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REVIEW ARTICLE

Deadly Bite: An Insight into Snake Envenomation, Components and Its Effects

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ABSTRACT
Snake bites are a significant global health issue, particularly in tropical and subtropical regions. The venom from these bites, composed of various proteins and molecules, causes severe local and systemic effects such as blood clotting issues, neurotoxicity, muscle damage, heart problems, and inflammation. Treating snake bites is complicated due to the venom's variability, influenced by the snake's age, species, and location. The highest incidence of snake bites occurs in South Asia, Southeast Asia, sub-Saharan Africa, and Latin America, with India having the most cases, especially during the monsoon season. Venomous snakes belong to five families: Colubridae, Atractaspididae, Elapidae, Viperidae, and Hydrophiidae, each with distinct characteristics. Clinical features of snake bites include local signs like fang marks, swelling, pain, necrosis, and systemic symptoms such as clotting issues, neurotoxicity, muscle damage, heart problems, kidney damage, and shock. Effective management involves quickly identifying the snake species, administering the correct antivenom, and providing supportive care. Developing antivenom is challenging due to the venom's complexity and variability, necessitating ongoing research to improve treatments and reduce morbidity and mortality from snake bites.
Keywords: *Snake bites, venom, neurotoxicity, blood clotting disorders, muscle damage, antivenom.*

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INTRODUCTION

The most feared poisonous animal in the world is the snake, due to the extensive illness and mortality that they produce. These reptiles are carnivorous and poikilothermic, and they are highly prevalent in hot climates worldwide. Snakes employ their glandular secretion, known as venom, to paralyze and eat their victims. It is also a tool for defense and survival. This deadly concoction consists of proteins, peptides, lipids, carbohydrates, nucleic acids and amino acids [1]. In addition to immunological analysis of venom and serum proteins, sequence analysis of DNA encoding mitochondrial and other enzymes, snakes are categorized based on their morphological traits, which include the arrangement of scales (lepidosis), dentition, osteology, myology, sensory organs, and the form of their hemipenes. Venomous snakes belong to 5 families: Colubridae, Actractaspididae, Elapidae, Viperidae, and Hydrophidae[2].Venom injected into the body from a snake bite is known as snake envenomation, and it is a complicated and sometimes fatal condition that presents major problems for healthcare systems around the globe. A wide variety of toxins, each with distinct physiological effects and biochemical characteristics, are used by venomous snakes in their venom. Snake venom is a special composite mixture of proteins, peptides, and other small molecules, both enzymatic and non-enzymatic. When absorbed through the bloodstream, it can cause a variety of progressive multisystem manifestations such as hematological, neurotoxic, myotoxic, cardiotoxic, local, inflammatory, and necrotic effects that occasionally call for intensive care.[3].

EPIDEMIOLOGY

The global burden of snake bites is not evenly distributed; higher incidence rates are reported in tropical and subtropical regions, particularly in South Asia, Southeast Asia, sub-Saharan Africa, and Latin America. Asia accounts for the highest number of snake bite cases globally, with an estimated 2.7 million envenomings and 46,000 to 94,000 deaths each year. Approximately 81,000 to 138,000 snake bite-

related deaths occur annually globally. However, the actual mortality figure may be higher due to underreporting and lack of comprehensive data collection in many regions. In India, the high morbidity and fatality rate from snake bites poses a serious threat to public health. Based on current studies, the epidemiology of snake bites in India is broken down as follows: India is the country that reports more than a million-snake bite cases a year, which makes it the world leader in this category. In India, snake bites cause between 46,000 and 58,000 fatalities annually. However, because of incomplete data collection and underreporting in rural regions, the true death rate may be greater. Although snakebite incidents are common in all of India, some states record greater incidence rates because of ecological variables and interactions between humans and snakes. The states with the largest number of reported cases of snake bites include Uttar Pradesh, Bihar, Maharashtra, West Bengal, and Andhra Pradesh. The monsoon season (June to September) and the months after it are usually the peak times for snake bites since agriculture is expanding during this time, increasing the exposure of rural regions to snakes [4-6].

