



## Neurotoxicity Related to Snakebite: Treatment, and Prevention

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**ABSTRACT:** Highest rates of snake envenoming and mortalities in South Asia, Southeast Asia, Sub-Saharan Africa with India reporting the most deaths. World Health Organization listed snakebite as a neglected disease. Clinical manifestations of snakebite include overwhelming fear, nausea vomiting diarrhea, vertigo, fainting tachycardia, and cold, clammy skin. Most snakes cause neurotoxicity. Paresthesia throughout the body, as well as difficulty in speaking and breathing. Several other neurological features have been reported after snake envenomation which is likely to be direct neurotoxic effects. Mechanisms of many these acute manifestations are not clear. Myokymia has been reported mainly from United States following rattlesnake (*Crotalus* spp). Altered consciousness and deep coma has been reported in 64 % of patient after common krait envenomation. Delayed neurotoxicity also been reported. Anti-venom treatment should be given as soon possible, low dose anti-snake venom (ASV) is not inferior to high dose ASV. Improvement in neurotoxicity has been reported when anti-venom had been administered early. Prevention by avoiding areas heavily infested with snakes. Bite from a dead snake often contains large amount of venom. There is an urgent need for better treatment in neurotoxic envenoming.

**Keywords:** Envenomation, Neurotoxicity, Snakebite, Treatment

### I. INTRODUCTION

Snakebite is an injury caused by the bite of a snake. It often results in two puncture wounds from the animal's fangs [1]. Estimates vary from 1.2 to 5.5 million snakebites, 421,000 to 2.5 envenomings, and 20,000 to 125,000 deaths [2]. Most snake envenomings and fatalities occur in South Asia, Southeast Asia, and sub-Saharan Africa, with India reporting the most snakebite deaths of any country [3]. Most snakebites are caused by non-venomous snakes. Of the roughly 3,000 known species of snake found worldwide, only 15% are considered dangerous to humans [3]. Most diverse and widely distributed snake family, the colubrid, has approximately 700 venomous species [4]. Researchers in India, reported 13 known poisonous species and of these four, e.g. the cobra (*Naja naja*), Russell's viper (*Daboia russelii*), saw-scaled viper (*Echiscarinatus*) and common krait (*Bungarus caeruleus*) [5]. The World Health Organization listed snakebite as a neglected disease [6]. Venom may cause bleeding, kidney failure, a severe allergic reaction, tissue death around the bite, or breathing problems [2]. Bites may result in the loss of a limb or other chronic problems [2]. Neurotoxicity is a well-known feature of envenoming due to elapids (family Elapidae) such as kraits (*Bungarus* spp), Cobras (*Naja* spp), taipans (*Oxyuranus* spp) [7, 8], coral snakes, and others. Acute neuromuscular paralysis is the main type of neurotoxicity and is an important cause of morbidity and mortality related to snakebite [9]. Treatment partly depends on the type of snake [1]. Washing the wound with soap and water and holding the limb still is recommended. Antivenom is effective at preventing death from bites, however, antivenoms frequently have side effects [2]. Prevention by wearing protective footwear, avoiding areas where snakes live, and not handling snakes [1]. The review describes neurotoxicity, treatment and the current concepts in snakebite.

### II. SNAKE TYPE ACCORDING TO REGION

In the developing world snakebites occur in those who work outside such as farmers, hunters, and fishermen. They often happen when a person steps on the snake or approaches it too closely. In the United

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States and Europe snakebites most commonly occur in those who keep them as pets [10]. The type of snake that most often delivers serious bites depends on the region of the world. In Africa it is mambas, Egyptian cobras, puffadders, and carpet vipers. In The Middle East it is carpet vipers and elapids. In the Central and South America it is snakes of the *Bothrops* and *Crotalid* types, the latter including rattlesnakes. In South Asia it was previously believed that Indian cobras, common kraits, Russell's viper and carpet vipers were the dangerous, other snakes, however, may also cause significant problems in this area of the world [10].

### **III. PATHOPHYSIOLOGY**

Since envenomation is completely voluntary, all venomous snakes are capable of biting without injecting venom into a person. Snakes may deliver such a "drybite" rather than waste their venom on a creature too large for them to eat [11]. However, the percentage of dry bites varies among species: 80 percent of bites inflicted by sea snakes, which are normally timid, do not result in envenomation [12], whereas only 25 percent of pit viper bites are dry [13]. Furthermore, some snake genera, such as rattlesnakes, significantly increase the amount of venom in defensive bites compared to predatory strikes [14].

