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Frequent and potentially fatal envenoming by hump-nosed pit vipers (*Hypnale hypnale* and *H. nepa*) in Sri Lanka: lack of effective antivenom

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Sri Lanka

Summary In a prospective study of snake bites involving 10 hospitals in Sri Lanka, 302 (35%) of 860 patients with bites by identified snakes proved to have been bitten by hump-nosed pit vipers (301 by *Hypnale hypnale* and 1 by *H. nepa*). Most victims were males aged between 11 years and 50 years who had been bitten on their feet or ankles while walking at night close to their homes. There was local swelling in 276 (91%) and local necrosis in 48 (16%). Eleven (4%) required amputation of fingers or toes and 12 (4%) received skin grafts. In 117 patients (39%) blood incoagulability was first detected between 15 min and 48 h after the bite, and in 116 of them this was present on admission to hospital. Spontaneous systemic bleeding was observed in 55 patients (18%). Acute renal failure developed in 10%, five of whom died to give an overall case fatality rate of 1.7%. Thus, bites by hump-nosed pit vipers can cause debilitating local and fatal systemic envenoming. In Sri Lanka and southwestern India where bites by these snakes are common, the only available antivenoms (raised against cobra, krait, Russell's viper and saw-scaled viper venoms) are ineffective and carry a high risk of reactions.

1. Introduction

In Sri Lanka, hump-nosed pit vipers (genus *Hypnale*, family Crotalinae) (Figure 1) are widely distributed up to an altitude of 1525 m in all climatic zones (dry, intermediate

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Figure 1 Sri Lankan specimens of Merrem's hump-nosed pit viper from Anuradhapura: (A) gravid female (scale in cm); (B) male 380 mm in total length; and (C) showing long, partially erect fangs and pit organ (arrow).

and wet) (de Silva, 1990). Presently, three species are known—*Hypnale hypnale*, *H. nepa* and *H. walli* (de Silva, 1990; Gloyd and Conant, 1990)—but the genus is due for taxonomic revision and descriptions of new species. Merrem's hump-nosed pit viper (*H. hypnale*) also occurs along the southwestern coast of India, inland up to an altitude of 600 m in the Western Ghats, from southern Kerala to perhaps as far north as Mumbai (Gloyd and Conant, 1990; Whitaker and Captain, 2004). Recently, the first cases of *H. hypnale* bites were reported from India (Joseph et al., 2007). In Kerala, five patients developed pain, swelling, haemorrhagic blistering, bruising, regional lymphadenopathy, headache, nausea, vomiting, and abdominal and chest pain. There was evidence of haemostatic dysfunction (coagulopathy, fibrinolysis, thrombocytopenia or spontaneous systemic haemorrhage) in all cases and of microangiopathic haemolysis in two. Two patients were haemodialysed for acute renal failure (Joseph et al., 2007). In that area, *H. hypnale* is called 'churruta' in Malayalam, and in most parts of Sri Lanka it is known in Sinhala as 'polonthelissa', meaning viper with upturned lip. The name 'kunakatuwa' refers to the necrotic effects of its bite. In Tamil it is called 'kopi viriyan', meaning coffee snake/viper. Davy (1821) mistakenly used the local name 'carawalla' or 'karawalla', which properly refers to kraits (genus *Bungarus*, family Elapidae).

Hypnale hypnale is recognised as a common causes of snake bite in Sri Lanka. Based on official returns, this species was found to be the major cause of venomous snake bites (27%) (de Silva and Ranasinghe, 1983). In Gampaha district, *H. hypnale* was implicated in 76.5% of snake bites by identification of the dead snake (in 37%) or recognition of a photograph (Seneviratne et al., 2000).

The present study, part of a prospective hospital-based survey of snake bites in Sri Lanka, was designed to evaluate the true medical importance of bites by this small and inappropriately neglected pit viper.

