CONCEPT ARTICLE

Snakes of Medical Importance in India: Is the Concept of the “Big 4” Still Relevant and Useful?

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Snakebites continue to be a major medical concern in India. However, there is very little hard evidence of a numerical nature to enable us to understand which species are responsible for mortality and morbidity. For many decades, the concept of the “Big 4” Snakes of Medical Importance has reflected the view that 4 species are responsible for Indian snakebite mortality—the Indian cobra (*Naja naja*), the common krait (*Bungarus caeruleus*), the Russell’s viper (*Daboia russelii*) and the saw-scaled viper (*Echis carinatus*). However, a recent discovery that another species, the hump-nosed pit viper (*Hypnale hypnale*), is capable of causing lethal envenomation, and that this problem was being concealed by systematic misidentification of this species as the saw-scaled viper, has necessitated a review of the concept of the “Big 4.” The concept of the “Big 4” snakes is reviewed to demonstrate its failure to include all currently known snakes of medical significance in India, and its negative effects related to clinical management of snakebite. The emergence of the hump-nosed pit viper (*Hypnale hypnale*) as a snake of medical significance has rendered the “Big 4” obsolete in terms of completeness. The concept of the “Big 4” is restricting sound epidemiological work and the development of effective snake antivenoms. It should be replaced by the model introduced in the 1980s by the World Health Organization, which has not received adequate circulation and implementation.

Key words: snakes, snakebites, snake envenomation, antivenom, India

Introduction

Venomous snakebite continues to be a matter of major medical concern in India, as it has been for at least the last 100 years. In the 1950s, a World Health Organization (WHO) survey estimated the number of bites at 200,000 in India alone with a mortality of 15,000 annually.¹ In the late 20th century, the number was estimated at 1.2–2.4 deaths per 100,000, which would equate to a mortality level of 25,000 per annum.² More recent WHO estimates state that the annual mortality due to snakebite in India is approximately 50,000.³ There are many causal factors that contribute to this mortality rate. There also remain a great many important, yet unanswered, questions relating to the treatment of snakebite victims. These questions include the correct dosage level of antivenom to be given to a victim with systemic envenomation upon arrival at hospital, the precise nature

of snake venoms, including their content and variability, and the lack of reliable means of identifying species of snakes responsible for bites, such as an enzyme-linked immuno sorbent assay (ELISA).⁴

Much of the information regarding Indian venomous snakes, on which we currently base decisions, has been known for many decades, particularly in respect to the number and geographical ranges of snake species, population densities, and snake habits.⁵ This knowledge has now become accepted wisdom in the field of snakebite and snakebite treatment. There has, however, been very little qualitative herpetological work in India, since the 1940s.

Original Concept

One of the widely accepted concepts in Indian snake venom discussions and research is the notion of the so-called “Big 4 Snakes of Medical Importance,” which includes the Russell’s viper (*Daboia russelii*), the saw-

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Figure 1. The Russell's viper (*Daboia russelii*).

scaled viper (*Echis carinatus*), the Indian or spectacled cobra (*Naja naja*), and the common krait (*Bungarus caeruleus*) (Figures 1 through 4). These 4 snakes have been believed to cause the vast majority, if not all, fatalities due to snakebite. It was recognised that species such as the king cobra (*Ophiophagus hannah*) were capable of causing lethal envenoming, but the number of bites and human contact with these other dangerously toxic species ensured that the number of fatalities each year was relatively negligible.

This paper examines the usefulness of the concept of the “Big 4” in light of recent discoveries that other snakes are capable of causing life-threatening envenoming in a significant number of cases. Whether the concept of the “Big Four” is still useful or whether this concept actually causes problems in epidemiology and snake identification is reviewed. Whilst we have largely abandoned antiquated methods of snakebite therapy such as the use of permanganate of potash, chloride of gold, silver nitrate, and the chloride and hypochloride of lime,⁶ other concepts from that same period, such as the “Big 4,” have remained unexamined.

