific gravity from 1.030 to 1,070. Variety of proteolytic enzymes, neurotoxic compounds, phospholipases, haemolycin, fibrinolycin and hyaluronidase are found in snake venoms. Primary function of the snake venom is to immobize and kill prey organisms. Venoms simultaneously commence the digestion of prey from within thereby augmenting assimilation efficiency. To accomplish these objectives, snakes employ a great variety of biochemical mechanisms which necessarily reflect both the biology of the snake and the nature of its principal prey. These mechanisms may be grouped into three fundamental enevenomation strategies. Two of these are prey immobilization strategies and may be denominated "hypotensive" and "paralytic" strategies. Both serve to limit the prey flight in case of snake taxa which strike and release the prey (most viperids) or to overcome the prey resistance, in the case of snakes that seize and bulldog their prey (mainly elapids and colubrids like cobras). The third strategy is "digestive" and commences degradation of the prey tissue even before the prey has been engulfed. Normally all three strategies operate simultaneously, and individual venom constituents frequently participate in more than one of them.

Biochemical Aspects of Snake Envenomation Strategies: (Aird SD 2002)

As stated earlier snake envenomation employs three well integrated strategies: prey immobilization via hypotension, prey immobilization via paralysis and prey digestion. Purines, the endogenous regulatory compounds in all vertebrates play central role in these snake envenomation strategies. Five purines are well known in biological

systems adenine, guanine, xanthine, hypoxanthine and uric acid. Purines are the end products of nucleoprotein digestion. They may be synthesized in the body. Purines constitute the perfect multi-functional toxins participating simultaneously in all three envenomation strategies and as they are endogenous regulatory and homeostatic compounds in all vertebrates, it is impossible for any prey organism to develop resistance to them. Purine generation from endogenous precursors also explains the presence of many hitherto unexplained enzyme activities in venoms, comprising 5-nucleotidase, endonucleases, ATPase, ADPase, alkaline and acid phosphomonoesterase, $PLA_{2s,}$ cytotoxins, myotoxins, and heparinases which play significant supporting roles in purine liberation cascade. Purines potentially contribute significantly to prey immobilization via several pathways.

1) First exogenous or released endogenous adenosine suppresses acetyl choline release from central and motor neurons principally via activation of adenosine A_1 receptors. It also suppresses liberation of other excitatory neurotransmiters like glutamate from other neurons.2) Second, adenosine and inosine potentiate venom induced hypotension by activating adenosine A_2 receptors in the vasculature and mast cell adenosine A_3 receptors.3) Third, guanosine may activate an unknown class of purine receptor or it may be taken up by purine transporters to increase vascular endothelial cell $_C$GMP levels.4) Adenosine exerts direct negative ionotropic effects on the heart via A_1 receptors.

Distribution of cobras and Pathogenesis of Indian Cobra (*Naja naja*) Envenomation:

All over the world total 15 species of Cobras are found, seven of which occur in Africa & 8 in Asia. Cobras are medium sized snakes with stocky cylindrical body. They are terrestrial hunters, and may be nocturnal or diurnal. Mainly feed on other reptiles, birds and mammals. All species are very dangerous to man. Indian cobra (*naja naja*) (Whitaker 1978) specifically known as "spectacled cobra" is found thought the country up to sea level 4000m. The spectacled cobra is varied in colour ranging from dark black, to brown or yellowish white. The underside is usually white or yellowish. The famous hood marking of the classic design shows a connected pair of rings. It is widely distributed in India, with its three-sub species. It is one of the famous big four dangerous snakes, including Russell's viper (Ghonus), Common Krait (Manyar) & Saw scaled Viper (Phoorsa). Cobra bite is often associated with severe necrosis of the local tissues & selective neuro muscular block leading to respiratory failure in human beings. (Reid *et al* 1983) Reports are also available about sudden respiratory failure in the patients bitten by the cobra, because of pulmonary hemorrhage (Bonta *et al* 1970) induced by the venom. Venom of the Indian cobra mainly contains three distinct substances (Parikh 1990), neurotoxin, haemolycin & cardiotoxin along with two basic, heat stable proteins (Larsen *et al* 1968) namely cobramine A & B. Enzymes like ATPase, cholineasterase, & Phospholipase A2 (Kini 2006) are also present. All these components of snake venom are responsible for its severe neurotoxic, cardiotoxic & local effects (Gupta 1999) in the human body. Reid (Reid 1964) has reported the systemic, cardiovascular & biochemical effects of venom in 47 patients bitten by common cobra in detail. Neuro toxins are the major components of the cobra venom, which are low molecular weight proteins. Neurotoxic action of the cobra venom components is primarily on the postsynaptic Ach receptor in the motor end plate of the muscle fiber, which interferes with impulse transmission leading to the respiratory paralysis. **(**Misra *et al* 1999**)** Cytotoxins constitute more than 50% of total venom proteins in some cobra venoms. These cytotoxins are lytic in nature and act synergistically with venom Phospholipase A_2 to rapidly lyse erythrocytes leading to the massive haemolysis and release of $K^{+,}$ causing cardiac arrest in victims.