2. Methods

2.1. Clinical studies

From August 1993 to July 1997 a prospective hospital-based survey of identified snake bites was carried out in Sri Lanka in 10 hospitals chosen because of their high incidence of snake bite and their locations in different climatic zones (Table 1) (de Silva, 1990). Only patients who brought the snake responsible (living or dead) for expert identification were included.

Patients were assessed on admission, during their stay in hospital. Some returned for follow-up. Patients were exam-

ined and the following investigations were carried out: urine microscopy; full blood count; 20-min whole blood clotting test (20WBCT) (Sano-Martins et al., 1994; Warrell et al., 1977); blood urea; serum creatinine; and electrolytes.

2.2. Examination of snakes brought by patients

Dead snakes were labelled with the patient's name, number and date of admission, and were provisionally identified on site and then preserved in formalin and transported to Colombo for definitive identification by the authors within months. Living snakes were kept in suitable containers and sent to Colombo as quickly as possible where they were held in the herpetarium of the Faculty of Medicine, University of Colombo. Identification was checked by AdS, a professional herpetologist, using standard keys (de Silva, 1990; Gloyd and Conant, 1990). Snakes were measured and their sex was determined using probes or dissection. The body cavity was exposed to reveal eggs and stomach contents.

2.3. Laboratory studies

The i.v. median lethal dose (LD_{50}) of *H. hypnale* venom was determined as described by Laing et al. (1992). Median effective neutralising doses (ED_{50}) of Thai Red Cross Malayan Pit Viper Antivenin (batch 13, expiry 05/08/2003) and Indian Haffkine Biopharmaceutical Co. Ltd. polyvalent anti-snake venom serum (batch 2551-2, expiry 10/2001) were measured by mixing different amounts of each antivenom with $5 \times$ i.v. LD_{50} of *H. hypnale* venom (Laing et al., 1992, 1995; Theakston and Reid, 1983). LD_{50}, ED_{50} and their 95% confidence limits were calculated using probit analysis (Finney, 1971).

3. Results

3.1. Snake identification

A total of 3411 patients were admitted with a history of snake bite to the 10 participating hospitals. Of these, 860 (25%) brought the snake responsible, 302 (35%) of which proved to be hump-nosed pit vipers (301 *H. hypnale* and 1 *H. nepa*) (Table 1). Other venomous species included Russell's vipers (*Daboia russelii*) (37%), cobras (*Naja naja*) (5%) and common kraits (*Bungarus caeruleus*) (10%). Forty-nine percent of the *Hypnale* were males. Their total lengths ranged from 140 mm to 501 mm (mean 255 mm); males 300—451 mm (mean 360 mm); females 264—501 mm (mean 354 mm). Of the females, 36% were gravid, containing nine to eleven eggs. Stomach contents included a shrew (*Suncus* spp.), rat, *Hemidactylus frenatus*, agamid lizards, punctured agamid (Otocryptis) eggs and frogs (Wall, 1921). The sole specimen of *H. nepa* was a male 341 mm in total length.

Table 1 Hump-nosed pit viper bite admissions to the 10 hospitals

Centre	*N* (%)	Climatic zone
Colombo	129 (43)	Wet zone
Colombo South	40 (13)	Wet zone
Colombo North	12 (4)	Wet zone
Negombo	5 (2)	Intermediate
Panadura	8 (3)	Wet zone
Watthupitiwela	20 (7)	Wet zone
Chillaw	8 (3)	Dry zone
Matale	8 (3)	Wet zone
Polonnaruwa	5 (2)	Dry zone
Anuradhapura	67 (22)	Dry zone
Total	302	

3.2. Patient characteristics (Table 2)

Male patients outnumbered females in frequency of bites. Most patients were aged 21—30 years.

3.3. Time of the bites

Bites occurred throughout the year and at the following times of day: 00:00—06:00 h, 17 (6%); 06:00—12:00 h, 48 (16%); 12:00—18:00 h, 86 (28%); and 18:00—00:00 h, 151 (50%). Thus, one-half of all bites occurred between 18:00 h and midnight, while people were returning home from work or recreational activities.