COMPONENTS OF SNAKE VENOM

When compared to the venoms of other creatures like spiders, scorpions, and cone snails, snake venom is noticeably more complicated. While the pharmacological effects of these animal venoms are mostly attributed to disulfide bridged peptides. The pharmacological and toxicological effects of snake venoms are derived from a more varied array of bigger proteins and peptides. These venoms consist of 50–200 components that are arranged in both dominant and secondary families and can manifest as different isoforms of proteins and peptides. Major snake venom proteins are generally classified into two categories: venoms with intrinsic enzymatic activity and non-enzymatic venoms. Three-finger peptides (3FTX), snake venom metalloproteinases (SVMP), disintegrins, L-amino acid oxidases, kunitz peptides, C-type lectins, and natriuretic peptides are among the secondary families, whereas secreted phospholipases A2 (PLA2s), SVMP, and SVSP are the dominant families. It's interesting to note that the composition of snake venom differs both intra- and interspecifically. Age, gender, location, nutrition, and season are just a few of the variables that affect this diversity. The diversity and multifunctionality of toxins are supported by this variability phenomena, which is crucial to take into account while producing antivenom and treating envenomation. There are three primary categories of pharmacological effects associated with snake venoms: cytotoxic, neurotoxic, and hemotoxic. The main toxins causing these effects are PLA2s, SVMPs, SVSPs, and 3FTXs. These toxins, either separately or in combination, are in charge of the many pharmacological effects that snakebite patients experience. As an antagonist of ion channels and nicotinic or muscarinic receptors, certain PLA2s and 3FTX, for instance, can operate on pre- or post-synaptic junctions to cause severe neurotoxicity, including paralysis and respiratory failure. Furthermore, SVMPs, in addition to other PLA2s and 3FTXs, cause systemic consequences such hypovolemic shock and local tissue damage that results in swelling, blistering, bruising, and necrosis. Moreover, coagulopathy, hypotension, and bleeding are hemostatic and cardiovascular consequences of SVSPs and SVMPs. It's interesting to note that certain PLA2s, SVSPs, and SVMPs can also cause severe pain by altering pain pathways by activating ion channels like acid-sensing ion channel (ASIC) and transient receptor potential vanilloid type 1 (TRPV1), or by making the body more sensitive to pain through inflammatory mediators. Elapid and viper venoms are known to cause inflammation, which in both human and experimental models has been shown to cause pain or hyperalgesia. Regretfully, antivenom and anti-inflammatory medications cannot totally reverse symptoms [7].

CLINICAL FEATURES:

LOCAL SIGNS AND SYMPTOMS:

Fang Marks: Typically two puncture wounds; non-venomous bites may show an arc of tiny punctures.
Pain: Intense, throbbing pain spreading proximally; sea snake and krait bites might be nearly painless.
Swelling: More severe with viper bites; can develop within minutes and spread extensively.
Necrosis: Blisters, bruising, and tissue necrosis, particularly with viper and some cobra bites.
Secondary Infection: Due to snake's oral flora[8,9].

SYSTEMIC FEATURES:

Clotting Deficiencies and Hemolysis: Common in viper bites, leading to prolonged bleeding, spontaneous hemorrhages, and intravascular hemolysis.
Neurotoxicity: Elapid and sea snake venoms cause paralysis, starting with ptosis and ophthalmoplegia and potentially leading to respiratory failure.
Myotoxicity: Sea snake venoms cause rhabdomyolysis, muscle pain, and myoglobinuria.
Cardiotoxicity: Venom can cause arrhythmias, bradycardia, tachycardia, or hypotension.
Nephrotoxicity: Ischemia and direct venom effects can lead to renal failure.
Shock: Due to fear, hypovolemia, cardiac depression, hemorrhage, and increased kinin production [9,10].