Current Situation

The recent recognition of a snake in India, previously considered essentially harmless, as a species capable of causing life-threatening envenoming brings the value of the concept of the “Big 4” into question. A study in Kerala, India, has established that out of 44 snakes killed and brought to 2 hospitals by snakebite victims from 2000 to 2004, 9 proved to be the hump-nosed pit viper (*Hypnale hypnale*) (Figure 5).⁷ All 9 of these snakes were misidentified by the treating physicians as saw-scaled vipers (*E carinatus*). This misidentification resulted from the belief that, as the victim was suffering from severe life-threatening envenoming, the offending snake had to be one of the “Big 4” snakes of medical significance. Combining 2 of these cases in which detailed clinical records were available with 3 other subsequently documented *H hypnale* bites from 2005 revealed the results found in Table 1.⁷

During prospective data collection in 2005, 88 victims of venomous snakebite with proven systemic envenomation were admitted to the Little Flower Hospital Med-

Figure 2. The saw-scaled viper (*Echis carinatus*).

ical Intensive Care Unit in Kerala.⁷ Of these, 8 (9.1%) were proven bites from *H hypnale*, with the dead snake being brought to the hospital. In another 7 (8%), the victim or bystanders identified *H hypnale* from a selection of photographs of both venomous and nonvenomous species from the surrounding area. The percentage of bites resulting from *H hypnale* but not supported by the dead snake or a positive identification by the victim is unknown. Before the study, however, all of these bites would have been recorded as bites by the saw-scaled viper (*E carinatus*).

The role of Indian polyvalent antivenom (AV) (an equine product made with *N naja*, *B caeruleus*, *D russelii*, and *E carinatus* venoms) was evaluated for effectiveness in dealing with bites of *H hypnale*. The primary criteria for success was restoration of coagulation as measured by the 20-Minute Whole Blood Clotting Test (20 WBCT).⁸ In the cases of coagulopathy caused by the other local vipers, Russell's viper (*D russelii*) and the saw-scaled viper (*E carinatus*), coagulation is normally restored within 18 hours of starting AV. AV is administered at 6-hour intervals, with the victim receiving up to 30 vials in a 12 hour period (ie, 10 vials at

T0, 10 vials at T0 + 6 hours, and 10 vials at T0 + 12 hours). The final blood test to establish coagulation is taken at T0 + 18 hours. In the Kerala study 4/5 (90%) of *H hypnale* cases remained coagulopathic for more than 18 hours despite AV administration,⁷ indicating a failure of Indian polyvalent AV to reverse coagulopathic effects of *H hypnale* venom.

This conclusion is further supported by evidence from Sri Lanka,^{10,11} which showed that Indian antivenom, the only antivenom available in that country, had very little efficacy in dealing with symptoms of severe local or systemic envenoming by *H hypnale*. In light of these observations, it is clear that current Indian polyvalent antivenoms have no efficacy against the hump-nosed pit viper, and their use for these bites merely adds risk of allergic sequela, incurs considerable additional cost for terribly indigent victims, and wastes precious resources.

As a result of the failure of antivenom to restore coagulation, a management protocol has been developed at Little Flower Hospital, whereby antivenom is withheld in proven hump-nosed pit viper bites with systemic envenoming. Treatment consists of conservative management with particular emphasis on monitoring and sup-

Figure 3. The Indian or spectacled cobra (*Naja naja*).

Figure 4. The common krait (*Bungarus caeruleus*).

Figure 5. The hump-nosed pit viper (*Hypnale hypnale*).

porting the indicators of renal performance, such as urine output, and serum creatinine and potassium. We are currently studying the effectiveness of this approach.

Based on our experience, we have prepared a table (Table 2) outlining the major groups of common clinical findings and responses to treatments encountered during snakebite management in Kerala. The findings related to *H hypnale* are tabulated alongside those of other snakes of medical significance.

