Understanding and Treatment of Neurotoxic Snakebite in the Developing World: Air Today or Gone Tomorrow!

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Abstract

Although neurotoxic snakebite mortality is exceeded by that from viperine species it remains a significant contributor to total figures. The rapidity of onset of life threatening respiratory compromise in a developing world context with little access to mechanical ventilation contributes to poor outcomes, particularly amongst children. The majority of hospitals in the developing world are primary care centers, with limited facilities, and yet are close to the scene of the bite. Most of the textbooks used in medical education are written from a tertiary hospital perspective with the assumption that access to a mechanical ventilator is available. Consequently guidelines for primary care hospitals are inapplicable and result in most patients being transferred to other hospitals in sub-optimal conditions.

This paper examines neurotoxic snakebite and recommends management techniques, use of anti snake venom and support drugs and the various methods of airway support that can be sourced or improvised in a primary care setting.

Key Words: Snake Bites, Neurotoxicity, Airway Management, Developing World, India

Introduction

A review of the snake species contributing to world mortality figures of children and adults establishes that viperine snakes are by far the largest contributors (1). From the Russell's viper (Daboia russelii) of India and Asia, to carpet vipers (Echis ocellatus) and puff adders (Bitis arietans) in the Middle East and Africa and lanceheads (Bothrops sp.) in Central and South America, vipers are the medically significant envenoming "heavy weights" of the developing world (1). Despite this, neurotoxic elapid species have retained a particular mystique due to the legendary speed of action of the venom. In areas such as northern Sindh Province, Pakistan, Chandigarh and Udaipur District in India, Terai in Nepal and Kindia in the Republic of Guinea, neurotoxic bites constitute the most significant portion of snake envenomations (2-3).

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The lack of clear guidelines and understanding of the management of neurotoxic snakebite in a primary setting determine that the doctor will inevitably refer the victim to a tertiary centre or medical college that possesses a mechanical ventilator, even though that centre may be hours away and the victim will have no anti venom or airway support on the journey.

Doctors are recommended to secure the airway by endotracheal intubation and place the victim on a mechanical ventilator (4-6). The reality, however, is that the vast majority of primary hospitals in the developing world are not supplied with adequate airway equipment in the emergency department nor any mechanical ventilators (7). Little attention is given in the textbooks as to how to manage patients in such situations or how to effectively provide a bridge between the reality of non-tertiary care hospitals and the eventual arrival at a location with a ventilator (6).

This paper reviews some of the key neurotoxic snake species and recommends how to treat

patients, particularly children, of neurotoxic bites in peripheral hospitals in developing countries.

Neurotoxic Snakes of Medical Importance

The majority of the medically significant neurotoxic species fall into three families, the cobras (Naja sp), the kraits (Bungarus sp.) and the mambas (Dendroaspis sp.). There are, of course, other medically significant neurotoxic snakes such as the king cobra (Ophiophagus hannah) and the Papuan taipan (Oxyuranus scutellatus canni), but the former three families are the key causes of neurotoxic mortality in the world. Some of the most medically significant members are described further below. The lack of detailed envenoming studies of these species is remarkable and an area ripe for research.

The Neurotoxic Cobras (Fig 1)

Middle East, Asia and Africa where neurotoxic cobras are major contributors to mortality and morbidity. They include the Indian or spectacled cobra (Naja naja) found in India, Pakistan, Sri Lanka (8-9) and Nepal (10); the monocled cobra (Naja kaouthia) found in northeastern India, Myanmar, Thailand, Bangladesh, China and Vietnam and in many parts of Southeast Asia (11-12); and the Philippine cobra (Naja philippinensis) (13-14). The Asian cobra (Naja oxiana) is also a species of note being found in Pakistan (Punjab and Northwest Frontier Province), Iran, Turkmenistan, Afghanistan, Uzbekistan and possibly northeast India (Jammu and Kashmir). However the precise range of this snake is not clear. A black patternless version of Naja naja has been positively identified in Punjab, Madhya Pradesh, and Rajasthan in India and in Sindh Province in Pakistan (7). These snakes, easily confused with Naja oxiana, may explain reports of the latter species being found in these areas (15).