DISORDERS AND ITS PATHOPHYSIOLOGY

LOCAL TISSUE DAMAGE OR INFLAMMATORY RESPONSE

Since the 1990s, it has been documented that the pathophysiology of snake envenomation involves an inflammatory process. It is commonly recognized that the venoms of snakes have a variety of actions that can activate many pathways [11]. It has been observed that snake envenomation increases capillary permeability and releases a number of mediators. Increased vascular permeability and subsequent cell infiltration are the first steps in the triggered inflammatory response, which is facilitated by a number of snake venom constituents, including PLA2s, bioamines, and proteinases [12]. According to a number of studies, SVMPs such as BaP1 from Bothropsasper and Jararhagin from Bothrops jararaca contribute to the inflammatory pathophysiology by increasing the production of pro-inflammatory cytokines [13,14]. The presence of metalloproteinases, serine proteases, phospholipases A2, and other non-enzymatic proteins like disintegrins and C-type lectins, which change the vessel walls and cause tissue damage, increases the inflammatory response that snake venoms, especially those of the Viperidae family, induce. A significant part of the intricate, multifaceted inflammatory reaction brought on by snakebite is played by SVMPs. In the muscle tissue of envenomed animals, high concentrations of IL-6 and IL-1β were detected by Bothrops asper venom. However, upon injection of Bothrops asper venom, there was a marked increase in IL-6 levels compared to a delayed onset of IL-1 and TNF-α [15]. Promutoxin (R49sPLA2), which was extracted from the venom of *Probothrops muscrosquamatus*, was found to cause the production of IL-12, TNF-α, IL-6, and IL-1β from human monocyte cell cultures as well as IL-2 cytokines, TNF, and IL-6 from human T cells. A number of inflammatory chemicals, including prostaglandins and leukotrienes, are precursors to arachidonic acid, which is released when certain SV-PLA2s hydrolyze the membrane phospholipids of platelets. Numerous additional degradation products are formed during activation of the complement system and function as significant mediators of inflammation. Snake venoms cause mast cell activation, which releases histamine and causes vascular permeability and vasodilatation, ultimately resulting in extravasation [16,17]. Moreover, the proteinases found in snake venoms have the ability to directly activate the kinin system by triggering the release of bradykinin. After tissue damage, Hageman factor (FXII) is activated, starting this mechanism. In the presence of kininogen, this plasmatic factor further activates the pre-kalikrein into kalikrein, resulting in vasoactive peptides that cause pain and fever. Bradykinin is a nanopeptide that binds to particular receptors on sensory neurons to promote vascular permeability. This activation of the alternative complement pathway intensifies the inflammatory response. SVMPs, including fibrolase that was extracted from the venom of Agkistrodon contortrix, are known to be involved in the pathways that lead to the manufacture and degradation of bradykinin [18-20].

ACUTE KIDNEY INJURY

Acute kidney damage is a potential side effect of both viperid and elapid snakebite envenomations. The pathophysiology of renal injury has been linked to the following pathways, depending on the type of venom: ischaemia secondary to decreased renal blood flow brought on by hemodynamic changes brought on by systemic bleeding and vascular leakage; SVMPs' proteolytic degradation of the glomerular basement membrane; the deposition of microthrombi in the renal microvasculature (thrombotic microangiopathy), which may also result in hemolysis; the direct cytotoxic action of venom components, such as cytotoxic PLA2s, in renal tubular cells; and the accumulation of large amounts of myoglobin in renal tubules with toxicity as a result [21,22].

MYOTOXICITY

The exact molecular process by which they damaged the muscular tissue is still unknown. Myotoxins cause irreversible damage to skeletal muscle fibers, which leads to myonecrosis. These molecules attach themselves to muscle cell plasma membranes, changing their integrity and permeability. The endocytosis of myotoxins into muscle cells, most likely via membrane receptors on the cell surface, or the hydrolysis of phospholipids, which results in membrane disruption, could be the cause of the caused muscle tissue injury. These chemicals penetrate muscle cell membranes, including the sarcoplasmic reticulum and mitochondrial membranes, and enter the cytosol. Only after these toxins' initial action on the plasma membrane, which signals the start of degenerative processes, can they have an intracellular effect [23,24]. Rhabdomyolysis is linked to venomings by sea snakes, certain terrestrial elapids from Australia, and certain viperid species. This impact is due to the activity of myotoxic PLA2s at the systemic level as a result of the binding of these toxins to receptors in muscle fibres. As previously mentioned, myotoxins that act locally damage the muscle cells' plasma membrane, leading to calcium inflow and cellular deterioration. As a result, significant amounts of myoglobin and creatine kinase, two cytosolic proteins found in muscles, are released. Myoglobin deposition in the renal tubules may be a factor in acute kidney damage [25,26].

