Review Article

Pathology of snakebite envenomation

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Abstract

Snakebites are one of the major neglected health problems in the tropics which comprise mostly of the developing and underdeveloped countries. Viper bites are more common than other poisonous snakebites in human beings. The venom of snakes of the family Viperidae, to which the Russell’s viper belongs, consists of a mixture of toxic proteins and enzymes which have hemotoxic and necrotizing properties. There is a profound difference in venom composition and enzymatic activity of these snakes found in different geographical locations. This is aptly reflected in mammoth degree of geographic variation in the pathological effects of its venom on human bite victims. The defective blood coagulability and renal failure are widespread. There are other pathological effects which show a strong geographic variation. Bites in Sri Lanka have resulted in neurotoxicity, rhabdomyolysis and intravascular haemolysis. Bites in Burma resulted furthermore in shock and generalized capillary permeability, whereas bites in Thailand resulted mostly in intravascular haemolysis and reduced coagulability. Pituitary hemorrhage and bleeding in the subarachnoid space has been reported after a bite by Russell’s viper in Southern India and in Burma. The death is most protracted in viper bites from massive cerebral and retroperitoneal bleeding. The present paper reviews the variations in snakebite manifestations and highlights on the pathology of envenomation resulting from snakebites and its management.

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1. Introduction

Snakebite is an important and preventable health hazard. Annually, there are more than 2.5 million cases of Snakebite, of which about 100,000 are fatal, occurring mostly in rural tropical areas.1 Annual incidence of Snakebites in India is reported to be 0.16% with a mortality of 0.016% per year.2 Russell's viper envenomation is a health hazard in many parts of South East Asia.3 An analysis of the snakebite cases in India reveals that the fatality from Russell's viper envenomation is highest in the Burdwan district of West Bengal,4 where 1301 deaths occur per year.5 However, the actual incidence may be much higher as majority of cases occurring in villages go unreported. Inspite of advances in the medical field, traditional remedies remain more popular in these villages. Also the lack of transport facilities in these areas
poses difficulty in seeking early medical aid.\textsuperscript{6-8} The mortality in different states of India due to snakebite envenomation is reported as 2.85-5.3\% of total hospital deaths per year as compared to five to six deaths per year in U.S.A and even a lower mortality of one death every three to five years in Europe. The high mortality rate in India can be attributed to geographical factors, rural predominance of population and their agricultural dependence and hence, India is known as the "Land of Exotic Snakebites".\textsuperscript{9,11}

2. Venom apparatus and snake venom- Its constituents and uses

Of approximately 3000 snake species worldwide, about 600 are venomous. These are found in four snake families: Colubridae, Elapidae, Viperidae and Atractaspididae.\textsuperscript{12} Venom apparatus consist of a pair of salivary glands, one on each side of the head, below and behind the eye, connected by ducts to hollow or grooved fangs. In Viperids and Crotalids these fangs are long and mobile, having a canal from base of the fang to the tip, that retract against the roof of the mouth when they are at rest. In Elapids and Hydrophids, the fangs are small, fixed in an erect position, having a canal, which is not fused completely. In Asian spitting cobras the fangs are modified to allow the snake to eject a spray of venom into the eyes of the aggressor. Instead of opening downwards at the tip of the fang the venom channel is angled forward. When snakes have bitten two or more victims in rapid succession the second or third victims are more severely envenomed than the first. The Russell’s viper however, appears to inject most of its available venom at the first strike. Snakes are also capable of biting defensively without injecting venom (dry bites). The snake’s venom apparatus has been evolved to deliver a mechanically effective bite with injection of a supra lethal dose of venom into the prey.\textsuperscript{13-15} Most of the snake venoms are clear, amber, yellow or straw-colored viscous fluids secreted from their modified parotid glands as a part of its food gathering mechanism, which enables it to immobilize the victim and begin digestive process prior to swallowing.\textsuperscript{15-18}

Therapeutically the major use of venom is for the preparation of antivenom. Other uses include-ARVIN, the active ingredient of Malayan Pitviper is used as an anticoagulant in ischaemic heart disease and in the purification of antihaemophilic factor; venom of Brazilian snake is used for developing angiotensin converting enzyme inhibitor drugs (ACE inhibitors). Saxatilin, an active ingredient of a Korean Snake is used in inhibiting breast tumor growth, arterial thrombosis and restenosis after angioplasty. Venoms of some species of viper in non-lethal dose are used as a cure for epilepsy and chorea. Diagnostically Russel’s viper venom is used as a reagent in clotting function tests (Clotting time, prothrombin time and activated partial thromboplastin time). Centre for cellular and molecular biology, Hyderabad uses probes derived from the venom of female Indian banded krait (Bangarus fasciatus) in DNA fingerprinting or genetic typing.\textsuperscript{1,15,19-23}

