Snake bite: A neglected problem in twenty-first century India

In the fourth century BC, India was invaded by Alexander the Great’s army, which was accompanied by a number of Macedonian physicians and observers. They were impressed by the achievements of the local Ayurvedic practitioners, particularly in the treatment of snake bite. Unfortunately, the legacy of ancient skills, experience and wisdom may have held back rather than encouraged the application of modern scientific research methods to manage this continuing scourge of rural life in India.

How many people are killed by snake bite in India?

In the 1870s, Joseph Fayrer of the Indian Medical Service first attempted to quantify human mortality due to snake bite: ‘The destruction of life in India by snake bites is so great, that … (it) probably destroys over 20 000 human beings annually…’. However, between 2004 and 2009, hospital returns to the Government of India from 31 of 35 states and union territories revealed that there was an average of only 1350 deaths each year. Community-based surveys in Bardhaman district, West Bengal and a neighbouring area of Nepal’s eastern Terai found that the annual incidence of snake bite deaths/100 000 population was 16.4 and 162, respectively. These data indicated the true scale of the problem and the degree of geographical variation. Recently, the Registrar General of India’s ‘Million Death Study’ has, for the first time, provided a direct estimate of mortality due to snake bite, nationally and in each state. Verbal autopsy (questioning the deceased’s family and neighbours) was used to identify the causes of all deaths in 6671 randomly chosen sample areas, each covering about 1000 people. In 2005, 46 000 people (99% CI 41 000–51 000) died of snake bite, approximately 1 for every 2 HIV/AIDS deaths. Verbal autopsy seems likely to be reliable in this context because snake bite is such a dramatic and distinctive event that leaves an impression, and causes death within a few days. It must be noted that the total number of deaths due to snake bite may be even higher since some victims of nocturnal krait envenoming do not realize that they have been bitten and present with mysterious ‘early morning paralysis’ or seizures.

Snake bite accounts for 3% of all deaths in children of the age of 5–14 years. Ninety-seven per cent of the victims of snake bite die in rural areas, 77% of them outside health facilities, presumably because they chose traditional therapy from tantriks, vaidyas and ojhas. Uttar Pradesh had the highest number of deaths (8700/year) and Andhra Pradesh the highest incidence of mortality due to snake bite (6.2/100 000 population/year). These figures should prompt the Ministry of Health to reassess its priorities in the context of snake bite and deploy resources where they are most needed.

Which species are responsible for snake bite envenoming in India? Should the classic Indian polyvalent antivenoms be redesigned to provide broader cover?

More than 60 species of venomous snakes are found on land and in water in India, some of which are abundant and frequently cause severe envenoming. The spectacled cobra (Naja naja), common krait (Bungarus caeruleus), saw-scaled viper (Echis carinatus) and Russell’s viper (Daboia russelii) have long been recognized as the most important...
species. Documented geographical variation in the composition of the venoms of *N. naja* and *D. russelli* have raised doubts about whether the antivenoms available can adequately cover envenoming in some regions.10 Envenoming by the larger northern sub-species of the saw-scaled viper (*Echis carinatus sochureki*) requires larger doses of antivenom.11 Some species are important in particular areas and others have been recently recognized as potential perpetrators of debilitating or fatal envenoming. The monocellate cobra (*N. kaouthia*) occurs in the North-East and the Central Asian or Oxus cobra (*Naja oxiana*) in the North (Kashmir and Himachal Pradesh). Wall’s krait (*Bungarus walli*) in the North-East and the Sind krait (*B. sindanus*) in the west were formerly regarded as sub-species. The greater black krait (*B. niger*) in the far North-East has proved capable of causing severe generalized rhabdomyolysis and acute kidney injury (AKI), besides the familiar paralytic symptoms.12 Among the 15 species of Indian pit-viper, the hump-nosed pit-viper (*Hypnale hypnale*) of the south-west coast and Western Ghats has been confused with *E. carinatus* and is capable of causing fatal antihaemostatic effects and AKI, 13 and the bamboo pit-viper (*Trimeresurus gramineus*) of the Western and Eastern Ghats, the large-scaled pit-viper (*Peltopelor macrolepis*) of the south-west and the Malabar pit-viper (*Trimeresurus malabaricus*) of the Western Ghats can cause local swelling, bruising and bleeding. Despite this diversity of potential pathogens, Indian polyvalent antivenoms continue to be raised against the venoms of only *N. naja, B. caeruleus, D. russelli* and *E. carinatus*. Envenoming by even these traditional ‘big four’ species may not be effectively covered because 80% of the venom currently used to raise Indian polyvalent antivenoms is collected from snakes inhabiting one small area around Mahabalipuram in Tamil Nadu.