Some dry bites may also be the result of imprecise timing on the snake's part, as venom may be prematurely released before the fangs have penetrated the person. Even without venom, some snakes, particularly large constrictors such as those belonging to the *Boidae* and *Pythonidae* families, can deliver damaging bites, large specimens often cause severe laceration, or the snake itself pulls away, causing flesh to be torn away by the needle sharp recurved teeth embedded in the person. While not as life threatening as a bite from a venomous species, the bite can be at least temporarily debilitating and could lead to dangerous infections if improperly dealt with [11]. While most snakes must open their mouths before biting, African and Middle Eastern snakes belonging to the family *Atractaspididae* are able to fold their fangs to the side of their head without opening their mouth and jab a person [15].

#### **Evolution of snake venom**

It has been suggested that snakes evolved the mechanisms necessary for venom formation and delivery sometimes during the Miocene epoch [16]. During the mid-Tertiary, most snakes were large ambush predators belonging to the superfamily *Henophidia*, which use constriction to kill their prey. As open grasslands replaced forested areas in parts of the world, some snake families evolved to become smaller and thus more agile. However, subduing and killing prey became more difficult for the smaller snakes, leading to the evolution of snake venom [16]. Other research on *Toxicofera*, a hypothetical clade thought to be ancestral to most living reptiles, suggests an earlier time frame for evolution of snake venom, possibly to the order of tens of millions of years, during the Late Cretaceous [17].

Snake venom is produced in modified parotid glands normally responsible for secreting saliva. It is stored in structures called alveoli behind the animal's eyes, and ejected voluntarily through its hollow tubular fangs. Venom is composed of hundreds to thousands of different proteins and enzymes, all serving a variety of purposes, such as interfering with prey's cardiac system or increasing tissue permeability so that venom is absorbed faster. Venom in many snakes, such as pit vipers, affects every organ system in the human body and can be a combination of many toxins, including cytotoxins, hemotoxins, neurotoxins, and mycotoxins, allowing for an enormous variety of symptoms [13]. Earlier, the venom of a particular snake was considered to be one kind only, i.e. either hemotoxic or neurotoxic, and this erroneous belief may still persist wherever type updated literature is hard to access. Although there is much known about the protein compositions of venom from Asian and American snakes, comparatively little is known of Australian snakes. The strength of venom differs markedly between species and even more so between families, as measured by median lethal dose ( $LD_{50}$ ) in mice. Subcutaneous  $LD_{50}$  varies by over 140-fold within elapids and by more than 100-fold in vipers. The amount of venom produced also differs among species, with Gaboon viper able to potentially deliver from 450- 600 milligrams of venom in a single bite, the most of any snake. *Opisthophthalmophis* have venom ranging from life-threatening (in the old boom slang) to barely noticeable (as in *Tantilla*) [18].

### **IV. CLINICAL MANIFESTATIONS**

The most common symptom of all snakebites is overwhelming fear, which contributes to other symptoms including nausea and vomiting, diarrhea, vertigo, fainting, tachycardia, and cold, clammy skin [19]. Television, literature, and folklore are in part responsible for the hype surrounding snakebites, and people may have unwarranted thoughts of imminent death. Dry snakebites and those inflicted by a non-venomous species can still cause severe injury. There are several reasons for this: snakebite may become infected with the snake's saliva and fangs sometimes harboring pathogenic microbial organisms, including *Clostridium tetani* infection is often reported with viper bites whose fangs are capable of deep puncture wounds. Bites may cause anaphylaxis in certain people. Most snakebite, whether by a venomous snake or not, will have some type of local effect. There is minor pain and redness in over 90 per cent of cases, although this varies depending on

the site[13].Bites by vipers and some cobras may be extremely painful, with the local tissue sometimes becoming tender and severely swollen within five minutes[20].This are may bleed and blister and can eventually lead to tissue necrosis. Other common initial symptoms of pit viper bites include lethargy,bleeding,weakness, nausea, andvomiting [13,20].Symptoms may become more life threatening over time, developing into hypotension, tachypnea, severe tachycardia, severe internal bleeding, altered sensorium, kidney failure, and respiratory failure [13,20].

Interestingly, bites caused by the Mojave rattlesnake, kraits, coralsnake, and the speckled rattlesnake reportedly cause little or no pain despite being serious injuries [13]. Those bitten may also describe a "rubbery","minty",or "metallic" taste if bitten by certain species of rattlesnake [13].Spitting cobras and rattlesnakes can spit venom in person's eyes. This results in immediate pain, ophthalmoparesis,and sometimes blindness[21].Some Australian and most viper envenomations will cause coagulopathy, sometimes so severe that a person may bleed spontaneously from the mouth, nose and even old, seemingly healed wounds. Internal organs may bleed, including the brain and intestines and will cause ecchymosis (bruising) of the skin [20].