The African Neurotoxic Cobras

The African neurotoxic species include the Egyptian cobra (Naja haje), Cape cobra (Naja nivea), and forest cobra (Naja melanoleuca). Whilst potential lightweights in terms of fatalities, compared to their Asian cousins, they do contribute to mortality in Africa (16). Some of the African cobras such as the black-necked spitting cobra (Naja nigricollis) cause no neurotoxic symptoms in humans.

The Kraits

The kraits are widely distributed in Asia. In particular areas, Udaipur District in India and Mithi District in Pakistan, kraits constitute a significant portion of venomous bites. In one study, krait bites constituted 27% of envenomations where the species could be identified (10).

The most medically significant kraits in terms of bites are the common krait (*Bungarus caeruleus*) in India, Pakistan, Nepal, Sri Lanka and Bangladesh; the Malayan krait (*Bungarus candidus*) in Malaysia, Thailand, Cambodia, Laos and Indonesia (12,17); and the Chinese krait (B*ungarus multicinctus*) found in southern China, Hong Kong, Myanmar, Laos and Taiwan (18-19). Other kraits are less significant in terms of numbers of bites and include the banded krait (*Bungarus fasciatus*) resident in India, Nepal, Bangladesh, Myanmar, Thailand, China, Malaysia and Indonesia (11, 19-20) and the sindanus kraits (*Bungarus sindanus sindanus and B sindanus walli)* in Pakistan (Sindh and Punjab) and India (Rajasthan, Maharashtra and West Bengal) (21).

Kraits are nocturnal and frequently enter human habitation at night, and often bite victims whilst they are sleeping on the floor (22). Many victims in Rajasthan and Sindh, however, sleep on cots and still suffer bites, so cots are not the complete protection they are sometimes assumed to be.

The Mambas

The mamba family, including the black mamba (**Dendroaspis polylepsis**), the green mambas (*Dendroaspis angusticeps* [East African] and D viridis [West African]), and Jameson's mamba (*Dendroaspis jamesoni*), have a fearsome reputation and yet there are few papers in the literature describing mamba *envenomation*. Despite their reputation they contribute a small number of snakebite deaths each year in Africa (23).

Venom Action and Neurotoxicity

Neurotoxic venoms may act by one or both of two major mechanisms - pre synaptically or post synaptically at the neuromuscular junction (24).

Postsynaptic venoms act at the neuromuscular junction and compete with acetylcholine to bind at the nicotinic receptor. The receptor is blocked, acetylcholine is unable to attach and the electrical signal cannot cross the neuromuscular junction. Muscular contraction is thus inhibited and paralysis of the muscle ensues. In the case of the diaphragm this causes progressive respiratory failure and death. Once respiratory arrest occurs, brain death will follow within 4-5 minutes in the absence of alternative airway support and artificial respiration. The major snake family possessing postsynaptic venoms is the cobra family.

Pre synaptic venoms act at the neuromuscular junction on the brain side of the synaptic gap (25). The venom contains phospholipase A2 enzymes that damage the motor end plate and destroy synaptic vesicles. Acetylcholine is thus eliminated, and paralysis and respiratory failure occur.

There are other neurotoxic components of venoms such as the fasiculins, found in mamba venoms, which inhibit the action of acetylcholinesterases and cause fasciculations due to the increased life and binding of acetylcholine (1). The most important neurotoxic effects in human envenoming, however, are those caused by the pre or post synaptic neurotoxins acting at the neuromuscular junction.

The Role of Anti Snake Venom

There is little contention that ASV is useful in the role of neutralizing freely circulating venom that has not yet attached to target cells. It has been argued, however, that neurotoxic envenomation can be handled without ASV, relying solely on mechanical ventilation (26). This option is only tenable in cases where there is no ASV but ready access to definitive airway equipment, a mechanical ventilator, and the skills to use them.

The victim should be monitored on arrival at

the hospital and ASV should be given in an adequate starting dose intravenously over 1 hour to any victim exhibiting signs or symptoms of neurotoxicity. Usual signs are descending paralysis commencing with muscles innervated by the cranial nerve (eg, ptosis, diplopia, ophthalmoplegia, numbness of the lips and tongue, difficulty protruding the tongue, pooling of secretions) and proceeding to "heaviness" of the head (weakness of the cervical muscles), extremity weakness, and paradoxical respiration with difficulty breathing.

in Table 1 and the same dose is given to children and adults. The assessment of whether a second dose is required should be made 1 hour following completion of the initial dose. If the victim's signs and symptoms are worsening, then a second dose should be given at this point. Two doses of ASV, if given in sufficient quantity, should neutralise most or all of the free flowing venom, and thus two doses of ASV marks the endpoint of ASV therapy. At this stage, the victim will either recover or require ventilatory support.