Almost 90\% of dry weight of venom is protein in nature consisting of enzymes, non-enzymatic polypeptide toxins and non-toxic proteins. Non-protein ingredients of venom include carbohydrates, metals, lipids, free amino acids, nucleosides, serotonin and acetylcholine.\textsuperscript{13}

2.1 Polypeptide toxins (\textit{\alpha} bungarotoxin, \textit{\beta} bungarotoxin, crototoxin, taipoxin): These are often called neurotoxins and are found almost exclusively in elapid and hydrophid venoms. It paralyses the respiratory centre and is the predominant agent in causing death in cases of cobra and krait bites. It acts on several centres in the brainstem producing symptoms that are similar to those seen in bulbar palsy where lips, tongue, throat and voice are paralyzed. It depresses the vasmotor centre and acts on the centers of 9th, 10th, 11th, and 12th cranial nerves and paralyses the nerve terminals (motor end
plates) of the muscles especially for those of the diaphragm.

2.2 Cytotoxins: Following are the various cytotoxins in snake venom-
   a) Haemolysin - causes destruction of red blood cells.
   b) Leucolysin - causes destruction of endothelial cells.
   c) Haemorrhagin - causes destruction of endothelial cells lining the blood vessels allowing blood to extravasate.
   d) Cytolysin - causes destruction of cells of liver, kidney, testis and of tissue cells at the site of the bite.

2.3 Antifibrin: This reduces the clotting power of the blood.

2.4 Cardiotoxin: This is found particularly in cobra venom and causes bradycardia, cardiac asystole and inhibition of skeletal muscle contraction by direct action on the muscle cells.

2.5 Thrombase: This causes thrombosis.

2.6 Proteases: This causes local inflammation, necrosis and damage to the vascular endothelium. Anticoagulant, fibrinolytic, antithromboplastic and enhancement of plasminogen activity are attributed to the action of proteases.

2.7 Hyaluronidase: This depolymerises the hyaluronic acid, which is an intercellular substance of most human tissues and allows other fractions of venom to penetrate the involved tissues, thus helping the spread of venom through tissues.

2.8 Phospholipase A2 (lecithinase): This causes hydrolysis of phospholipids, releases lysolecithin that is a strong hemolytic agent. It damages mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular endothelium and other membranes. It attacks mast cell membranes releasing pharmacologically active substances known as autocoids (e.g. histamine, kinins and 5-hydroxytryptamine).

2.9 Cholinesterase: This is found in cobra and krait venoms and causes hydrolysis of acetyl choline to choline and acetic acid; thus impairing the neuro-muscular transmission.

2.10 Phoshodiesterase: This is responsible for hypotension produced during envenomation.

2.11 Biogenic amines or autocoids (histamine, 5 hydroxytryptamine and kinins): This is found particularly in viper venom and is responsible for local effects such as bruise and swelling.

2.12 L-aminoo acid oxidase: This has a digestive action and also imparts yellow color to the snake venom (due to the presence of Riboflavin as a coenzyme).

The exact mode of action of snake venom is not fully known. In snakes of family Elapidae (cobra, krait and coral snakes) the predominating toxic factor is neurotoxin whereas among the snakes of Viperidae family (Russell’s viper and saw scaled viper), the predominating toxic factor is haemorrhagin. The anticoagulant activity is more important in case of viper bite and may result from destruction of fibrinogen to prothrombin, inhibition of thrombin formation or destruction of platelets. The venom of Crotolus terrificus, a rattlesnake, is strongly neurotoxic. As a result of their heterogeneous compositions, exact classification as neurotoxic, cardiotoxic, or myotoxic is impossible.