**Why is it necessary to identify the snake responsible for a bite if polyvalent antivenom is available?**

Even if polyvalent antivenom covered the venoms of all the medically important snakes of India, there would be clinical and research reasons for wanting to know the specific identity of the snake causing the bite. This may guide the use of an appropriate initial dose of antivenom and allow the clinician to anticipate, prevent or be prepared to treat major complications such as AKI. From the research point of view, the study of series of patients envenomed by rigorously identified species enables one to define the clinical phenotype as a basis for syndromic diagnosis and management, and the establishment of reliable dosage guidelines for envenoming by major species. It also stimulates the search for causative toxins and pathophysiological mechanisms. Reliable methods for diagnosis are expert examination of the snake, if it is brought with the patient,14,15 and enzyme immunoassay detection of venom antigens in the victim’s blood or tissue fluids.16 Unreliable methods include identification based on descriptions of the snake by the victims or their companions, or recognition of pictures, or on observation of clinical features in areas where more than one species causes a particular clinical syndrome. All too often, healthcare personnel take no interest in the dead snake despite its being valuable evidence of causation. Preservation of such specimens, labelled with the patient’s details, for eventual definitive identification by a herpetologist allows retrospective confirmation of the diagnosis for research purposes and helps to establish the medically important herpetofauna of an area, the relative medical importance of different species and their geographical distribution.14,15

**How effective are Indian antivenoms? What initial dosage should be used?**

Despite the vast clinical experience accumulated during almost a century of the use of antivenoms in India, there are very few published data to document their effectiveness or serve as a guide for the initial dosage. The label on the vial states the amount of each venom neutralized by 1 ml of antivenom, but this is not a reliable guide for dosage. Package inserts are usually unhelpful or misleading. No clinical dose-finding studies have been published from India that fulfil the basic criteria of acceptability: recruitment of patients bitten by the same identified species and showing evidence of similar severity of envenoming (since dose requirements differ between species and with
severity of envenoming); randomized, controlled design (as in any other branch of therapeutics); and defined entry criteria and objective end-points (such as measurable clinical response, restoration of blood coagulability or extinction of venom antigenaemia). As a result, there are no evidence-based, as opposed to experience-based, guidelines for the initial dose and repeated doses of any Indian antivenom. In Sri Lanka, in 14 victims of proven D. russelii bite envenoming, who were admitted with incoagulable blood (assessed by the 20-minute whole blood clotting test) and were treated with a single dose of 10 vials of Haffkine antivenom, blood coagulability was restored within 6 hours and venom antigenaemia became undetectable within 1 hour.17 However, experience in some parts of India suggests that an initial dose of 10 vials is inadequate for treating D. russelii envenoming. By analogy with studies in other countries, and on the basis of clinical impression, Indian polyvalent antivenoms, if administered in a sufficient dose, can be expected to correct bleeding and clotting disorders in patients envenomed by D. russelii and E. carinatus. After an initial dose of 10–20 vials (D. russelii) or 5–10 vials (E. carinatus), the repeated dose is administered on the basis of the restoration of blood coagulability (20WBCT), which is assessed approximately every 6 hours. However, the antivenoms available are ineffective for envenoming by any of the Indian pit-vipers. Also, their effectiveness against neurotoxic envenoming is controversial. Naja naja neurotoxins are post-synaptic in action and their binding to acetylcholine receptors at neuromuscular junctions is reversible. Improvement in paralytic signs may become clinically evident within 30–60 minutes of an initial dose of 10–20 vials of antivenom, while anticholinesterase drugs such as neostigmine are even more rapidly effective.18,19 In contrast, krait venoms contain pre-synaptic toxins that bind irreversibly to nerve endings and destroy them. Early antivenom treatment (10–20 vials loading dose) might prevent paralysis by neutralizing the β-bungarotoxins before they have bound to their tissue targets but, once developed, paralysis cannot be reversed and anticholinesterases are usually ineffective. There is no scientific or clinical basis for prolonged administration of antivenom to paralysed krait bite victims on ventilators.

How safe are Indian antivenoms?

No prospectively gathered data on antivenom safety have been published from India, but in Sri Lanka, early pyrogenic and anaphylactic reactions occurred in 43%–81% of recipients of Indian antivenoms.17 Forty-three per cent of the reactions were considered severe, but fatal reactions were rarely reported. A recent, well-designed study discovered that prophylactic adrenaline (0.25 ml of a 0.1% solution given subcutaneously) reduced the rate of severe adverse reactions; over 1 hour by 43% (OR 0.57, 95% CI 0.43–0.75, p=0.001); and over 48 hours by 38% (OR 0.62, 95% CI 0.51–0.74, p=0.001).20 Intravenous promethazine and hydrocortisone proved useless.

How can the risk of snake bite be reduced?

The ‘Million Death Study’ confirmed that the majority of snake bite victims were bitten in rural areas and died outside hospitals.5 These fatalities might be prevented by community education that promotes behavioural change to reduce the risk of bites.21 Villagers should be warned of the types of environment most likely to harbour venomous snakes, and the most dangerous season of the year and time of day. They should be encouraged to use footwear22 and a light after dark in order to be safe while walking and working. They could be protected from krait bites while sleeping by using a well tucked-in mosquito net23 or sleeping on a raised bed or hammock. If bitten, patients should seek proper medical care as quickly as possible, without wasting time on traditional therapists. In the eastern Terai of Nepal, training volunteer motorcyclists in villages has speeded up the transfer of patients to local health clinics and reduced mortality (S.K. Sharma, personal communication, 2011).

Conclusion: An exciting opportunity for Indian medical science

The enormous wealth of clinical experience and skill in the treatment of snake bite in India should be harnessed to help design and perform clinical research studies no less
rigorous than those demanded in all other branches of twenty-first century medicine. Such studies could address some of the important questions raised in this editorial to provide evidence upon which to base future strategies for preventing and treating this most neglected of all the neglected tropical diseases.  

REFERENCES

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