NEUROTOXICITY

The neurotoxins found in the venom of most elapid and some viperid snake species cause a descending flaccid neuromuscular paralysis that can potentially be fatal due to the blockage of the respiratory and bulbar muscles (the mouth and throat muscles that control speech and swallowing). Snake venom has two primary categories of neurotoxins: α-neurotoxins and β-neurotoxins. α-Neurotoxins function postsynaptically at neuromuscular junctions and are members of the three-finger toxin family. They highly bind selectively to the cholinergic receptor located at the motor end plate of the fibers of muscles, which prevents acetylcholine from binding and causes flaccid paralysis [27]. On the other hand, β-neurotoxins are usually PLA2s that function at the neuromuscular junction's presynaptic nerve terminal [28]. A voltage-gated potassium channel, for instance, is the receptor for the krait *Bungarus multicinctus* (family Elapidae)'s β-bungarotoxin. Neurotoxic PLA2s generate neurotoxicity by attaching to their targets and causing phospholipids at the nerve terminal plasma membrane to be hydrolyzed enzymatically. In fact, biophysical alterations brought about by the production of lysophospholipids and fatty acids in the membrane result in the fusing of synaptic vesicles with the membrane and the exocytosis of the pool of vesicles that are ready for release [29].

Moreover, an increase in membrane permeability to ions causes depolarization and the influx of calcium, which in turn causes the reserve pool of vesicles to be exocytosed [30]. Depletion of presynaptic vesicles leads to intracellular degenerative processes, including alterations to the mitochondria, which ultimately cause the destruction of nerve terminals [31,32]. These occurrences provide an explanation for the patients' severe and protracted paralysis. Certain neurotoxic PLA2s can also operate intracellularly after passing through damaged plasma membranes or endocytosis to reach the cytosol. PLA2s in the nerve terminal induce further degenerative processes in the mitochondria [33]. Other neurotoxins found in African mamba venoms include fasciculins and dendrotoxins (*Dendroaspis* spp., family Elapidae). Voltage-gated potassium channels at the presynaptic nerve terminal are blocked by dendrotoxins. Fasciculins are acetylcholinesterase inhibitors and are also members of the three-finger toxin family. These neurotoxins work together to produce fasciculations, which are small-scale, involuntary contractions of muscle fibers. They also have excitatory effects. Certain venoms' cysteine-rich secretory proteins cause smooth muscle paralysis [34].

CARDIOVASCULAR AND HAEMOSTATIC DISTURBANCES

Systemic hemorrhage can arise from Australian elapid envenomations as well as from envenomations by viperids and certain non-front-fanged colubroid species. Systemic hemorrhage in viperid venoms is mostly caused by SVMPs, particularly those belonging to class PIII. These toxins can target the microvasculature because of their multi-domain structure, which includes exosites—molecular sites other than the active catalytic site that act as secondary binding locations. Numerous organs may experience bleeding, which can have a variety of pathological effects. For instance, in envenomations, cerebral hemorrhage has been reported to result in ischaemia, stroke, and other neurological effects[35-38]. Haemostasis is impacted by snake venom in several ways. Enzymes that promote coagulation are found in many viperid venoms as well as in some elapid and non-front-fanged colubroid venoms. These enzymes are either SVMPs or serine proteinases found in snake venom that function in the coagulation cascade, such as prothrombin, X, or V activators or thrombin-like enzymes. Additionally, some venom enzymes hydrolyze fibrin and fibrinogen. Furthermore, SVMPs influence endothelial function in a number of ways and release tissue factor 74. While these procoagulant components can lead to intravascular coagulation, they usually create a consumption coagulopathy that alters blood clotting tests by defibrinogenating the blood and making it less coagulable. This illness may exacerbate systemic bleeding, particularly in cases where venoms containing hemorrhagic toxins cause blood vessel disruption. Systemic bleeding is frequently brought on by some Australian elapid venoms, which lack hemorrhagic SVMPs but produce coagulopathy as a result of serine proteinase prothrombin activators [39-42]. The venom of several snakes affects platelets. The reduction in platelet counts is caused by C-type lectin-like proteins and SVMP-mediated microvascular injury. Moreover, by inhibiting platelet receptors or by interacting with von Willebrand factor, disintegrins, C-type lectin-like proteins, snake venom serine proteinases, and certain SVMPs reduce platelet aggregation. An increased risk of systemic bleeding in envenomations by hemorrhagic venoms has been linked to thrombocytopenia. On the other hand, although not directly procoagulant, the venoms of two indigenous species of viperids found in the Caribbean cause severe thrombosis that results in infarcts in the heart, brain, and lungs. Thrombosis most likely depends on systemic endothelial dysfunction brought on by SVMP. Certain viperid bites result in acute pituitary insufficiency due to thrombi forming and localized hemorrhage in the anterior pituitary glands[43-47]. One of the main reasons why patients envenomed by viperids have hemodynamic