3. Pathogenesis

Several complications are likely to develop during the clinical course of snake-envenomed patients. Cobra and Viperine bites produce extensive skin blistering, necrosis and even gangrene. This may even end up in loosing digit or affected limb if there is secondary infection. Shock in early phase of viper bite is attributed to kinins and complement activation, which is a
transient phenomenon. Later, shock is the consequence of venom effects, sepsis and multiple organ system failure. Some patients may develop acute adrenal insufficiency due to pituitary necrosis seen commonly in Russell’s viper bites. Acute renal failure is most often seen following viperine bites and sometimes following bites by Elapids and Hydrophids. 32-36

Renal failure is the major cause of death in viper bite. The possible mechanism of acute renal failure (ARF) is prolonged hypotension, disseminated intravascular coagulation (DIC), intravascular haemolysis, nephrotoxicity of the venom and myoglobinuria. 37 Hypotension can result in ischemic acute tubular necrosis (ATN). The presence of fibrin thrombi in the renal microvasculature and in the glomerular capillaries suggest that DIC plays an important pathogenic role in snake-bite induced ARF. 25,38 Intravascular haemolysis is also thought to have a pathogenic role in Snakebite induced ARF. 39,40 Studies have revealed that the levels of plasma free haemoglobin observed were much lower than the toxic levels. 38 It is suggested that when it is combined with other factors like hypotension and hypovolaemia, it can contribute to the onset of renal failure. Snake venom is thought to have a direct cytotoxic effect on the kidney. 25 Chugh et al. did not observe any nephrotoxic lesions in rhesus monkeys on administration of a lethal dose of Russell’s viper or Echis carinatus venom. They however, found fibrin thrombi in glomerular capillaries and ATN in the majority of animals who were given sublethal doses and concluded that direct nephrotoxicity is not a major factor in the pathogenesis of renal failure. 38 Phospholipase A, 41 an important toxic component of the venom, stimulates hypothalamus-pituitary and immune axes to increase adrenocorticotropic hormone, corticosteroid, arginine, vasopressin and acute phase response. 42 Histamine, kinins, eicosanoids, platelet activating factor, catecholamines and endothelin are among the involved mediators. Zinc metalloprotease can cleave glutathione-S-transferase-tumour necrosis factor-alpha fusion protein (GST-TNF-alpha) substrate to generate biologically active TNF. 43 Snake venom proteins that affect the haemostatic system can cause (a) lowering of blood coagulability, (b) damage to blood vessels resulting in bleeding, (c) secondary effects of bleeding, e.g. hypovolaemic shock and organ damage, and (d) thrombosis. 12 Disturbances of haemostasis, the system of all reactions that contribute to the effective arrest of bleeding, are among the most severe effects following Snakebite and are caused by members of several genera from all four families. 44,45 Incoagulable blood is caused by defibrination resulting from consumption of the components of the haemostatic system. 3 This may lead to bleeding causing haemostasis and haemoptysis of Russell’s viper bite victims. Therefore once the patients’ blood has become defibrinated and incoagulable, the activity of hemorrhagins, which damage the vascular wall endothelium, may lead to spontaneous systematic bleeding from vital organs. 3

4. Clinical manifestations

The severity of clinical manifestations is dependent on a number of factors. The symptoms are severe in a child or young adult. Physical exertion after a bite aggravates the symptoms, as more poison will be absorbed. Bites on the extremities and adipose tissue are less dangerous than those on the trunk and face. Toxicity of juvenile snake venom is more than that of the adult snake. Larger the size of the snake larger will be the size of the venom gland and greater the venom injected on biting. If it has eaten a prey or bitten an animal previously, less venom will be present in the gland. A direct stroke with the entry of fangs deep into the tissues is more dangerous than a glancing stroke, which causes superficial abrasions. The entry of fangs into a vein directly causes severe envenomation. The vipers and crotalids (Rattle snake and pit vipers) discharge most of the
venom without any leakage at the moment the fangs penetrate the skin. They can bite through the clothing.\textsuperscript{13,18,32}

The most common symptom following snakebite is “fright” – particularly the fear of rapid and unpleasant death, which often dominates the clinical picture. Victim of snakebite is usually convinced that he has no chance of survival, and goes into a state of neurogenic shock within minutes, characterized by a semiconscious state, cold and clammy skin, feeble pulse, rapid and shallow breathing. All these will respond to a simple reassurance or a placebo injection.\textsuperscript{7,47} In viper bites there will be burning sensation followed by continuous oozing of blood from the site of bite. Localized swelling starts within fifteen minutes after the bite, if venom is injected. The absence of detectable local swelling two hours after a viper bite indicates that no venom has been injected. If large amount of venom is injected, the swelling may reach above the knee or elbow depending on the site of bite within one to three hours. The swelling is due to venom diffusing through the cutaneous tissues and affecting the vascular permeability. This is followed by ecchymosis and appearance of blebs or bullae filled with serum and later necrosis.\textsuperscript{24,47,48} The necrosis becomes well established within 24 hours. Local necrosis in viper bites is mainly ischaemic, thrombotic, blocking local blood vessels and causing ‘dry gangrene’.\textsuperscript{24,47,48}