The role of ASV in the treatment of venom-induced neurotoxicity has been the source of some significant confusion regarding "reversal" of symptoms. The definitional issues here have direct impact on the assessment of the clinical endpoint of ASV therapy.

Species	Anti Snake Venom	Starting Dose
Naja naja, N. kaouthia, N. oxiana	Indian or NIH Islamabad Pakistan Polyvalent Liquid or Lyophilized	10 vials/100 ml
Naja kaouthia	Thai Red Cross Monospecific	100ml
Naja haje, N. melanoleuca, N. nivea	Sanofi Pasteur Polyvalent	80 ml
Bungarus caeruleus, B. sindanus ssp, B. fasciatus, B. niger	Indian or NIH Islamabad Pakistan Polyvalent Liquid or Lyophilized	10 vials/100 ml
Dendroaspis sp.	South African Vaccine Producers (SAVP)	80 ml
Dendroaspis sp.	Sanofi Pasteur Polyvalent	80 ml

Table 1 Anti Snake Venom Initial Dosage Guide (7,43,46)

NIH = National Institute of Health

It is common in the literature to talk about "reversibility" of neurotoxic envenoming (5-6, 27-30), and it is important to be clear what the term "reversal" is referring to in this context. Two main interpretations are possible – the first clearly correct, and the second largely unproven:

1. ASV neutralises free, circulating venom which prevents it binding to target tissues, thus reducing overall neurotoxic effects. In so doing, ASV allows the victim to recover more quickly. Reversal is used in this context as meaning overall recovery.

2. ASV "reverses" the action of the venom by detaching venom molecules from target cells, and thereby improves the patient's clinical condition.

This distinction is critical due to the fact that argument 1 has a clinical endpoint - give sufficient ASV to achieve neutralization and then stop. In argument 2 it is possible to interpret the statement as "give ASV until the venom has been detached," and all symptoms have reversed. This argument may result in considerable amounts of ASV being given to the patient whilst waiting for symptoms to reverse. The literature clearly demonstrates that argument 2 holds great sway with doctors treating neurotoxic snakebite victims, and compels them to give very large doses of ASV (27, 31-33). Physicians in India and Pakistan frequently refer to "reversing" envenomation by such a detachment mechanism (34).

There is little dispute that argument 1 is universally accepted; the role of ASV in

envenomation is to neutralise circulating venom. However, the evidence for argument 2 is far from convincing, and such practice carries the major risk of ASV being wasted for no useful purpose.

Pre synaptic envenomation is almost universally accepted as not being "reversible" as defined in argument 2 (25, 35-37). The destruction of synaptic vesicles can only be overcome by regeneration of the vesicles and the subsequent resumption of acetylcholine production, which is usually evident by 5 days post envenomation (25). The role of ASV is therefore to minimize the impact of the venom on the vesicles by neutralizing as much venom as possible before it can inflict damage. ASV is not curative in this scenario.

In the case of postsynaptic envenoming there is a paucity of evidence suggesting that ASV may be able to speed the detachment of venom from target receptors (37). The balance of opinion, however, is that this evidence is far from conclusive (38). In the absence of definitive evidence that ASV can increase detachment of venom from target receptors, the need for doses of ASV, in excess of the amount required to neutralise circulating venom is not established.

ASV doses in both post and pre synaptic envenomings should therefore be limited to that required to neutralise circulating venom. ASV should not be administered in larger doses for the purpose of attempting to "reverse" envenomation in the sense of argument 2. To do so would simply waste a costly resource that is believed to be scarce.

Anticholinesterase Therapy

As an adjunct to ASV therapy in cases of postsynaptic envenoming, treatment is supported by the use of anticholinesterase drugs such as neostigmine (Prostigmin) and edrophonium (Tensilon). A great deal has been written on this topic, including the recommendation for use of a "Tensilon test" (6). In this test, 0.25mg/kg of edrophonium is given IV (10 mg for adults) together with 0.05mg/kg of atropine (0.6 mg for adults) (to counter the muscarinic effects of the anticholinesterase) to a victim of snake venom induced neurotoxicity. The victim is observed for 10-20 minutes for any objective improvement. However, edrophonium is rarely available in the developing world due to issues of cost and access (39).