abnormalities, which can lead to cardiovascular shock, is venom-induced systemic bleeding. Hypovolemia in these envenomations is also caused by increased vascular permeability, which includes systemic plasma leakage. Bradykinin is released by serine proteinases found in snake venom, and other vasoactive endogenous inflammatory mediators also play a role in this function. Furthermore, several of the bradykinin-potentiating peptides found in viperid venoms block the angiotensin-converting enzyme, which modifies hemodynamics [48].

BLOOD DISORDERS

COAGULATION AND FIBRINOLYSIS

The fibrinogenases α, β, or γ were identified as proteolytic enzymes extracted from snake venoms based on their capacity to hydrolyze fibrinogen *in vitro* [49]. Either fibrinopeptides A or B, or both, are released in response to a number of thrombin-like compounds that have been identified from snake venoms [50]. These fibrinopeptides cause neutrophil chemotaxis, vascular permeability, and function as mediators of inflammation [51]. A strong chemotactic agent for neutrophils and for vascular permeability that acts on the kinin system is thought to be the generated thrombus. The venoms of Viperidae and Crotalidae can also cause fibrinolysis. After the three procoagulant proteinases (RP34, Afaâcytin, and CC3-SPase proteinase) from Cerastes venom were purified and characterized, SDS-PAGE analysis revealed fibrinogenolytic activity. RP34 and Afaâcytin, in particular, demonstrated α,ß-fibrinogenase and α-fibrinogenase, respectively [50,52]. CC3-SPase is classified as an α,β-fibrinogenase since it releases both A and B fibrinopeptides, just like afaâcytin. The venom of *Trimeresurus stajnegeri* contains a serine proteinase known as TSV-PA, which functions as a plasminogen activator. It transforms plasminogen to plasmin by the same mechanism as the latter does—by cleaving a bond—and it shares roughly 70% of homology with other serine proteases and t-PA. Arg561–Val562[53,54].

HEMORRHAGE

The vascular endothelium is harmed by hemorrhages, which result in spontaneous systemic bleeding. Severe bleeding is a major cause of mortality following bites by the Viperidae, Elapidae, and Colubridae families of snakes. Additional symptoms of snake envenomations include coagulopathies, hemorrhage, defective and weak platelets, and vessel wall destruction. By virtue of their disintegrin domain, SVMPs may play a variety of functions. For example, they may enhance the hemorragin action that influences platelet aggregation [55]. Through their integrin-binding tripeptide motifs, disintegrins connect with platelets integrins and block them. The most prevalent motif among disintegrins is RGD (arginine-glycine-aspartate), while several disintegrins also contain variants of this motif, including as KGD, WGD, MGD, KTS, RTS, and MLD. Because these motifs bind to integrins like GPIIb/IIIa or αIIBβ3, they can selectively limit platelet aggregation. Additionally, platelet membrane glycoproteins and their ligands, including collagen, GPIb, and Von Willbrand factor, are broken down by SVMPs [56].

PITUITARY DISORDERS

HYPOPITUITARISM

A rare but well-known side effect of viperid envenomations, especially of RV species (both *Daboia russelii* and *Daboia siamensis*), is hypopituitarism.The earliest reports from India of anterior and later posterior pituitary dysfunction following *D. russelii* bite were made by Wolff in 1958, following a bite by *Bothrops jararacussu* operating in Angamaly, Kerala. Wolff also described hypopituitarism following snake envenomation. It is unclear what precise pathophysiology leads to HP after RVE. Theories suggest that the causes could be related to Sheehan's syndrome (SS), in which a swollen, susceptible gland with a restricted blood supply experiences pituitary apoplexy. After RVE, the pituitary gland is more susceptible to vascular insults, most likely due to two mechanisms:

1. A gland's engorgement brought on by CLS
2. Direct stimulatory effects of RV toxin on pituitary cells: Without causing cell lysis, RV venom can induce the dose-dependent release of Thyroid-stimulating hormone (TSH), Growth hormone (GH), and Adrenocorticotrophic hormone (ACTH) from rat pituitary cell cultures.