Discussion

The recognition of an additional species of medical importance in India calls into question the usefulness of the concept of the “Big 4.” In the absence of a reliable clinical means of species identification such as an ELISA, the notion of the “Big 4” has led to misidentification in clinical cases with life-threatening signs and symptoms. In victims bitten by hump-nosed pit vipers, victims and physicians can relatively easily rule out cobras, kraits, and Russell’s vipers as the offending reptile

based on size or markings. The saw-scaled viper, however, has a superficially similar appearance to the hump-nosed pit viper in that it is small and brown. It has, therefore, previously consistently and erroneously been considered responsible for these bites. This was the case even when a simple examination of head scalation on the dead snake by a knowledgeable observer would have revealed the correct identification. The saw-scaled viper possesses multiple small scales across the top of its head (between the eyes), while the hump-nosed pit viper has 5 large plates, including the supraocular, frontal, and parietal plates (Figure 6). There are a number of other species in India, which, like the hump-nosed pit viper, are considered harmless under the old classification scheme. These include the remainder of the pit viper subfamily (Crotalinae), amounting to some 15 species in India, and the coral snake family (Elapidae). Venom research has, for example, shown that the Malabar pit viper (*Trimeresurus malabaricus*) is capable of causing local necrosis in animals. Whether this species is medically significant to humans needs further study, but it has been recorded

Table 1. Clinical features of 5 proven hump-nosed pit viper (*Hypnale hypnale*) bites from Kerala, India

Feature	2 Cases from 2004–05 with case data	3 Prospective cases from 2005
Haemostatic dysfunction (abnormal 20 WBCT* or Lee and White Method ⁹)	2	3
Acute renal failure requiring dialysis	2	0
Pulmonary oedema	1	0
Late onset coagulopathy (>12 hours)	0	2
Polyvalent AV* given with haemostasis restored after > 24 hours	2	2

*20 WBCT indicates 20-minute whole blood clotting test⁸; AV, antivenom.

as causing 500 bites per annum amongst plantation workers in one hospital in Karnataka alone.¹² Urgent work should be undertaken to establish the definitive position of these Indian species in relation to medical significance.

The recognition of new species of medical importance also has great significance in the field of snake antivenom design and manufacture. The current Indian polyvalent snake antivenoms, produced by 7 manufacturers, have remained unchanged for many decades. The snake AV producers have argued that their products cover all the snakes of medical significance as defined by the “Big 4.” It has therefore been impossible, to date, to convince them to produce new AVs against the species of emerging medical importance. Some snake AV manufacturers claim para-specific efficacy of polyvalent snake AV against bites of *H hypnale*.¹³ Serum Institute of India snake AV was believed to be effective against bites of this species although doubt has previously been cast on this claim,¹⁴ and the Kerala review adds evidence that there is no para-specific efficacy against *H hypnale*, as Serum Institute snake AV was used during that study.

Further, the 4 species mentioned in Indian snake AV product inserts as being covered by these antiserums are *N naja*, *B caeruleus*, *D russelii*, and *E carinatus*. We know from other research that there are 3 other species of cobra in India, the monocled cobra (*Naja kaouthia*),

the black or Asiatic cobra (*Naja oxiana*), and the Andaman cobra (*Naja sagittifera*).¹⁵ The effectiveness of polyvalent snake AV against these other species is unknown. Likewise, the saw-scaled viper of northern India appears to be a separate species (*Echis sochureki*) from *E carinatus*,¹⁶ and the effectiveness of standard Indian polyvalent snake AV is not established for this snake.

Even within a single species, there may be wide geographic variability in the constituent elements of venom. Research has shown, for example, that the phospholipase components may vary widely between northern and southern Indian *D russelii*.¹⁷ Indian snake AVs are all currently manufactured using venoms extracted from snakes (*D russelii*, *E carinatus*, *N naja*, and *B caeruleus*) captured in a small geographic region of Tamil Nadu in south India. These AVs appear effective in bites occurring in Tamil Nadu by any of these species. The true efficacy of these AVs against specific snakes in other regions, however, requires further study. On a daily basis, doctors proceed on the basis that snake AV is effective against all these regional and species variations, even when there are serious doubts by snake venom experts. The notion of the “Big 4” and its effect on thinking has underpinned this contradiction.

The notion of the “Big 4” has also obfuscated symptomatology. Indian snakebite research generally refers to members of the family Viperidae as generic “vipers.”