### **Neurotoxicity**

Venom emitted from elapids, including sea snakes,kraits cobras, king cobra, mambas, and many Australian species contain toxins which attack nervous system, causingneurotoxicity [3,20,12].The person may present with strange disturbances to their vision, includingblurriness. Paresthesia throughout the body, as well as difficulty in speaking and breathing may be reported [13].Several other acute neurological features have been reported after snake envenomation which are likely to be direct neurotoxic effects. The mechanisms of many of these acute manifestations neither are nor clear, and there has been no systematic study of these in a large series [9].

Myokymia has been reported mainly from the United States following rattlesnake(*Crotalus*spp)envenomation providing further evidence of variation in neurotoxicity with species and geographical differences[22].Respiratory failure developed in some patients who hadmyokymia involving the shoulders or chest, perhaps due to underlying diaphragmatic involvement[22].Myokymia is believed to be due to a biochemical effect on axonal ion channels leading to increased peripheral nerve excitability[22,].Crotamine in South American rattlesnake(*Crotalus*Spp) venom has been shown to act on voltage-gated sodium and potassium channels[23],and similar molecules may be responsible for myokymia in envenomation by North American rattlesnakes(*Crotalus*spp).Inhibition of pre-synaptic voltage-gated potassium channels is seen in neuromyotonia,which is an autoimmune disorder presenting with continuous fasciculations.It would be interesting to see whether a similar mechanism exists in myokymia due to rattlesnake envenoming [24].

A large series of common krait envenomation has been reported altered consciousness in 64% of patients, and deep coma in 17%[25].Drowsiness was common among children with cobra bites[26].Seizures have been noted in several reports[7].Alternation in smell sense have been reported in envenomation by several snake species, and whether these central effects or due peripheral cranial nerve involvement is not clear[27].

### **Delayed neurotoxicity**

There are several reports of delayed neurological manifestations after snake envenomation. Some are reports of persistence of neurological deficits which first developed during the acute stage. Distinction from critical illness neuropathy and myopathy may be difficult when symptoms are first noticed soon after recovery from the acute phase, especially with a background of ventilation, ICU care, or sepsis [28].There are several other reports of neurological deficit developing at variable time points after recovery from the acute phase of envenoming, Some the reports are confined to reporting prolonged symptoms[29].In a series of 210 patients bitten by the common krait(*Bungaruscaeruleus*),38 patients had delayed neurological deficit. Fourteen of them had severe conduction defects that lasted for 2 weeks to 6 months before complete recovery [25].There are several reports suggestive of polyneuropathy after acute phase of envenoming, with persistence of symptoms for several months[7].Several cases of possible Gillian-Bare syndrome (GBS) have been reported. One patient developed motor and sensory neuropathy 2 weeks after an unidentified snakebite and treatment with antivenin and tetanus toxoid. His clinical, biochemical, and electrophysiological features were suggestive ofGBS [30]. Another report of a patient who had acute neuropathy and respiratory arrest after a krait bite and developed quadriplegia 3 weeks later with elevated CSF protein and evidence of a sensorimotor axonal-type polyneuropathy [31]. However, GBS seems unlikely here as he had a coma with dilated pupils. Perhaps the most interesting report is by Neil et al(2012)who describe a case of GBS after a bite by *Viper aspis*.They have demonstrated a potential immunological basis for the syndrome, with cross reactivity shown between glycoside epitopes of venom proteins and neuronal GM2 ganglioside, without evidence of direct neurotoxicity of the venom[32].

## V. TREATMENT

It is not an easy task determining whether or not a bite by any species of snake is life threatening. A bite by a North American copperhead on the ankle is usually a moderate injury to a healthy adult, but a bite to a child's abdomen or face by the same snake may be fatal. The outcome of all snakebite depends on a multitude of the factors: the size, physical condition of the person, the area and tissue bitten (e.g. foot, torso, vein, or muscle), the amount of venom injected, the time it takes for the person to find treatment, and finally the quality of that treatment [3,33]. Identification of the snake is important in planning treatment in certain areas of the world, but is not always possible. Ideally dead snake would be brought in with the person, but in areas where snake bite is more common, local knowledge may be sufficient to recognize the snake, three types of venomous snakes that cause the majority of the major clinical problems are vipers, kraits, and cobras. Knowledge of what species are present locally can be crucial, as is knowledge of signs and symptoms of envenomation by each type of snake. A scoring can be used to try to determine the biting snake based on clinical features, but these scoring systems are extremely specific to particular geographical areas [34].