Changes that may result in vascular injury to this aroused and engorged pituitary gland include:

1. Overt bleeding or microthrombi deposition brought on by DIC, which affects the pituitary vascular supply.
2. Pituitary intravascular pressure variations brought on by CLS.
3. Because the anterior pituitary vasculature is situated in the confined, bony sella turcica, it is susceptible to the compressive effects of even small intrasellar pressure increments.
4. Circulatory shock resulting in hypotension.
5. A rise in the pressure inside the skull.

DIABETES INSIPIDUS

Large amounts of hypotonic urine are a hallmark of diabetes insipidus, which is brought on by arginine vasopressin (AVP) deficit (central) or resistance (nephrogenic). Being an uncommon illness in and of itself, its presence in snake envenomation is even more peculiar. Only when 80–90% of AVP-producing hypothalamic magnocellular neurons are lost—their ability to synthesis AVP considerably exceeds the daily requirements—can central diabetes insipidus develop. Since the posterior pituitary functions more as a secretory and storage organ than a site of synthesis, a major disruption to the hypothalamus is required for CDI. A low-pressure hypothalamo-pituitary portal pathway from the superior hypophyseal artery supplies the anterior pituitary. On the other hand, the inferior hypophyseal artery provides direct blood feed to the posterior pituitary. Unlike the low-pressure portal system in the anterior portion, the intrasellar pressure changes that can precede CLS and DIC might not be sufficient to jeopardize the posterior pituitary artery circulation. As a result, RVE-related CDI is uncommon and the posterior pituitary is robust to vascular insults.

ADRENAL DISORDERS

Primary AI and adrenal hemorrhage are uncommon side effects of snakebite envenomation. Following an acute phase diagnosis of secondary AI in two individuals, primary AI was determined based on the persistence of an unsatisfactory response to the Synacthen stimulation test and the recovery of ACTH levels. When HP is present, a main AI diagnosis could go unnoticed. The adrenal gland is a highly vascular organ, similar to pituitary. The etiology of bleeding and necrosis is similar to that of Waterhouse-Friderichsen syndrome, which is linked to severe bacterial sepsis caused by infections with *Streptococcus pneumoniae* and *Neisseria meningitidis*. Active ingredients in snake venom have hemorrhagic and procoagulant properties that make patients more susceptible to developing DIC and, consequently, adrenal necrosis or hemorrhage. When RVE is present, bleeding or CLS may produce circulatory shock, which can lead to bilateral adrenal hemorrhage.

ELECTROLYTE IMBALANCES

HYPONATREMIA

According to early accounts, the syndrome of inappropriate antidiuretic hormone (SIADH) was the cause of hyponatremia. It's interesting to note that fluid restriction, the usual treatment for SIADH, caused severe dehydration in three children. This ruled out SIADH as a potential cause, and treating all hyponatremic patients with regular saline infusions afterward produced positive results. In vasculotoxic envenoming (e.g., RVE), hyponatremia can be caused by HP; however, in neurotoxic envenoming, a separate mechanism is responsible for hyponatremia. Given that natriuretic peptides (NPs) have been found in the venom of multiple snake species, it could be a direct result of the venom's constituent parts. Dendroaspis NP is more potent and stable than mammalian NP after being extracted from the venom glands of the green mamba (*Dendroaspis angusticeps*). Its potential therapeutic value in heart failure was studied. Other snakes' venoms, including those of the inland taipan (*Oxyuranus microlepidotus*), Iranian viper (*Pseudocerastes persicus*), Brazilian rattle snake (*Crotalus durissus cascavella*), blunt-nosed viper (*Macrovipera lebetina*), eastern brown snake *(Pseudonaja textilis*), and mulga snake (*Pseudechis australis*), have yielded novel natural products that have been isolated and characterized. Even though the majority of hyponatremia cases following snakebite envenoming are acute, routine precautions involving the gradual normalization of serum sodium levels should be followed if persistent hyponatremia (lasting more than 48 hours) is suspected in order to prevent osmotic demyelination syndrome.