Understanding the structure and function of Cobra toxins: (Kumar TKS ***et*** *al* 1999)

Lethality cobra venom is attributed to the presence of certain low molecular weight (6.5-9.0 kDa) homologus proteins known as cardiotoxins & neurotoxins with a high degree of disulfide crosslinking. Despite of their homology these toxins differ in their biological properties. Neurotoxins act on the acetycholine receptor at the post synaptic level of the neuromuscular junction while cardiotoxins exhibit a wide array of the biological activities like 1) depolarization and contraction of muscular cells, 2) prevention of platelet aggregation and 3) lysis of cells like erythrocytes, epithelial cells, fetal lung cells as well as a certain type of tumour cells. Apart from that cardiotoxins also inhibit the activities of certain enzymes such as Na^+, K^+ ATPase and protein kinase C.

Cardiotoxins: Cardiotoxins are single chained, sixty amino acid, and highly basic small molecular weight (6.5-7.0 kDa) proteins. To date, the amino acid sequences of about 52 cardiotoxins are known. Comparison of primary sequences of the members belonging to this class reveals that they are highly conserved, sharing more than 90%

amino acid sequence homology. In general, the disulfide bonds in cardiotoxins are located at 3-21, 14-38, 42-53 and 54-59.

Neurotoxins: Based on the length of the amino acid sequence they are conventionally classified as short and long neurotoxins. The short neurotoxins are mostly sixty-two amino acids long, cross linked by four disulfide bridges while long neurotoxins consist of more than seventy amino acids and characteristically contain an extra disulfide bridge as compared to the short neurotoxin counterparts.

Mode of action of neuro and cardiotoxins:

Functionally the important difference between the short and long neurotoxins lies in the rates of association and dissociation with the cholinergic receptors. Long neurotoxins are generally found to associate and dissociate with the receptor more slowly than short neurotoxins. On the other hand, cardiotoxins exhibit variety of biological activities. Because of their positively charged nature, they bind with high affinity to membranes / vesicles composed of the negatively charged lipids. It has been reported that cardiotoxin analogues from the Indian cobra (*Naja naja*) venom binds to calcium ions. (Kumar *et al* 1990) Moreover the toxins present in the cobra venom show great affinity towards acetylcholine receptors on the motor endplate. Neurotoxin from Indian cobra venom produces neuromuscular block without causing muscle contraction. This blockade leads to the respiratory arrest in the victim. Venom of the spectacled Indian cobra contains two principal neurotoxins A and B, which differ only by a serine/isoleucine substitution. Both toxins have same amino acid composition except that toxin B has one more serine residue and one less isoleucine residue than toxin A. (Mitsuhiro O *et al* 1976).

Later Effects:

Blisters (Reid HA 1968) around the site of bite are common in cobra bite. Local swelling and necrosis is the characteristic of poisoning from Asian cobra bites. Necrosis is extensive but superficial and involvement of tendons, muscles and bones is exceptional. Most of the times bacterial infection follows the necrosis and spreads to the joints. A constant feature of local swelling from cobra bite is a dusky discolouration around the bite marks. This deepens in colour each day. Sanguineous blisters develop over the middle of the dusky area. They are usually small, rarely extending 2-3 cm in diameter. After four to five days of the bite sloughing occurs and reveals necrosis of the subcutaneous tissue.