3.4. Circumstances, place and anatomical site of the bites

One hundred and forty-two (47%) of the patients were bitten while walking along roads or foot paths, 47 (16%) while gardening, 33 (11%) while doing agricultural activities, 33 (11%) while doing other work and 17 (6%) while collecting fire wood. Only four (1%) were bitten while sleeping. One hundred and forty-six bites (48%) occurred within the patient's compound, 90 (30%) on roads or footpaths and 33 (11%) in paddy fields. Only six bites (2%) occurred within the patient's house. Two hundred and forty-six (81%) of the patients were bitten on their lower limbs and 56 (19%) on their upper limbs. In 212 patients (70%) the feet or ankles were involved when the patient inadvertently trod on the snake. One hundred and thirty-two (44%) of the victims were admitted to hospital within 1 h of the bite. One hundred and thirty-five (45%) had applied a tourniquet as a first-aid measure, using cloth or long grass. Only 29 (10%) had sought traditional treatment

Table 2 Numbers of hump-nosed pit viper bite cases by patient age and sex

Age (years)	Total (*N*)	Males (*n*)
0—10	6	5
11—20	50	37
21—30	78	45
31—40	75	53
41—50	43	35
51—60	28	23
61—70	16	12
71—80	6	4
Total	302	214

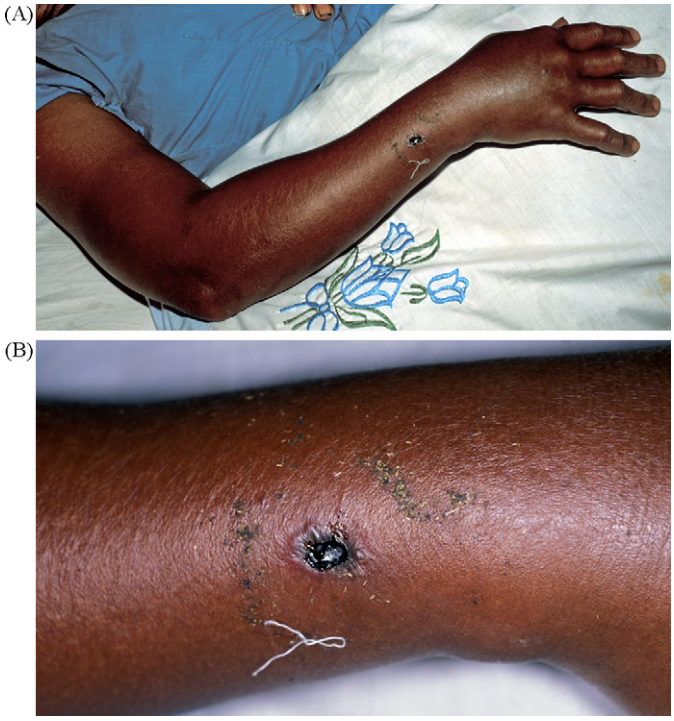

Figure 2 (A) Persistent local swelling 4 days after a bite by Merrem's hump-nosed pit viper. (B) There is a small area of tissue necrosis at the site of the bite.

from snake bite specialists such as Ayurvedic physicians ('veda mahaththaya', 'nattu vaiththaya' or 'vedarala') (Abercromby, 1911) in their villages before they came to the hospital.

3.5. Clinical features (Table 3)

3.5.1. 'Dry' bites

Twenty-six patients (9%) showed no evidence of envenoming at any stage despite proven bites by hump-nosed pit vipers. Local envenoming was observed in 276 patients (91%): there was local swelling (276; 91%), pain (270; 89%), bruising (145; 48%) and blistering (186; 62%) (Figure 2). Forty-eight patients (16%) developed local necrosis, for which 11 (4%) required amputation of fingers or toes and 12 (4%) received skin grafts (Figure 3).