Systemic symptoms in viper bites appear within minutes and include nausea, circulatory collapse, hypotension, tachycardia, bleeding from the gums and nose, cutaneous haemorrhages, haematuria, haematemesis, haemoptysis and melena. Death is most protracted in viper bites (average of two to three days after the bite) from massive cerebral or retroperitoneal bleeding. If a large dose of venom is injected, death may take place within few hours. Convulsions usually precede death. About fifteen drops of viper venom proves fatal for an adult.\textsuperscript{13,19,24,35,47-49}

5. Management

Snakebite is a medical emergency and first aid, if given early can reduce the morbidity and mortality to a minimum. First aid in snakebite (reassurance and immobilizing the bitten limb) is meant to delay absorption and spread of the venom from the site of bite, while the patient is being shifted to the nearest medical centre with facilities of antivenom administration. Venom will be confined to the local site of bite for an hour; therefore a victim who can reach the hospital within an hour may not need any first aid measures.\textsuperscript{6,7,13,15,51,52} In the hospital, intravenous access is gained first followed by administration of tetanus toxoid and patient nursed in a lateral position to avoid aspiration. Patient has to be carefully monitored for features of systemic envenomation for a period of at least not less than 24 hours.\textsuperscript{35} Antivenom is the only effective and specific treatment available for the envenomation. If the identity of the snake is known, the ideal treatment is with monovalent/monospecific antivenom. This involves administration of a low dose of antivenom protein than polyspecific/polyvalent antivenom. However, the difficulty in identifying the snake leads to the use of polyvalent antivenom as the main form of treatment.\textsuperscript{33,53}

Polyvalent antivenom available in India is effective against the four common poisonous snakes, namely common cobra, common krait, Russell’s viper and saw scaled viper. It is available in a liquid or in lyophilized form. Lyophilised antivenom is superior to liquefied antivenom because of its stability. One ml of polyvalent anti-snake venom neutralizes 0.6mg, 0.45mg, 0.6mg and 0.45mg of venoms of common cobra, common krait, Russell’s viper and saw scaled viper.\textsuperscript{54,55} Freeze dried
(lyophilized) antivenoms are reconstituted, with 10ml of sterile water; 0.1ml of it is given intradermally as a test dose. The patient is carefully observed for allergic manifestations. Then the reconstituted venom is diluted in 500ml of isotonic saline or 5% dextrose and is infused at a constant rate over a period of about one hour. When the prothrombin level remains 80% or more of normal for twenty-four hours in a case of viper bite there is no need for further administration of antivenom.56,57 During the administration of antivenom, care should be taken to avoid anaphylactoid reactions. These are due to compliment activation by immune complexes. They may develop by 10 minutes to two hours after starting the antivenom therapy and the probability increases with the dose and decreases when more refined antivenom is used. 40% of the patients may develop anaphylactoid reactions-hypotension, bronchospasm and angioedema. They readily respond to antihistaminics. Pyrogenic reaction may occur due to presence of endotoxin like compounds in the antivenom. This is characterized by fever, rigors, vasodilation and fall in blood pressure. These symptoms usually appear twelve hours after the treatment. Cooling measures (ice packs) and antipyretics control these reactions. Late reaction in the form of serum sickness may be noticed, which is an immune complex disease characterized by fever, itching, urticaria, arthralgia, lymphadenopathy, periaricular swelling, albuminuria and rarely encephalopathy. This reaction responds to corticosteroids and antihistaminics. Antihistaminics and use of steroid umbrella before the administration of antivenom will prevent the dangerous anaphylactoid reactions.6,13,19,30,58

6. Conclusion

Snakebites are one of the major neglected health problems in the tropics which comprise mostly of the developing and underdeveloped countries. Immobilization, prompt medical advice and administration of ASV remain the mainstay to managing a case of snakebite. Awareness on snakebites and preventive measures can bring down the morbidity and morbidity associated with snakebites.

References

34. Sathyangathan VP, Mathew MT. Raynaud’s Phenomenon and Gangrene following snake envenomation. J Assoc Physicians India 1993;41:122-123.


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