HYPOKALEMIA

Hypokalemia is a potential side effect of neurotoxic envenoming that may aggravate the muscle weakness brought on by these bites. It was once thought that pulmonary alkalosis brought on by hyperventilation was the cause of hypokalemia.The authors postulated that an intracellular shift in potassium caused hypokalemia as a result of β-adrenergic stimulation resulting from autonomic dysfunction associated with neurotoxic envenoming. Another report from India of hypokalemia following a bite from a Sind krait (Bungarus sindanus) where the patient experienced severe autonomic abnormalities and cardiac problems supports this relationship between the potential pathogenic role of autonomic dysfunction in hypokalemia. Another report described two common krait bite victims who experienced hypokalemia and a severe coma. They also showed no signs of gastrointestinal potassium loss, such as ileus or diarrhea, and had low renal potassium excretion. The authors postulated that a mechanism akin to barium poisoning caused an intracellular shift, which resulted in hypokalemia. Extracellular potassium decreases as a result of barium ions' inhibition of potassium channels and increase in activity of the Na+-K+-ATPase enzyme, which obstructs the enzyme's passive diffusion [57].

DIAGNOSIS

PHYSICAL EXAMINATION

Fang Marks

a. Traditionally, depending on the species involved, there should be two puncture wounds spaced 8 mm to 4 cm apart from one another. But a sideswipe might only result in one puncture, but several bites might leave numerous fang marks. It's also crucial to keep in mind that many poisonous animals have multiple sets of fangs, so even during normal development, there may be multiple fang scars.
b. Furthermore, a lot of non-venomous animals, including the Common Wolf Snake, have big front teeth that cause bites that resemble fang marks.
c. Fang marks are sometimes difficult to see.

Identification of the Snake

a. As previously indicated, this is difficult, but it can be tried in situations where the victim or his companions bring the dead snake that is the culprit.
b. In this situation, extreme caution is necessary because there have been documented cases of dead snakes causing bites when touched! In this sense, even a fully severed head is not always harmless.

INVESTIGATIONS

The 20-minute whole blood clotting test (20WBCT) is regarded as a dependable coagulation test that can be performed at the patient's bedside and is thought to be more effective than the "capillary tube" method for determining clotting capability in cases of snakebite. A test tube or other fresh, clean, and dry glass vessel should hold a few milliliters of fresh venous blood. It should be left undisturbed at room temperature for 20 minutes. The blood should next be checked to see if it is still liquid by gently tilting the tube; if it is, the blood is incoagulable. Following admission, the test should be administered every 30 minutes for three hours, and then hourly.

OTHER TESTS

Laboratory investigations include the following:

a. Haematological: fragmented RBC (schistoocytes or helmet cells) as evidence of hemolysis; prolonged clotting and prothrombin times; prolonged partial thromboplastin times; depressed fibrinogen levels; elevated fibrin degradation products; High haematocrit initially, but it later falls; Leucocytosis and thrombocytopenia.
b. ECG: Bradycardia with ST segment elevation or depression, T wave inversion, QT prolongation, and hyperkalaemia-related alterations are common ECG abnormalities.
c. Metabolic: Elevated anion gap in metabolic acidosis or lactic acidosis; hypoxaemia with respiratory acidosis; hyperkalaemia.
d. Urine Analysis: Haematuria, Proteinuria, Haemoglobinuria, Myoglobinuria. Renal— Every sign of azotaemia will manifest in acute renal failure.
e. Chest X-ray: pleural effusion, intrapulmonary hemorrhages, and pulmonary edema[2].

MANAGEMENT

General Principles of Snakebite Management

1. Snake Identification

- Do not attempt to identify the snake as this is unreliable and unnecessary for treatment.
- Avoid catching or killing the snake.

2. Clinical Syndromes

Neurotoxic: Symptoms include ptosis, diplopia, respiratory muscle weakness.

Hemotoxic: Symptoms include local or systemic bleeding, persistent bleeding at the bite site.