In developing world countries, neostigmine is cheaper and more readily available. Thus a "neostigmine test" is more usual, and has differences in timings of action compared to edrophonium. The first step in applying such a test is to take a reproducible, objective baseline reading of neurological function utilizing single breath count, length of time upward gaze can be maintained or similar. Neostigmine methylsulphate 0.04mg/kg (1.5 mg for adults) is then administered intramuscularly (IM) with 0.05mg/kg of atropine given intravenously (IV) (0.6 mg for adults). Every 10 minutes for 1 hour the objective test is repeated and results noted. Neostigmine takes approximately 20 minutes for peak onset of effects. If improvement in the objective measure is observed, neostigmine should be continued with 0.02 mg/kg being given IM, half hourly with further atropine as needed. If there is no improvement, there is no further role for anticholinesterase drugs (7).

It is not clear whether anticholinesterase has any role in presynaptic envenomings such as by the krait. Very little trial evidence is available to enable an informed view. Some authors have reported beneficial effects in respect to some krait species (39-41), while others have concluded that there is no benefit (35, 40,42). Caution must be exercised in interpreting past studies as they may have been based on unreliable species identification (40). In light of the fact that there is no conclusive evidence to support use or non use of anticholinesterase and given the difficulty in definitively identifying the responsible species, it is probably wise to administer an initial anticholinesterase test to all victims with neurotoxic clinical findings.

Treatment in a Primary Setting and Referral Criteria

For the purposes of this paper, primary care hospitals are defined as those that have no mechanical ventilator and refer patients requiring mechanical ventilation to larger and better equipped hospitals, which in the developing world are usually attached to a medical college (7).

Treatment of Neurotoxic Snake Envenomation in Primary Care Hospitals

Victims who arrive at the primary facilities should be assessed for visible neurological signs such as ptosis. If signs of envenomation develop, the victim should be administered an initial dose of ASV. The victim should be closely observed and any anaphylactoid reaction managed with intramuscular adrenaline, 0.01 mg/kg for children, and 0.5 mg for adults, as needed every 8 to 12 minutes for up to three doses. A steroid and an antihistamine should also be given in the event of an anaphylactoid reaction for long term support.

An anticholinesterase test should be carried out using objective change in neurological findings to assess efficacy.

The patient should be re-assessed at 1 hour following completion of the initial ASV infusion. If at this stage symptoms have worsened (i.e. descended further), a second similar dose of ASV should be administered over 1 hour. If, however, symptoms have not worsened but have remained the same, a further hour should be allowed to elapse. If the patient still shows no sign of improvement or deteriorates; a second dose of ASV should be given at this stage. Patients who improve and stabilize with therapy and without signs of respiratory failure should be observed for 24 hours, and can then be discharged locally. Patients who develop signs worrisome for impending respiratory failure need to be referred to a hospital that can provide definitive airway control and mechanical ventilatory support.

Referral to Better Equipped Hospitals

A useful bedside test of central muscle strength and adequacy of respiratory effort in a primary setting is the ability of the patient to perform a supine neck lift (7). If this ability is still present it indicates that paralysis of the neck muscles has not taken place, and is a sign that respiratory failure is likely not imminent. The descending nature of neurological impairment makes it very likely that neck muscle impairment will precede respiratory failure. If the patient is unable to perform the neck lift or if sudden respiratory failure occurs, then transfer to a higher level of care is the preferred option and airway support for the journey is the key concern.

Airway Support

It is necessary to maintain a sense of reality with regard to airway support in developing countries. The following are key considerations in drawing up the below guidelines:

1. In most areas, neurotoxic snakebite will be less significant in terms of numbers when compared to viperine snakebite which is mainly coagulopathic

2. The ideal solution with respiratory compromise or failure is endotracheal intubation and support on a mechanical ventilator

3. Many doctors are not sufficiently well trained, experienced or confident to carry out endotracheal intubation and therefore do not attempt it

4. The vast majority of medical facilities are NOT equipped with mechanical ventilators

5. Those facilities that are equipped with ventilators have very few and they are invariably already in use and under pressure

6. In disaster situations, such as floods or cyclones e.g. Cyclone Nargis, power will be interrupted and road travel will be virtually impossible due to flooding and fallen trees! The focus of W.H.O. nominated experts in the aftermath of Cyclone Nargis who concentrated on mechanical ventilation and intubation in the snakebite guidelines, demonstrates the lack of understanding of airway support in developing countries.