Distribution of Russell's viper and Pathogenesis of Russell's Viper (*Vipera russellii*) Envenomation:

Russell's viper or *Daboia* is a monotypic genus of old world viper, found all over the Asian as well as in Indian subcontinent. This snake has a patchy distribution over large area of Asia from India, Pakistan to Taiwan and the lesser Sunda Islands. Russell's viper bite is a serious medical problem in these areas. With distinct split in organismal phylogeny, prominent, diagnosable eastern & western forms (full species) *Daboia russellii* (West of the Bay of Bengal) & *Daboia saimensis* (East of the Bay of Bengal) have been recognized & reported by the workers. (Thorpe *et al* 2007). Clinical symptoms of human envenoming have also been reported to show marked geographic variations. Numerous sub species *D. russelli* , *D pulchella, D siamensis, D. limitis, D. formosensis* have also been previously reported. Vipers are medium sized snakes with stocky cylindrical body. They are terrestrial hunters, and may be nocturnal or diurnal. They mainly feed on other reptiles, birds and rodents. All species are very dangerous to man. Indian Russell's viper (*Daboia or Vipera russelli*) (Whitaker 1978) specifically known as "Ghonus" is found thought the country up to sea level 3000m. Russell's viper is varied in colour ranging from brown to yellowish brown. The underside is usually white in western or partly speckled in southeastern & heavily speckled in northeastern races. The chain like marking of the classic design shows dark round spots edged with white & black. It is widely distributed in India, with its three-sub species. It is one of the famous big four dangerous snakes, including Spectacled cobra (Nag), Common Krait (Manyar) & Saw scaled Viper (Phoorsa). Russell's viper venom is the rich source of different enzymes (Vishwanath *et al* 1987, Kini *et al* 1982) including Phospholipase A_2, ATPase, Hyaluronidase, & certain other components which act on the different parts of the human blood & induce severe haemostatic disturbances. (Than-Than *et al* 1988) in the human beings. This procoagulant activity of the Russell's viper venom is because of the presence of specific peptide components of the venom which activate different clotting factors. (Orten *et al* 1993) in the blood including factor IX (Christmas factor), factor X (Stuart Prower factor) factor V as well as platelets. (Refer cascade). This activation of many factors simultaneously produces a very contradictory effect in the systemic circulation of the humans, enhancing blood clotting as well as severe haemorrhage (Uma *et al* 2000), bleeding and haemolysis (Phillips *et al* 1988), called as Disseminated

Intravascular Coagulation (DIC) of the blood. Because of edema of muscle and bleeding there is development of compartment syndrome characterized by swelling, pain full passive movement and loss of sensation over the nerve areas passing through the compartment. Subsequently there is development of wet gangrene or non-healing ulcers. If untreated the bitten part usually toe or finger results in auto amputations. On the other hand, in smaller animals, Russell's viper venom promptly produces blood coagulation leading to the death of the animal because of the blocking of blood vessels of heart, kidneys & lungs.

Understanding the Structure and Function of Russell's viper Venom Components: (Suntravat *et al* 2011*)*

Lethality of Russell's viper venom is attributed to the presence of several toxins and enzymes like phospholipase A_2 (PLA2), Russell's viper venom factor X activator (RVV-X), Russell's viper venom factor V (RVV-V), proteinases, and certain unidentified proteins. Changes in the hemodynamics of the patients bitten by Russell's viper are suggested to be due to presence of proteolytic enzymes in the venom.

RVV-X: It is mainly known for its procoagulant activity. It activates coagulation factor X by cleaving a specific peptide bond (Arg_{52}-IIe_{53}) of the heavy chain of the clotting factor and it requires calcium ions for this proteolytic activity. In general, this proteolytic activity leads to the activation of normal coagulation pathway leading to the rapid formation of blood clots. RVV-X is the major lethal factor in Russell's viper venom which also affects the renal haemodynamics & renal functions apart from coagulation cascade.

Cytotoxins: Based on the sequence of the 20 N-terminal residues, a cytotoxin known as drCT-I is also reported (Roy Choudhury *et al* 2006) to be present in Russell's viper venom. Its molecular weight is found to be 7.2 kDa. Togather with cytotoxicity, drCT-I is also responsible for neurotoxicity, cardiotoxicity & myotoxicity of the snake venom.

Phospholipase A_2 (PLA_2): (Inn-Ho-Tsai 1997)**.** Two types of venom PLA_2s are present in the venom of R. viper in Asia. One has the N-terminal residue Asn & the other has residue Ser. All Asian sub species of Russell's viper venoms contain a potent heterodimeric PLA_2 neurotoxin (Russtoxin) except *D. pulchella*. It has been reported that venom of the species *D. formosensis, D. siamensis & D. russellii* (Pakistan) contain hypotensive & neurotoxic PLA_2s having an Asn residue at the N-terminus while species *D. pulchella* (Southern India & Sri Lanka) venom contains myonecrotic PLA_2s with N-terminal Ser residue. Apart from these heterodimeric toxic PLA_2s, some monomeric PLA_2s of low lethal potency are also reported to be present in viper venoms which are responsible for hypotensive & anti platelet effect of the venom.