3.5.2. Systemic envenoming

In 117 patients (39%) blood incoagulability was first detected between 15 min and 48 h after the bite, and in 116 of them blood was already incoagulable when they were admitted to hospital. Spontaneous systemic bleeding in the form of gingival bleeding, haematuria and haematemesis was observed in 55 patients (18%). Neurological manifestations were not observed in any patient. Thirty patients (10%) developed acute renal failure requiring dialysis.

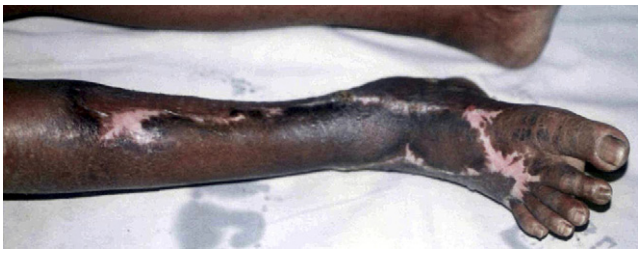

Figure 3 Extensive local necrosis at the site of a Merrem's hump-nosed pit viper bite requiring skin grafting 32 days after the bite.

3.6. Treatment

In 57 (19%) of the 302 patients proven to have been bitten by *Hypnale* spp., the attending physicians decided to treat with Haffkine polyvalent antivenom in doses of 50—550 ml (mean 310 ml). Thirty (53%) of these patients became feverish with chills and rigors. Twenty-two of them also developed urticaria, the systolic blood pressure dropped to <90 mmHg in nine patients and one patient's blood pressure became unrecordable and he had bilateral wheezes and severe dyspnoea. In no case was there restoration of blood coagulation, cessation of spontaneous bleeding or any other detectable benefit of antivenom treatment.

3.7. Outcome

Three patients with coagulopathy and acute renal failure died early of complications related to acute renal failure despite receiving dialysis. In one, septicaemia complicated peritonitis from peritoneal dialysis and in two patients pulmonary oedema was caused by fluid overload. Among the 27 survivors of acute renal failure, 2 developed chronic renal failure (Figure 4). Their abnormal renal function, anaemia and oliguria persisted. Six weeks after the bite, ultrasound scans showed bilateral contracted kidneys with increased echogenicity. The patients could not afford long-term dial-

Table 3 Clinical features of 302 cases of proven hump-nosed pit viper bite

	No. of cases (%)
Envenomed	276 (91)
Not envenomed	26 (9)
Local envenoming: total	276 (91)
Swelling	276 (91)
Local pain	270 (89)
Local bleeding	125 (41)
Bruising	145 (48)
Blistering	186 (62)
Necrosis	48 (16)
Amputations	11 (4)
Skin grafting	12 (4)
Systemic envenoming: total	117 (39)
Haemostatic abnormalities: total	117 (39)
Coagulopathy (incoagulable blood (20WBCT))	117 (39)
Spontaneous systemic haemorrhage: total	55 (18)
Gum bleeding	25 (8)
Haematuria	18 (6)
Haematemesis	12 (4)
Acute renal failure (increased blood urea concentration and oliguria)	30 (10)
Non-specific symptoms	65 (22)
Abdominal pain	45 (15)
Nausea and vomiting	60 (20)
Giddiness	22 (7)

20WBCT: 20-min whole blood clotting test.