Basic Support

In many cases in the developing world, primary care hospitals will have a resuscitation bag and mask. Family members or friends can be instructed in the use of this equipment should it become necessary on the journey. The important points to communicate are that the mask should be placed over both the nose and mouth in a rolling manner starting at the bridge of the nose. Preferably, bag-valve-mask ventilations are given using the "C-E" grips [thumb and index finger of each hand forming a "C" over top of the mask and long, ring and little fingers forming an "E" under the jaw (Fig 2) – pressing the mask onto the face]. The bag should be squeezed at a specific cadence of "squeeze – release – release." This

method ensures the victim receives a good quantity of air but also allows time for exhalation.

Improvised Solution

However, in cases of neurotoxic envenomation, if respiratory failure occurs it will be due to flaccid

Fig 2 C-E Grip for Resuscitation Bag

paralysis and there is a strong likelihood that the tongue will fall back and obstruct the airway. The use of a resuscitation bag in these circumstances will be compromised. Nasopharyngeal airway (NPA) support is an excellent emergency measure in these situations if available (43-44). If available, NPAs should be inserted before transportation to the referral hospital, which will dramatically increase the probability of effective respiratory support during the journey.

It is possible however to improvise nasopharyngeal tubes (NT) from endotracheal tubes (ET), which are usually readily available or can be obtained easily. Two rubber or plastic size 3 ET tubes for children (6.5 ET tubes for females, size 7 for males) can be adapted to provide NT (45). The tubes are cut to the distance between the nostril and the tragus, lubricated and inserted into the nostrils of a conscious or unconscious patient (46-47).

Cut to the correct length (Fig 3) they will not trigger the gagging reflex and thus can be used when a patient is conscious. In the event that a patient cannot perform a neck lift and is to be transferred to a better-equipped hospital, the tubes can be inserted and the individuals accompanying the victim instructed to use the resuscitation bag if the victim stops breathing.

Bridging Devices

An improved solution is the use of an airway-bridging device such as a laryngeal tube (LT) or laryngeal mask airway (LMA) [7]. These devices are not "definitive" airways (defined as a cuffed endotracheal tube positioned below the vocal cords), but provide excellent airway support. They are inserted blindly and give a very high percentage possibility of being inserted correctly (48-53)

Use of such airways by accompanying laypersons has not been studied, but it is very possible that the lay provider can adequately ventilate the unconscious victim during transfer using a properly placed laryngeal tube. The creation of a better seal makes it more likely that the LT tube is preferable over rough journeys experienced when transporting snakebite victims in many developing countries (54-55).

Use of the LMA requires greater skill in maintaining proper positioning, making it a less optimal choice for use by untrained individuals.

The Ideal Solution

The ideal solution is the ability to endotracheally intubate the victim and provide a definitive airway defined as placing a cuffed tube