Many organizations, including the American Medical Association, and American Red Cross, recommend washing the bite with soap and water. Australian recommendations for snake bite treatment recommend against cleaning wound. Traces of venom left over the skin/bandages from the strike can be used in combination with a snake bite identify the species of snake. This speeds determining of which anti-venom to administer in emergency room [35].

Indian National snake bite protocol (2007) includes: [36].

- a. Reassure patient, that 70 percent of snakebite are from non-venomous species, and only half bites from venomous species poison the person
- b. Immobilize (patient) in the same way as a fractured limb.
- c. Get to hospital immediately.
- d. Tell the Doctor of any systemic symptoms, such as droopiness of a body part, that manifest on the way to the hospital.

### **Pressure immobilization** [37].

As of 2008, clinical evidence for pressure immobilization via the use of an elastic bandage is limited [37]. The British military recommends pressure immobilization in all cases where the type of snake is unknown [38]. The object of pressure immobilization is to contain venom within a bitten limb and prevent it from moving through the lymphatic system to the vital organs. This therapy has two components: pressure to lymphatic drainage, and immobilization of the bitten limb to prevent the pumping action of the skeletal muscles [38].

### **Antivenom therapy**

Until the advent of antivenom bites from some species of snake were almost universally fatal. [39]. The first antivenom was developed in 1885 by French physician Albert Calmette for the treatment of Indian cobra bites [39, rpt]. Antivenom is injected into the person intravenously, and works by binding to and neutralizing venom enzymes. It cannot undo damage already caused by venom, so antivenom treatment should be sought as soon as possible. Modern antivenoms are usually polyvalent, making them effective against the venom of numerous snake species. Pharmaceutical companies which produce antivenom target their products against the species native to particular area. Although some people may develop serious adverse reactions to antivenom, such as anaphylaxis, which is treatable and hence the benefit outweighs the potential consequences of not using antivenom. Giving adrenaline (epinephrine) to prevent adverse effect to antivenom before they occur might be reasonable where they occur commonly [40]. Antihistamines do not appear to provide any benefit in preventing adverse reactions [40]. In a series of 2295 snake bite patients, Vetriveeran *et al* concluded that low dose antivenom (ASV) is not inferior to high dose ASV [5].

### **Neurotoxicity and Antivenom**

There are few well-documented reports of benefit with antivenom [41]. Even in such reports, benefits have not been consistent and were seen only in some patients. In contrast, many of the well-documented case series report no benefit with antivenom in neuromuscular failure [25]. However, several studies have observed improvement in neurotoxicity when antivenom had been administered very early [8]. Antivenom cannot neutralize bound venom and can be effective only if given early enough to neutralize circulating venom before it binds to target sites [42]. In a randomized double-blind trial in Philippine cobra (*Naja philippinensis*) envenoming, antivenom was not found to be effective [33]. Given the high morbidity and mortality, better treatment options are clearly needed in neurotoxic envenoming. There are several exciting reports of the use of plant extracts in the treatment of neurotoxicity [43].



Following treatments, while once recommended are considered of no use or harmful, including tourniquets, incisions, suction, application of cold, application of electricity, and drinking alcohol [44,45].

## VI. PREVENTION

Snakes are most likely to bite when they feel threatened, are startled, are provoked, or when they have been cornered. It is beneficial to know the species of snakes that are common in local areas, or while travelling or hiking, Africa, Australia, the neotropics, and southern Asia particular are populated by many dangerous species of snake. Being aware of and ultimately avoiding areas known to be heavily populated by dangerous snakes is strongly recommended. When in the wilderness, treading heavily creates ground vibrations and noise, which will often cause snakes to flee from the area. However this generally applies to vipers, as some larger and more aggressive snakes in other parts of the world, such as mambas and cobras, will respond more aggressively [46].

In the United States, more than 40 per cent of people bitten by snake intentionally put themselves in harm's way by attempting to capture wild snakes or by carelessly handling their dangerous pets, 40 percent of that number had a blood alcohol level 0.1 percent or more [47]. It is also important to avoid snakes that appear to be dead, as some species will actually roll over on their backs and stick out their tongue to fool potential threats. A snake's detached head can immediately act by reflex and potentially bite. The induced bite can just as severe as that of a live snake [13,48]. Dead snakes are also incapable of regulating the venom they inject, so a bite from a dead snake can often contain large amount of venom [49].

## VII. CONCLUSION

Worldwide snakebites have high morbidity and mortality there is an urgent need for effective treatment in neurotoxicity, muscular paralysis envenomation. Snakebite should not be regarded as a neglected disease, especially in the low income countries with high mortality.

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