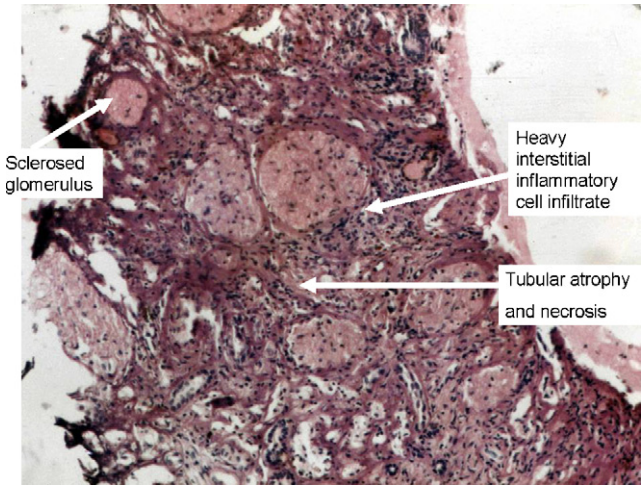

Figure 4 Renal biopsy taken from a patient bitten by a Merrem's hump-nosed pit viper who developed chronic renal failure. The principal histological features are indicated by arrows (haematoxylin/eosin staining, original magnification 4 × 10).

ysis or renal transplantation. They were therefore managed conservatively and died at home within 1 year. Thus, the acute case fatality was 3/302 (1.0%) and the total case fatality was 5/302 (1.7%).

3.8. Laboratory studies

The LD_{50} of Sri Lankan *H. hypnale* venom was 65.4 μg/mouse (95% confidence limits 39.1—109.9 μg/mouse). Haffkine and Thai Red Cross antivenoms were tested against 5 × i.v. LD_{50} (327 μg/mouse) of this venom as described above, but no mice survived despite receiving the maximum permitted dose of antivenom (200 μl/mouse) by i.v. injection.

4. Discussion

Merrem's hump-nosed pit viper (*H. hypnale*) is one of the commonest venomous snakes of Sri Lanka. Mainly nocturnal and both arboreal and terrestrial, it inhabits both wet and dry deciduous and secondary forests and tea, rubber, coconut and coffee plantations, hence one of its local names 'coffee polonga'. During the day it may be encountered resting under dry fallen leaves beneath trees and bushes and in undergrowth, rocks and rubble. Being well camouflaged, it is easily trodden upon. People gardening, visiting wells or latrines in their compounds, picking firewood or building are vulnerable to bites in semiurban areas even in the day time. It is notable that 48% of our patients were bitten inside their compounds at home.

This species has proved capable of causing life-threatening envenoming both in Sri Lanka and, more recently, in India. Clinical and laboratory studies of *H. hypnale* venom have demonstrated that the venom is procoagulant and fibrinolytic (de Silva et al., 1994; Mangili, 1956; Premawardena et al., 1998) and contains phospholipases A_2 similar to those in the venom of the Malayan pit viper (*Calloselasma rhodostoma*) (Wang et al., 1999) to which it is thought to be closely related (Gloyd and Conant, 1990; Vidal and Lecointre, 1998). In Sri Lanka, opinions about the potency of its bite have varied greatly. Davy (1821), who described and illustrated *H. hypnale*,

considered that 'next to the hooded snake (cobra), [*H. hypnale*] is the most common of the poisonous kind in Ceylon.' He demonstrated locally necrotic, haemorrhagic and lethal effects in animals but found that the bite was rarely fatal to small animals. 'But—the diseased action being more local, and much more inflammatory (than cobra bite) commencing in the bitten part, spreading, progressively, losing its force as it extends, and probably, never proving fatal, except it reach a vital organ.' However, according to Tennent (1861): 'Dr. Davy's estimate of the venom of the *carawala* ('*Trigonocephalus hypnale*, Merr.') is below the truth, as cases have been authenticated to me, in which death from its bite ensued within a few days.' Wall (1921) disagreed: 'The venom is probably never fatal to man, in spite of what Tennent says to the contrary. It is more than likely case may end fatally, however, from emotional causes, as in the case of harmless snakes, where the bitten subjects die of fright.' Abercromby (1911) observed purely local effects mainly attributable to a tourniquet. Following a bite on the wrist, Deraniyagala (1955) described swelling of the arm and shoulder, generalised abdominal pain, vomiting, haematemesis, faintness, fever and unconsciousness that took 3 weeks to recover fully. All 62 cases of *H. hypnale* bites seen at Avissawella had local pain and swelling, some developed a haemorrhagic blister and regional lymphadenopathy but none showed systemic envenoming (Sellahewa and Kumararatne, 1994). However, in proved or suspected cases of *H. hypnale* bite, local necrosis, coagulopathy, bleeding, microangiopathic haemolysis and fatal renal failure have been well documented (de Silva et al., 1994; Dharmaratne and Gunawardena, 1988–1989; Kularatne and Ratnatunga, 1999; Karunatilaka et al., 2001; Perumainar, 1975, 1977; Premawardena et al., 1996, 1998; Varagunam and Panabokke, 1970).