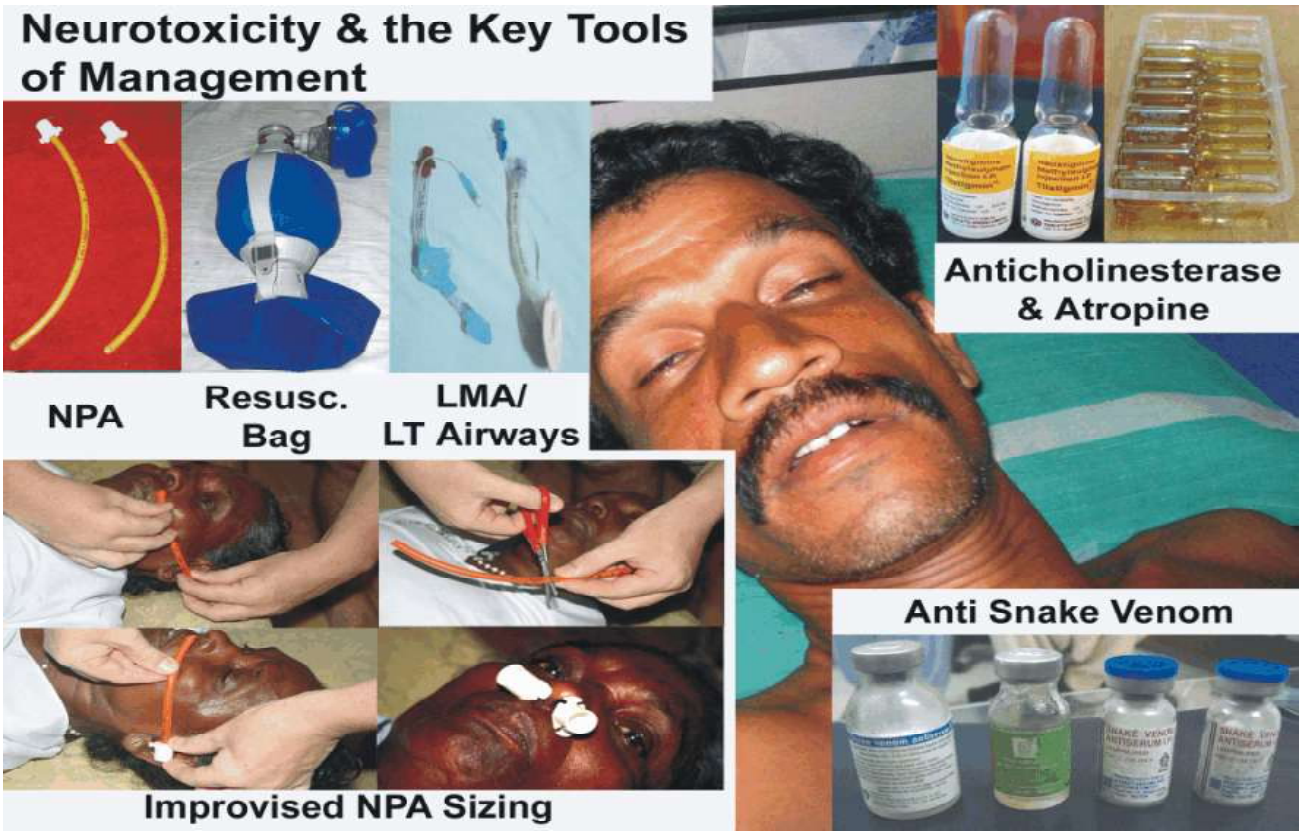

Fig 3 Improvising NPAs and the tools of Neurotoxic Snakebite Management

below the vocal chords. The endpoint therapy will be a mechanical ventilator to provide long-term respiratory support. It is worth remembering that in presynaptic envenoming, the time to recovery and the need for mechanical ventilation may take several days or weeks, until synaptic vesicles have been restored. Developed world derived protocols advising endotracheal intubation or tracheostomy, once loss of the gag reflex or pooling of secretions occurs is simply impractical (6).

Conclusion

Despite the fearsome reputation of neurotoxic snake species, neutralisation of circulating venom at the earliest indication of neurotoxicity, protection of the airway, and ventilatory support are key considerations. When necessary, the airway can be managed with simple and easily improvisable tools that can be made in a very basic setting.

References

1. Chippaux JP. Snake venoms and envenomations. Florida. Krieger Publishing Company, 2006.
2. Sharma SK et al. Impact of Snakebites and Determinants of Fatal Outcomes in Southeastern Nepal. Am J Trop Med Hyg 2004; 71:234-238.
3. Stock RP et al. Bringing Antivenoms to Sub-Saharan Africa. Nature 2007; 25:173-177.
4. Auerbach PS, Norris RL. Disorders caused by reptile bites and marine animal Exposures. In: Kaspar DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL eds Harrison's Principles of Internal Medicine New York, McGraw-Hill 2005.
5. Warrell DA. Injuries, envenoming, poisoning, and allergic reactions caused by animals In. Warrell DA, Cox TM, Firth JD eds. Oxford Textbook of Medicine, Oxford, Oxford University Press, 2005.
6. Warrell DA. WHO/SEARO guidelines for the clinical management of snakebite in the Southeast Asian Region. SE Asian J Trop Med Pub Hlth 1999;30:1–85.
7. Simpson ID. Snakebite management in India, the first few hours: a guide for primary care physicians. J Indian Med Assoc 2007;105:324-335.
8. De Silva A. Snakebites in Anuradhapura District. The Snake 1981;13:117-130.