Mode of Action of Russell's viper Venom:

Functionally the important elements of viper venom toxicity are the high affinity & the availability of the specific receptors for presynaptically toxic PLA_2s. Recently synaptic binding proteins of daboia toxin, the myotoxic & neurotoxic PLA_2 from Russell's viper venom has been reported to be a 110 kDa protein with two subunits of 25kDa & 75kDa. Though hypotensive PLA_2s of Indian Russell's viper venom binds to receptors in a slightly different way, it is still unclear. (Inn Ho Tsai 1997). Moreover, the basic PLA_2 from *Vipera russellii* venom induces multiple toxic effects like neurotoxicity, myotoxicity, edema and haemorrhage. Russell's viper venom specifically causes lung haemorrhagic activity in the victims of the bite which is always massive in nature. Specific sites or overlapping sites in the human cells are responsible for this haemorrhagic activity. (Gowda *et al* 2000). It is also reported that direct Russell's viper bite over a vein leads to the direct intravenous envenoming causing myocardial infarction and myocardial ischemia in the victim. (Silva *et al* 2012). Moreover, haemorrhagic PLA_2s from viper venom block neuromascular transmission apparently via phospholipolytic action on both nerve and muscles. They also induce significant hypotension by perforation of capillary walls leading to the escape of whole blood into the tissues which is the most common symptom in viperid envenomation. Presence of extremely active proteases (Haemorrhagins) also contribute to the prey digestion by allowing other venom constituents and released endogenous catabolic enzymes access to the tissues. PLA_2s also contribute to the hypotension by increasing capillary permeability and histamine release. Apoptosis or programmed cell death occurs due to DNA degradation, membrane bleb formation and cell disintegration. (Aird 2002). (Fig 1)

Later Effects:

Russell's bite victims subsequently develop amenorrhoea, Sheehan's syndrome, loss of libido due to hypo-pituitaries. Enhanced capillary permeability may also be seen in the form of plural, pericardial effusion, ascities and conjunctivitis, hemorrhage or congestions. Many cases subsequently develop anuria, oliguria and acute renal

failure. Renal angle tenderness is the most important clinical sign for early diagnosis of renal failure. There is serial rise in blood urea and serum creatinine with acidosis and hyperkalemia. Generalized anasarca, renal failure is due to tubular damage by venom itself, hemoglobinuria, hypotension, micro thrombi in the kidney contribute to the acute tubular necrosis which is the commonest cause of death. Ptosis, bulbar palsy, inter-nuclear opthlamoplegia and respiratory paralysis due to presynaptic neuromuscular block in a Russell's viper bite poisoning are often seen and reported.

Distribution of Common Krait and Pathogenesis of Common Krait (*Bungarus caeruleus & Bungarus fasciatus*) Envenomation: (Kumar *et al* 2006)

Out of the two varieties of *Bungarus* species found in the subcontinent, common krait (*Bungarus caeruleus*) and banded krait (*Bungarus fasciatus*), the former is responsible for nocturnal human bites and large mortality. The latter is not so aggressive and envenomation by this snake in the subcontinent has not been reported in literature. The common krait has small and fixed front fangs. Its bite may not be painful, and the local symptoms are barely discernible, but systemic symptoms and abdominal pain are the distinctive features of a krait envenomation, along with hypokalemia. The neurotoxins in the krait venom are prominently pre-synaptic and prevent release of acetylcholine at the neuromuscular junctions. Krait venom has a fatal dose of 6 mg with an average deliverable dose of 20 mg. An attempt has been made to develop an ISFET (ion sensitive field effect transistor)-based immunosensor for the detection of β-Bungarotoxin, a major constituent of krait venom, in order to identify such venom in the victim.