In the present series of hump-nosed viper bites, 276 (91%) were locally envenomed and 117 (39%) were systemically envenomed, all with haemostatic abnormalities and 30 with acute renal failure. In a series of 14 children bitten by this species, 38.5% showed systemic envenoming (Karunatilaka et al., 2001).

The lives of severely envenomed patients can be saved using ancillary and supportive treatments, notably renal dialysis (de Silva et al., 1994; Karunatilaka et al., 2001). However, the mainstay and only specific treatment for snake bite envenoming is antivenom. Both in India and Sri Lanka, victims of *H. hypnale* bites have been treated with the only available polyvalent antivenom, raised in India against the venoms of local *Naja*, *Bungarus*, *Daboia* and *Echis* spp. even though this antivenom lacks specificity for the *Hypnale* venom. In Gampaha district, Sri Lanka, 99 of 184 patients bitten by hump-nosed pit vipers were treated with Indian polyvalent antivenom. More than 55% experienced adverse reactions and there was no obvious clinical efficacy (Seneviratne et al., 2000). In a randomised placebo-controlled trial in Avissawella, Sri Lanka, Haffkine polyvalent antivenom did not hasten the resolution of local envenoming but caused reactions in 45% of patients (Sellahewa et al., 1995). In the present study, 30 (53%) of 57 patients developed antivenom reactions, some potentially life-threatening, and the standard laboratory rodent assay showed that Haffkine polyvalent antivenom was totally ineffective against *H. hypnale* venom.

In this series, the only case of a bite by one of the other two species of Sri Lankan *Hypnale*, *H. nepa*, showed only mild local envenoming. The only other published case of *H. nepa* bite was also mildly envenomed (de Silva, 1989).

The conclusion of all these studies is that the currently produced Indian polyvalent antivenoms should never be used in the treatment of *H. hypnale* envenoming on the grounds of their inefficacy and high reactogenicity. There is a strong case for the development of a polyvalent antivenom that includes activity against *H. hypnale* venom for use in south-west India and Sri Lanka. A practical problem is that *H. hypnale* is a tiny snake with a small venom yield and so it may prove difficult to accumulate sufficient venom for antivenom manufacture. This prompted us to test the efficacy of Thai Red Cross Malayan Pit Viper antivenom because of the close phylogenetic relationship between *H. hypnale* and *C. rhodostoma* (Gloyd and Conant, 1990; Vidal and Lecointre, 1998). Although no protection was found in the rodent assay, it remains possible that *C. rhodostoma* antivenom might be effective against some of the medically important toxins in *H. hypnale* venom. The clinical features of envenoming by these two pit vipers are similar in most respects, allowing for their difference in size and hence the amount of venom injected, but acute renal failure is not a feature of *C. rhodostoma* envenoming (Warrell et al., 1986).

Authors' contributions: DAW, RDGT, MHRS and CAA designed the study protocol; CAA, DAW, SAMK and VT carried out the clinical assessment; AdS, RDGT, CAA and DAW identified the species of snakes; RDGT carried out the laboratory analysis; CAA and DAW carried out the analysis and interpretation of the data; CAA and DAW drafted the manuscript. All authors read and approved the final manuscript. DAW and CAA are guarantors of the paper.

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