9. Theakston RDG et al, Envenoming by the common krait (Bungarus caeruleus) and Sri Lankan cobra (Naja naja naja): efficacy and complications of therapy with Haffkine antivenom. Trans R Soc Trop Med Hyg 1990;84:301-308.

10. Ahuja ML, Singh G. Snake bite in India. Indian J Med Res 1954;42:661-686.

11. Viravan C et al. A national hospital-based survey of snakes responsible for bites in Thailand. Trans RSoc Trop Med Hyg 1992;86:100-106.

12. Looareesuwan S, Viravan C, Warrell DA. Factors contributing to fatal snake bite in the rural tropics: analysis of 46 cases in Thailand. Trans R Soc Trop Med Hyg 1988;82:930-934.

13. Watt G et al. Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). A placebo-controlled study. N Engl J Med 1986;315:1444-8.

14. Watt G et al, Bites by the Philippine cobra (Naja naja philippinensis): an important cause of death among rice farmers. Am J Trop Med Hyg 1987;37:636-9.

15. Davidson TM, Schafer S, Killfoil J. Cobras. Wilderness Environ Med 1995;6:203-19.

16. Warrell DA, Barnes HJ, Piburn MF. Neurotoxic effects of bites by the Egyptian cobra (Naja haje) in Nigeria. Trans R Soc Trop Med Hyg 1976;70:78-79.

17. Pochanugool C et al, Spontaneous recovery from severe neurotoxic envenoming by a Malayan krait Bungarus candidus (Linnaeus) in Thailand. Wilderness Environ Med 1997;8:223-5.

18. Kuo T-P, Wu C-S. Clinicopathological studies on snake bites in Taiwan. The Snake 1972;4:1-22.

19. Sawai Y et al. An epidemiological study on the snakebites in Guangxi Zhuang autonomous region, China in 1990. The Snake 1992;24:1-15.

20. Tun Pe et al. Envenoming by Chinese Krait (Bungarus multicinctus) and Banded Krait (B. fasciatus) in Myanmar. Trans Roy Soc Trop Med Hyg 1997;91:686-688.

21. Kuch U, et al. Kraits with 17-dorsal-scale-rows (Bungarus sindanus complex): unrecognised causes of severe neurotoxic envenoming in South Asia. (Abstract) 15th World Congress on Animal, Plant and Microbial Toxins. 23rd July to 28th July (2006) Glasgow.

22. Saini RK et al. Snake bite poisoning presenting as early morning neuroparalytic syndrome in jhuggi dwellers. J Assoc Physns India 1986;34:415-417.

23. Chapman DS. The symptomatology, pathology and treatment of the bites of venomous snakes of Central and Southern Africa. In: Bucherl W, Buckley EE, Deulofeu V, eds. Venomous animals and their venoms New York, Academic Press, 1968.

24. Harris JB. Snake venoms in science and clinical medicine: neuropharmacological aspects of the activity of snake venoms. Trans Roy Soc Trop Med Hyg 1989;83:745-747.

25. Dixon RW, Harris JB. Nerve terminal damage by B-Bungaratoxin. Am J Pathol 1999;154:447-455.

26. Bomb BS et al. Do we need antisnake venom (ASV) for management of elapid ophitoxaemia? J Assoc Phys Pakistan 1996;44: 31-33.

27. Sharma SK, Koirala S, Dahal G. Krait bite requiring high dose antivenom: a case report. Southeast Asian J Trop Med Public Health 2002;33:170-171.

28. Warrell DA. Animal toxins In: Cook GC, Zumla AI. eds. Manson's Tropical Diseases. Philadelphia, W. B. Saunders, 2003.

29. Warrell DA. Bites by Venomous Snakes Outside the Americas In: Auerbach PS ed. Wilderness Medicine, St. Louis, Moseby, 2007.

30. White J. Bites and stings from venomous animals: A Global Overview. Therapeutic Drug Monitoring 2000;22:65-68.

31. Agrawal PN et al. Management of respiratory failure in severe neuroparalytic snake envenomation. Neurol India 2001;40:25-28.