Table 2. Syndromic picture of venomous snakebite in Kerala, India

Item	Cobra	Krait	Russell's viper	Saw-scaled viper	Hump-nosed pit viper
Local pain/tissue damage	Yes	No	Yes	Yes	Yes
Ptosis/neurological signs	Yes	Yes	Yes	No	No
Haemostatic abnormalities	No	No	Yes	Yes	Yes
Renal problems	No	No	Yes	No	Yes
Response to AV*	Yes	Yes	Yes	Yes	No
Response to neostigmine	Yes	Unconfirmed	Unconfirmed	No	No

*AV indicates antivenom.

Figure 6. Comparison of the head scalation of *Echis carinatus* (a) compared to *Hypnale hypnale* (b). Note the multiple tiny scales running between the eyes in *Echis* compared to the large plates in *Hypnale*.

Little distinction has been made between species as symptoms are often assumed to be identical for both Russell's and saw-scaled vipers. Coagulopathy and renal failure have both been ascribed to these 2 species.¹⁸ Evidence suggests, however, that *Echis* species rarely pro-

duce renal failure.^{8,19} Despite this evidence, the belief, propagated by the concept of the "Big 4," that saw-scaled vipers cause renal failure is still common in India. Many clinicians who hold this view work in areas in which *H hypnale*, a snake proven to cause renal failure, is found. The assumption that only the "Big 4" are capable of causing life-threatening symptoms has, therefore, led to the saw-scaled viper being wrongly ascribed renal failure as a key feature.

Treating the "Big 4" as a single and fixed entity by both the antivenom manufacturers and medical professionals is, therefore, giving rise to numerous erroneous assumptions that are negatively impacting patient care.

Proposed Concept Replacement

If we are to abandon the concept of the "Big 4," we need to substitute a more useful classification scheme for the medically important venomous snakes of India. The WHO developed the following methodology in 1981 for the identification of snakes of medical significance:²⁰

- **Class I**—Commonly cause death or serious disability
- **Class II**—Uncommonly cause bites but are recorded to cause serious effects (death or local necrosis)
- **Class III**—Commonly cause bites but serious effects are very uncommon.

This methodology is considerably more valuable than the concept of the "Big 4," particularly in light of the fact that hard, numerical, epidemiological data are not available in India. The WHO mortality figure of 50,000 is itself only an estimate. The numerical contribution of each particular species to these mortality figures is unknown. Therefore, a methodology such as the WHO definition, which provides the ability to assess medical significance without the reliance on specific numbers, is a more useful tool for doctors and medical professionals.

The following are listed by WHO as Indian Snakes of Medical Importance:²⁰

- **Class I**—Cobra/Russell's Viper/Saw-Scaled Viper
- **Class II**—Krait/King Cobra
- **Class III**—White Lipped Pit Viper (*Trimeresurus albolabris*)

However, on the basis of the WHO definition, we can see that the hump-nosed pit viper satisfies the criteria for joining the list as a class II member, in that it causes both life-threatening symptoms and necrosis.

When the concept of the "Big 4" snakes of medical importance was developed, it was undoubtedly useful in focusing attention on these 4 species as causes of significant mortality and morbidity in India. However, the

recognition of the hump-nosed pit viper as a snake of medical significance, particularly in light of the confusion between this species and the saw-scaled viper, demonstrates the inadequacy of the "Big 4" concept in the current environment. The WHO criteria for listing snakes of medical importance is a much more practical tool as it allows for the possibility that other snakes may yet emerge, following sound epidemiological work, as being medically important.

Hospitals are a rich source of epidemiological data in respect to snakebite.²¹ A significant number of dead species are brought to hospital by the victims, and it is essential that these specimens be preserved in formalin and properly identified by a qualified herpetologist. This will provide sound epidemiological data and positively identify which species are causing morbidity and mortality in a given area. This is a high priority as it directly impacts patient care. If there are species that are currently regarded as harmless, yet are causing morbidity and mortality, it is essential that this be established and that effective antivenoms are developed in order to reduce morbidity and save lives.

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