Research article

Study of neurotoxic manifestations of snake bite in a tertiary centre in North Kerala

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Abstract

Background: Snake bite is an important cause of mortality and morbidity in India. This study was designed to determine the neurotoxic snakes, neurological manifestations, disease course, and outcome in neurotoxic envenomation in north Kerala. Hemotoxic snake bites with viper are common in this area. However neurotoxic snakebites with cobra and Krait, though comparatively rare, also produce significant morbidity, and studies of neurotoxic snake bites from this area are sparse.

Materials & Methods

Study Design: A retrospective descriptive study in Academy of Medical education, Pariyaram, Kannur district in North Kerala. The study centre is a tertiary hospital catering to patients from three districts in North Kerala - Kannur, Kasargode and Wynad. Data were obtained from medical record section of hospital. Clinical profile of patients including age, sex, residence, site of snake bite, neurological symptoms and signs, time taken for onset of symptoms, and time taken for recovery and outcome were recorded in pre-designed proformas.

Study period was from January 2018 to September 2018.

Results: 90 cases of snake bite with envenomation came in the study period. A total of 12 cases of neurotoxic snake bites were included in the study. The species of snake bites with neurological manifestations were Krait in 6 patients, Cobra in 2 patients, Russells viper in 3 patients and species could not be identified in 1 patient. Ptosis was the commonest neurological manifestation seen in 10 patients, ophthalmoplegia in 4 patients, limb weakness 4 patients, respiratory failure 4 patients, palatal weakness 1 patient, neck muscle weakness 4 patients. Neurological symptoms were experienced usually within 6 hours after the bite. Following administration of antivenom, the signs of recovery became evident within a few hours to several days. The duration for complete recovery ranged from four hours to 1 week.

Conclusions: Complete recovery of neuromuscular weakness was observed in all patients. Training of the peripheral doctors regarding early recognition of neurotoxic snakebite, species diagnosis as per the WHO syndromic approach, prompt institution of initial management and quick referral to a higher centre with ventilator facility would help in reducing the morbidity and mortality due to neurotoxic snake bites.

Keywords: North Kerala, Russell’s viper, common krait, neurotoxic.
Introduction
Snakebite is an important health problem in India, particularly in rural and farming areas. In India, the main poisonous snakes are cobra (Naja naja), Russell’s viper (Daboia russelii), common krait (Bungarus caeruleus), and saw scaled viper (Echis carinatus).

The principal effects of envenomation with snake toxins are related to neurotoxicity, nephrotoxicity, myotoxicity, cardiotoxicity, coagulopathy, vascular endothelial damage and local reactions. Muscle weakness following snake bite has been reported by several authors. Neurotoxic snakes belong to the family Elapidae which includes cobra and krait. Russell viper’s venom has also been reported to cause neurotoxicity in some patients. Majority of neurotoxic snakebite-related deaths in India’s rural population are caused by kraits and cobras. The type of snakes found in particular area varies considerably. Furthermore, the symptoms and signs of neurotoxic envenomation vary according to the species of snake responsible for the bite and the amount of venom injected. Diagnosis of species of the snake responsible for bite is, therefore, important for optimal management and can be strongly suspected from the patient’s description of the snake, the circumstances of the bite, or from knowledge of the clinical effects of the venom of that species.

Cobra bites tend to occur during daytime and early darkness while walking outside, and improper or careless handling while rescuing the cobra. Bite by cobra results in tender local swelling, blistering, and necrosis. Victims experience severe pain at bite site having fang marks, with rapid progression of swelling. Skin at or around the bite site is ecchymosed. Subsequent formation of tense blebs and massive damage of skin and subcutaneous tissue occurs due to myocytolysis. This rapidity of the onset of symptoms prompts the rural victim in India to seek care quickly after cobra bite.

The common krait, is nocturnal, terrestrial snake that enters human dwellings in search of prey such as rats, mice, and lizards during the course of hunting activity. It resides in the vicinity of human habitation, near the wattle and daub, mud, and small hut dwelling, hunts nocturnally, and is quick to bite people sleeping on the floor, often without waking their victims since venom is painless and associated with minimal local changes.

Cobra venom is rich in postsynaptic neurotoxins called alpha-bungarotoxin and cobra toxin, which bind, especially to postsynaptic acetylcholine receptors, preventing the interaction between Ach and receptors on postsynaptic membrane, resulting in neuromuscular blockade. Cardiotoxin content of cobra venom has direct action on cardiac and smooth muscles causing circulatory failure, cardiac arrhythmias, various heart blocks, and cardiac arrest. Cobra venom is of smaller molecular size and rapidly absorbed into circulation. Cobra unlike the krait deposits its venom deeply. This in combination with hyaluronidase allows spread of the venom rapidly and symptoms to arise abruptly. Absorption is further accelerated by running due to fear and the liberated catecholamines can kill the victim within 8 min. Interestingly, severe, irreparable local tissue is lost at the bite site of cobra envenoming due to myocytolysis. Paralysis is heralded by ptosis followed by ophthalmoplegia. Blurring of vision and loss of accommodation are earliest sign of neurological envenomation. Paralysis of facial, palatal, tongue, and neck muscles follow. Respiratory failure, precipitated by upper airway obstruction and paralysis of intercostals and diaphragm, is the usual cause of death.