32. Harish R, Digra SK. Snake bite neurotoxicity: reversal after 84 hours. Indian Pediatics 2007;44:233.

33. Sharma N et al. Snake envenomation in a North Indian hospital. Emerg Med J 2006; 22:118-120.

34. Khan, B., Naseem, A. Guidelines for management of snake bite cases. Pak Armed Forces Med J, 2000;50:51-55.

35. Cheng AC, Currie BJ. Venomous snakebites worldwide with a focus on the Australia-Pacific Region: current management and controversies. J Intensive Care Med 2004; 19:259-269.

36. Gutierrez JM, Theakston RDG, Warrell DA. Confronting the neglected problem of snakebite envenoming: the need for a global partnership. PLoS Med 2006, 3(6):e150.DOI:10:1371/ journal.pmed.0030150

37. Harris JB, Goonetilleke A. Animal poisons and the

nervous system: what the neurologist needs to know. J Neurol Neurosurg Psychiatry 2004; 75:40-6.

38. Warrell DA. Clinical toxicology of snakebite in Asia In: White J Meier J eds. Handbook of Clinical Toxicology of Animal Venoms and Poisons. Boca Raton, CRC Press, 1995.
39. Seneviratne U, Dissanayake S. Neurological manifestations of snakebite in Sri Lanka. J Postgrad Med 2002;48:275-278.
40 Ramakrishnan MR et al. External opthalmoplegia in elapidae bites and its response to neostigmine. Neurology India 1975;23:109-110.
41. Warrell DA et al, Severe neurotoxin envenoming by the Malayan Krait Bungarus candidus (Linnaeus): response to anticholinesterase. BMJ 1983;286:670-680.
42 .Bambery P, Malhotra HS, Chugh KS. Clinical problems of snakebites in India. In: Tu A., eds. Toxin Related Diseases. New Delhi, IBH. 1993.
43. Blaylock RS. The Identification and syndromic management of snakebite in South Africa. SA Fam Pract 2005;47:48-53.
44. Bajaj Y, Gadepalli C, Knight LC. Securing a nasopharyngeal airway. J Laryngol Otol 2008;122:733-4.
45. Roberts K, Whalley H, Bleetman A. The nasopharyngeal airway: dispelling myths and establishing the facts. Emerg Med J 2005;6:394-6.
46. Quraishi NA, Qureshi HI, Simpson ID. A contextual approach to managing snake bite in Pakistan: snake bite treatment with particular reference to neurotoxieity and the ideal hospital snake bite kit.J Pak Med Assoc2008;58:325-31.
47. Government of India. National snakebite protocol. New Delhi: Health & Family Welfare Department:2007
48. Bailey AR, Hett DA. The laryngeal mask airway in resuscitation. Resuscitation 1994; 28:107-110
49. Springer DK, Jahr JS. The laryngeal mask airway. Safety, efficacy, and current use. Am J Anesthesiol 1995;22(2):65-9.
50. Pollack CV. The laryngeal mask airway: a comprehensive review for the Emergency Physician. J Emerg Med 2001 Jan;20(1):53-66.
51 Murphy MF. 2004. Laryngeal mask airways. In: Walls RM (ed): Emergency Airway Management. Philadelphia, Lippincott Williams & Wilkins, pp 97-109.
52. Murphy MF, Schneider RE. 2004. Supraglottic devices. In: Walls RM (ed): Emergency Airway Management. Philadelphia, Lippincott Williams & Wilkins, pp 110-119.
53. Weiss CH, Semmel T, Müller JU, Bahr J, Ocker H, Graf BM. The use of the laryngeal tube disposable (LT-D) by paramedics during out-of-hospital resuscitation-An observational study concerning ERC guidelines 2005. Resuscitation 2008 Nov 14. [Epub ahead of print]
54. Ocker H, Wenzel V, Schmucker P, Steinfath M, Dörges V. A comparison of the laryngeal tube with the laryngeal mask airway during routine surgical procedures. Anesth Analg 2002;95(4):1094-7
55. Gaitini L, Madrid V, Capdevila M, Arino JJ. The Laryngeal tube. Rev Esp Anestesiol Reanim. 2008;55(4):232-41.