Understanding the Structure and Function of Common Krait Venom Components:

The venom of kraits contains three major types of neurotoxin. α-Bungarotoxins cause a failure of neuromuscular transmission by binding to post-synaptic nAChR at the neuromuscular junction (NMJ). Similar toxins are found in the venoms of all elapid snakes and their close relatives, the sea snakes. κ-Bungarotoxins are found exclusively in the venom of kraits. They are structurally similar to the α-bungarotoxins, bind to neuronal nAChR but are minor components of the venom. The β-bungarotoxins constitute >20% of the protein content of the venom and are the most toxic components of the venom. They are pre-synaptically active neurotoxic phospholipases A_2. Exposure to these toxins *in vivo* and *in vitro* causes the failure of neuromuscular transmission for 2–3 h, and the depletion of synaptic vesicles from nerve terminal boutons is a primary pathological feature of. Structural damage to the motor nerve terminal and terminal components of the motor axon follows rapidly and destruction of the nerve terminal is complete by 12–24 h. It has been suggested that β-bungarotoxin (alone or in combination with α-bungarotoxin) is primarily responsible for the severe paralysis associated with envenoming bites by kraits. The underlying hypothesis is that the onset of paralysis is caused by the depletion of synaptic vesicles from the nerve terminal, the destruction of the terminal boutons explains the phase of profound treatment-resistant paralysis and the slow recovery of neuromuscular function reflects the regeneration of nerve terminals and the re-innervation of the denervated muscle. (Prasarnpun *et al* 2005)

Mode of Action of Common Krait Venom:

The common krait's venom consists mainly of powerful neurotoxins, which induce muscle paralysis. This venom contains pre-synaptic and post synaptic neurotoxins, which generally affect the nerve endings near the synaptic cleft of the brain. Incidents occur mainly at night because kraits are nocturnal. Frequently little or no pain occurs from a krait bite. Krait bites are significant for inducing minimal amounts of local inflammation or swelling and this usually gives the false reassurance to the victim. Typical symptoms after a krait bite are abdominal cramps, accompanied by progressive paralysis. Cause of death is generally respiratory failure and suffocation. The few symptoms of having bitten are that the facial muscles get tightened in one or two hours, the patient may be unable to talk or see and if left untreated the patient may die from respiratory paralysis within four to five hours. (Prasarnpun *et al* 2005)

Distribution of Saw Scaled Viper and Pathogenesis of Saw scaled viper (*Echis carinatus*) Envenomation:

Echis carinatus, commonly called the ***saw-scaled viper***, is a venomous viper species found in parts of the Middle East and Central Asia, and especially the Indian subcontinent. It is the smallest member of the big four snakes that are responsible for causing the most snakebite cases and deaths, due to various factors including their frequent occurrence in highly populated regions, and their inconspicuous nature. This species produces on the average of about 18 mg of dry venom by weight, with a recorded maximum of 72 mg. It may inject as much as 12 mg, whereas the lethal dose for an adult is estimated to

be only 5 mg. (Daniels 2002). Envenomation results in local symptoms as well as severe systemic symptoms that may prove fatal. Local symptoms include swelling and pain, which appear within minutes of a bite. In very bad cases the swelling may extend up the entire affected limb within 12–24 hours and blisters form on the skin. The venom yield from individual specimens varies considerably, as does the quantity injected per bite. The mortality rate from their bites is about 20%, and due to the availability of the anti-venom, deaths are currently quite rare.

Understanding the Structure and Function of Echis carinatus Venom Components:

The venom of *E. carinatus* affects the blood circulation. This venom is very toxic causing severe tissue and organ damage. The venom of *E. carinatus* is rich in proteins and peptides effective on the hemostatic system, i.e., its acts against some types of factors involving coagulation and fibrinolysis. *E. carinatus* snake venom especially contains proteins affecting the transformation of the prothrombin into thrombin. Prothrombin is the protein which is broken in plasma by ecarin. In fact, this protein cleaves the bond in prothrombin and produces meizothrombin, which is converted into α-thrombin by autolysis. The conversion of the prothrombin into thrombin is one of the central reactions of blood coagulation. The physiological activation of prothrombin to the serine proteinase α-thrombin is catalysed by prothrombinase complex consisting of the serine proteinase, factor Xa, cofactor Va and Ca^{2+}. Membranes containing anionic phospholipids are essential for the optimal function of this enzyme complex. However, the rate of activation is five orders of magnitude lower than the activation by prothrombinase complex, and the mechanism of cleavage proceeds through prethrombin-2 rather than through meizothrombin. The venom of Viperidae presents a high level of haemorrhagic, coagulant and proteolytic activities. (Mahdi Babaie *et al* 2013).