Cytotoxic: Symptoms include pain, swelling, tissue destruction.

Each syndrome has specific signs and symptoms which should guide treatment rather than the snake species.

3. Antivenom

- Antivenom treatment should be based on clinical presentation and symptoms, not snake identification.
- Early administration of antivenom is crucial and should be given intravenously (IV) or intraosseously (IO), not intramuscularly (IM) or subcutaneously (SQ).
- Dosage is not weight-based and should be repeated as necessary until envenomation control is achieved.

Clinical Pearls

1. Dry Bites

- About 25% of venomous snake bites are “dry bites” with no venom injection.
- Symptoms should guide treatment, not the snake's venomous status.

2. Symptom-based Treatment

- Treat based on the development of symptoms rather than the snake species.
- Monitor for signs of envenomation even if the snake species is known to be dangerous.

3. Antivenom Administration

- No absolute contraindications exist for antivenom in symptomatic envenomation.
- Observe for allergic reactions, manage with antihistamines or steroids if necessary.

Universal Approach to Snakebite Patients

1. Initial Priorities

- Ensure airway, breathing, and circulation (ABCs) are stable.
- Administer antivenom promptly.
- Avoid constricting bandages or tourniquets.

2. Focused Assessment

- Perform physical examination for signs of neurotoxic, hemotoxic, and cytotoxic syndromes.
- Circle the bite wound and mark the leading edge of pain and swelling with a permanent marker.
- Monitor for local and systemic bleeding, and neuromuscular weakness.

3. Laboratory Tests

- Conduct CBC, PT/PTT/INR, fibrinogen, CMP, CK, and WBCT if available.

Supportive Care & Ongoing Management

1. Neurotoxic Envenomation

- Prepare for aggressive airway management and prolonged ventilation.
- Consider atropine and neostigmine for respiratory muscle weakness.

2. Hemotoxic Envenomation

- Cease active bleeding within 30-60 minutes of antivenom administration.
- Consider blood transfusion if necessary.

3. Pain Management

- Use ketamine and fentanyl for analgesia.
- Avoid routine de-roofing of blisters unless necessary for comfort or abscess management.

Ongoing Monitoring

1. Serial Assessments

- Repeat assessments at regular intervals (H2, H4, H6, H12, H24) to monitor the progression or resolution of symptoms.
- Document and trend clinical findings over time.

2. Criteria for Additional Antivenom

- Administer additional antivenom if symptoms persist or recur.
- Monitor for signs of recurrent envenomation and treat accordingly.

3. Discharge Criteria

- If asymptomatic after 24 hours, likely a dry bite and the patient can be discharged.[56]

CONCLUSION

In conclusion, snake bites remain a significant public health issue, particularly in rural and tropical regions. Effective management and treatment of snake bites are crucial for reducing morbidity and mortality. Timely administration of antivenom, along with supportive care, plays a pivotal role in patient recovery. Public awareness and education about snake bite prevention, first aid, and the importance of seeking immediate medical attention are essential components in mitigating the impact of snake bites. Continuous research and development of more effective and accessible antivenoms are also imperative to improve treatment outcomes.

ABBREVIATIONS

DNA- Deoxyribonucleic acid, SVMP- Snake venom metalloproteinases, SVSP snake venom serine protease, PLA2s - Secreted phospholipases A2, 3FTX - Three-finger peptides, ASIC-Acid-Sensing Ion Channel, TRPV1 - transient receptor potential vanilloid type 1,BaP1 -biofilm-associated protein1, IL-6 interleukin 6, Interleukin-1β (IL-1β), IL-1 interleukin 1, TNF - α Tumor necrosis factor, IL-12 interleukin 12, SDS-PAGE - Sodium dodecyl-sulfate polyacrylamide gel electrophoresis, RP34 - retinitis pigmentosa 34, TSV-PA- Trimeresurus stejnegeri venom plasminogen activator, DIC - Disseminated intravascular coagulation .

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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AUTHORS CONTRIBUTIONS
Samyuktha: Conceived the study, designing the study, literature review, and writing the manuscript.
Periswaran: Designed the study and contributed to writing the manuscript.
Haja Sherief: Review and editing the manuscript.

CONFLICT OF INTERESTS
There are no conflicts of interest

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