Although the krait venom is 10 times more lethal than cobra, it is absorbed slowly as skin has poor circulation and reflexes are blunted during sleep. The common Indian krait venom contains both presynaptic beta-bungarotoxin and alpha-bungarotoxin. Beta-bungarotoxin in the krait venom has a great affinity toward presynaptic Ach receptors. These toxins initially release Ach at the nerve endings, at neuromuscular junction, and then damage it subsequently preventing the
release of Ach. The tissue having high concentration of these receptors is affected in the following order, such as sphincter pupillae, levator palpebrae superioris, neck muscles, bulbar muscles, subsequently limbs, and, finally, the diaphragm and intercostals muscles. Venom acts as early as 30 min and till 18 h.

Proteins such as enzymes, non-enzymatic polypeptide toxins, and non-toxic proteins are major components of snake venom. Neurotoxins bind to neuromuscular junction both pre- and post-synaptically causing muscle weakness. Alpha-bungarotoxin of krait binds to acetylcholine receptors and is used experimentally to demonstrate reduction in acetylcholine receptor sites in postsynaptic membrane. Alpha-cobra toxin which has a similar action produces features of myasthenia gravis in the experimental animals. Phospholipase A2 enzyme and Beta-bungarotoxin act pre-synaptically to cause neurotoxicity. The epidemiology, clinical profile and outcome of neurotoxic snakebite in North Kerala has not been adequately studied. Many snakebite cases are still not treated in hospitals but by traditional healers.

Materials & Methods

Study Design
A retrospective descriptive study in Academy of Medical education, Pariyaram, Kannur district in North Kerala. All the patients admitted in Toxicology ICU and medical wards during the period January 2018 to Sept 2018 with neurological manifestations after snake bite.

Aims & Objectives
To study the clinical profile and outcome of neurotoxic snakebites

Inclusion Criteria: Patients older than 12 years with a definite history of snake bite and developed neurological features of envenomation. This symptoms included ptosis, ophthalmoplegia, Neck muscle weakness, respiratory muscle weakness.

Exclusion Criteria: Patients with snake bite with no neurological signs of envenomation after a period of observation, were excluded. Patients with any pre-existing neurological illness were also excluded.

The majority of the population is engaged in farming and rubber plantations and snakebite is a major occupational hazard particularly during the harvesting season. The study was carried out over nine month-period beginning January 2018. The offending snake was identified either by direct examination (when the snake was brought to the hospital) or on the basis of eye-witness account. This evidence was further verified by showing photographs of snakes to the eye witness. An attempt was made to interpret the clinical signs and identify the species based on the WHO syndromic approach. Local envenoming (swelling etc.) with paralysis was suggestive of cobra bite while paralysis with minimal or no local envenoming was suggestive of krait bite.

Details of history were obtained and patients were subjected to neurological examination soon after admission. They were regularly assessed hourly for the first six hours, 12 hourly for next 72 hours, and then daily until complete recovery. Information regarding progression, onset of recovery and results of biochemical investigations were entered in a pre-designed proformas. The patients were treated with lyophilised polyvalent enzyme refined equine immunoglobulins (antivenom serum; Haffkine Institute, Mumbai, India) produced against Naja naja, Bangarus caeruleus, Vipera russelii, and Echis carinatus. Based on previous evidence, a single dose of 10 ampoules, each reconstituted with 10 ml of diluent, and further diluted in 500 ml of isotonic saline was infused intravenously over one hour. Those who elicited a positive response to Tensilon test were treated with neostigmine until complete neurological recovery.

Results
A total of 12 cases were studied. 8 of them were males. Most of them (6 patients) were between...
20-40 years age group. The snake could be identified in 11 of the cases. Common Krait was most common (6 patients) Russell’s viper bites in 3 cases and cobra in 2 patients.

For 1 patient, snake could not be specified. 4 patients developed neurological symptoms within 30 minutes of the bite whereas 3 patients from 30 minutes to two hours after the bite. The onset of symptoms was from two to four hours after the bite in 2 patients. Symptoms occurred after four hours in 3 patients. The most common symptom was ptosis (10 patients) followed by double vision (4 patients) and dysphagia (2 patients). Neck muscle weakness was found in four patients. Weakness of limb and jaw muscles was detected in three and one cases respectively.