Mode of action of Echis carinatus venom: (Ali et al 2004)

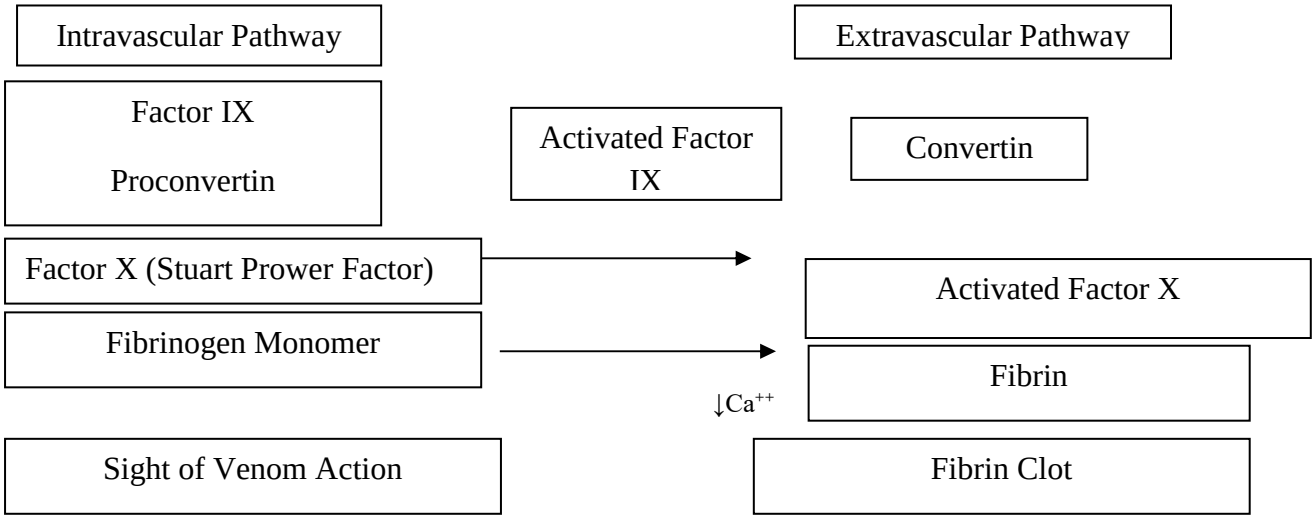
Of the more dangerous systemic symptoms, hemorrhage and coagulation defects are the most striking. Hematemesis, melena, hemoptysis, hematuria and epistax is also occur and may lead to hypovolemic shock. Almost all patients develop oliguria or anuria within a few hours to as late as 6 days post bite. In some cases, kidney dialysis is necessary due to acute renal failure (ARF), but this is not often caused by hypotension. It is more often the result of intravascular hemolysis, which occurs in about half of all cases. In other cases, ARF is often caused by disseminated intravascular coagulation. The victim of a Saw scaled viper will experience severe pain in the bitten area and sometimes the bitten area may be swollen. If the poison spreads in the blood of the victim then the patient may start shivering, vomiting, feel feverish, may experience chillness and oozing of blood from the gums. Normally blood may ooze out between one to fourteen hours. If the bite is severe blood may ooze out within one hour from the gums of the patient. With the passage of time the patient may have renal failure, blood may ooze out from the tongue of the victim, blood may also start coming from the different parts of the body like nose, eyes and ears. Finally, blood may also bleed from the brain and may lead to heart attack which is one of the common causes for the death of the victim. Acute renal failure is one of the most life-threatening complication of Echis carinatus envenomation. It occurs in about 17% of cases and mortality is around 25%. The viper venom causes several clinical abnormalities that favour development of acute renal failure. These changes include varying degrees of bleeding, hypotension, intravascular haemolysis and acute or compensated DIC. Thrombocytopenia can occur without DIC and could be responsible for bleeding. Haemodialysis is preferred. Indications for dialysis include anuria of more than 48 hours, hyperkalemia pulmonary oedema, severe acidosis, convulsions and rising blood urea and creatinine. Acute renal failure is largely preventable. It is usually associated with oliguria. It generally occurs within 48 hours following the bite, but may be delayed by even 2 weeks.

Conclusion:

According to the recommendations of WHO, the most effective treatment for snakebite is the administration of monospecific Anti Snake Venom Serum. Hence, the identification of the snake species becomes the utmost requirement for medical management. Attempts have been made to develop field ELISA kits and electronic immunosensors for identification of the species. Until the definitive methods become commercially available and viable, the attending medical staffs have to depend on their wisdom and capability to classify the species and assess the envenomation severity. In this paper, an attempt was made to explain the toxicity of individual species and species-specific symptoms developed in the victims of snakebites, which may help in the proper identification of

the aggressor and in grading the envenomation. However, due to a variety of reasons, management of snakebite cases in the Indian subcontinent is a challenge and needs a networked and well-coordinated effort across the boundaries of the nations.

Figure 1. Blood cascade



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