The evidence of recovery was seen as early as two hours after the infusion of antivenom in 8 patients. Complete recovery was noted within ten hours in 7 patients while the longest duration reported was 1 week. 4 patients developed respiratory muscle weakness necessitating mechanical ventilation. No patient with neuromuscular weakness had permanent sequelae.

There was no death in the study group.

**Discussion**

The age of the patients range from 22 years to 70 years. Most of the victims were between 20-40 years of age which shows that the active youth is affected most. Males are higher than the females as they are more involved in outdoor and agricultural activities.

Cobra bites showed neuromuscular curare like effects, especially the effect on respiratory muscles which frequently led to breathing failure and second was its necrotic effect on skin and subcutaneous tissue around the bite site, which in many cases resulted in wide slough lesions. Broken neck sign was a useful predictor of impending respiratory muscle paralysis.

Average time between the bite and development of muscle paralysis was 4 hrs. with a range of 1 to 12 hours. Which showed that a significant time gap between bite onset and signs of neuroparalysis especially in case of krait bites.

The first sign of neuroparalysis in the study was ptosis with external opthalmoplegia which showed that the paralysis always appears first in the muscles supplied by the cranial nerves, usually in the external ocular muscles or the muscles which elevate the upper eye lids.

The next common sign observed in this series was dysphagia and dysphonia which indicate the relatively early involvement of muscles of tongue, palate, pharynx and jaw rather than limbs or chest muscles.

In this study, commonest abnormal laboratory result during first few days after bite was mild to moderate leukocytosis with neutrophilia. Raised serum CPK was found in 5 cases with most of them had tight tourniquet for long duration suggesting muscle damage by pressure effect.

Identification of the offending snake is not very easy, because the incident is very sudden and mostly accidental and in most cases happens in dark bushy areas or at night. In spite of above facts, in this study offending snake was identified in 11 cases. Cases with Krait bite had only minimal local reaction but that with Viper and cobra had severe local reaction.

All patients of this study were treated with Haffkine’s polyvalent anti-venom. This anti-venom is effective against envenomation by Cobra, Krait, Russell’s viper and Saw-scaled viper. A single dose of A/V consists of 10 vials (each-10 mg). Most of the patients responded to 20 vials of ASV.

Mechanical ventilation was required in 4 patients; the duration ranged from 1 hour to 48 hours. All these patients could die of snakebite without the facility of artificial ventilation. Therefore, facilities for endotracheal intubation and artificial ventilation are mandatory for total and comprehensive management of neurotoxic snake bite.

As the anti-venom that was used was horse serum, ASV reaction was very common. But all reactions could be managed easily with recommended
regimen. It indicates that, frequent ASV reactions should not be taken as frightening thing and ASV therapy must be given in all cases where indicated.

**Conclusions**

Complete recovery of neuromuscular weakness was observed in all patients. Training of the peripheral doctors regarding early recognition of neurotoxic snakebite, species diagnosis as per the WHO syndromic approach, prompt institution of initial management and quick referral to a higher centre with ventilator facility would help in reducing the morbidity and mortality due to neurotoxic snake bites.

**References**

1. Warrell DA. Injuries, envenoming, poisoning, and allergic reactions caused by animals. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford Textbook of Medicine. 3rd ed. Oxford: Oxford University Press; 1996. pp 1124-51
2. Warrell DA. Snake venoms in science and clinical medicine. 1. Russell’s viper: biology, venom, and treatment of bites. Trans R Soc Trop Med Hyg 1989;83:732-40.
3. Kalantri S, Singh A, Joshi R, et al. Clinical predictors of in-hospital mortality in patients with snakebite: a retrospective study from a rural hospital in central India. Trop Med Int Health. 2006; 11(1):22–30.
4. Kasturiratne A, Wickremasinghe AR, de Silva N, and et al. estimating the global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 2008;5:e218
5. Mohapatra B, Warrell DA, Suraweera W, et al. Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis. 2011;5(4):e1018.
6. Singh G, Pannu HS, Chawla PS, Malhotra S. Neuromuscular transmission failure due to common krait (*Bungarus caeruleus*) envenomation. Muscle Nerve 1999; 22:1637-43.
7. Ariaratnam CA, Sjostrom L, Raziek Z, Kularatne SA, Arachchi RW, Sheriff MH, et al. An open, randomized comparative trial of two antivenoms for the treatment of envenoming by Sri Lankan Russel’s viper (Daboia russelii russelii). Trans R Soc Trop Med Hyg 2001;95:74-80.
8. Kumar S, Usgaonkar RS. Myasthenia gravis like picture resulting from snake bite. J Indian Med Assoc 1968;50:428-9
9. Dixon RW, Harris JB. Nerve terminal damage by beta-bungarotoxin: its clinical significance. Am J Pathol 1999;154:447-55
10. Silva A, Hodgson WC, Isbister GK. Antivenom for neuromuscular paralysis resulting from snake envenoming. Toxins (Basel) 2017;9:143.