Hump-nosed pit vipers and their bites in Sri Lanka

Hypnale hypnale (Merrem, 1820)*, H. nepa* (Laurenti, 1768) and *H. zara* (Gray, 1849)

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Introduction

The hump-nosed pit viper (*Hypnale hypnale*, Merrem's pit viper) is a snake widely distributed in Sri Lanka and the Southwestern coastal region of India. It is the commonest snake responsible for venomous snakebite in Sri Lanka, estimated to be between 22 to 77% of all snakebites (de Silva, 1981; Seneviratne, 2000). For centuries it was considered to be a relatively innocuous snake till in 1821, for the first time, swelling and bleeding due to bites by *H. hypnale* was reported in animals (Davy, 1821).

Since then, apart from a few isolated case reports of renal injury and death, very little was published about the clinical features following its bites and the morbidity and mortality that resulted. *H. hypnale*, Merrem's pit viper, was the species recognised to cause morbidity. However, clear detailed information about other species of hump-nosed vipers, and their clinical, toxinological and biological properties were not well studied nor documented till the turn of the twentieth century. Thereafter, many accurately documented papers about hump-nosed viper envenoming have appeared in the published literature.

The hump-nosed viper (HNV) is widely distributed in all the peneplanes of the country and is commonly found in coconut, rubber, and tea plantations. Three species of hump-nosed vipers of the genus *Hypnale* are found in Sri Lanka. *H. hypnale* is widely distributed except in Jaffna. *H. nepa* is confined to the central hills and *H. zara* to the lowland rain forests of the south-western wet-zone and the foothills of the central highlands. All are venomous and look alike superficially, being different as regards scale counts. *H. nepa* and *H. zara* are endemic to Sri Lanka while *H. hypnale* occurs in the Western Ghats of peninsular India as well (Maduwage et al, 2009).

The hump-nosed pit viper is a medically important, highly venomous snake. The World Health Organization placed *H. hypnale* in Medical Importance Category I that requires antivenom (Anonymous, 2010). This is based on reports that envenoming causes significant morbidity, disability and even fatalities (Kularatne and Ratnatunga, 1999; Joseph et al, 2007; Ariaratnam et al, 2008; Wijewantha & Sellahewa, 2010; Rathnayaka et al, 2018a, 2019a, 2019c, 2021a, 2021b, 2021c). The unpredictability of developing severe envenoming and complications is intriguing and requires study to strengthen the deadly nature of this snake. No antivenom is currently available for HNV bites in Sri Lanka or India.

The three species of *Hypnale* in Sri Lanka—*H. hypnale, H. zara* and *H. nepa*

Epidemiology

Recent studies have focused on identifying possible differences between envenoming caused by the three species. There does not appear to be a difference shown by results published so far; larger series are needed to show any possible variations (Maduwage et al, 2013; Rathnayaka et al, 2017a).

The majority of bites occur in the evening hours. As a result of the short striking distance most bites are seen in the extremities—the fingers, toes, and feet, below the ankles. In the study by Maduwage et al (2013) of 114 bites (93 *H. hypnale,* 16 *H. zara* and 5 *H. nepa*) most were on the lower limbs and had occurred in the daytime.

Toxinology

The venom of all three species is essentially similar with potent cytotoxicity, mild anticoagulant, pro coagulant, and haemolytic activity. It also has weak myotoxic, neurotoxic and nephrotoxic effects. Most clinical effects are due to phospholipase A2 activity (Maduwage et al, 2011b). The same workers showed that Indian polyvalent antivenom raised against *Naja naja*, *Daboia russelii*, *Bungarus caeruleus* and *Echis carinatus* did not neutralize the venom effects, consistent with what the previous studies of Tan et al (2011) had shown. Sellahewa et al (1995) had shown that polyvalent antivenom was not effective in treating severe local envenoming caused by hump-nosed viper bites. It was demonstrated that the three *Hypnale* venoms are similar, and cytotoxicity appears to be the most potent effect (Maduwage et al, 2011b).

Clinical features of envenoming

Clinical features following HNV bites include

- **Nonspecific features**—abdominal pain, nausea, vomiting, faintishness, fever, headache.
- **Local envenoming**: 90%—local pain, swelling, necrosis at the bite site, haemorrhagic blisters, regional lymphadenopathy, bruising, local bleeding.
- **Systemic manifestations**: Venom induced consumption coagulopathy (VICC) and acute kidney injury (10%) — are the commonest systemic effects. In addition, a number of systemic manifestations may occur rarely. (See **Box**)

The most consistent effects of envenoming are severe local pain and local swelling (90%). Dry bites are not common: in the series of 152 bites (*H. hypnale* 122, *H. zara* 22 and *H. nepa* 8) reported by Rathnayaka (2017a) there were only nine (5.92%). A haemorrhagic blister at the bite site and painful, tender regional lymphadenopathy are the commonly encountered local effects, which, when present may be useful clinical features to identify the biting snake as hump-nosed viper when the biting snake is not available for identification. However, it is a nonspecific feature and is present following many other viperid bites as well.

Systemic manifestations and syndromes that may be rarely encountered

Snakebite-associated thrombotic micro-angiopathy (Wijewickrama et al, 2021; Herath et al, 2021; Rathnayaka et al, 2019a and 2019b), myocardial infarction (de Silva et al, 2017), haemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) (Rathnayaka et al, 2019b), microangiopathic haemolysis, acute ischemic changes in ECG, bradycardia (Thillainathan et al, 2015; Rathnayaka et al, 2021d), atrial fibrillation (Rathnayaka et al, 2018a), Kounis syndrome (Rathnayaka et al, 2021b), purpura fulminans (Rathnayaka et al, 2021c), generalized ecchymoses (Rathnayaka et al, 2017b), pulmonary haemorrhage (Rathnayaka et al, 2019), intracerebral haemorrhage (Rathnayaka et al, 2020a), acute ischemic infarction (Jeevagan et al, 2012), coma, shock, severe diarrhoea (Wijewantha & Sellahewa, 2010), and hyponatraemia resulting in seizures (de Silva et al 2018).

Systemic effects are rare, and their occurrence is sporadic and unpredictable. In a series of 1,543 patients with hump-nosed viper bites observed in five hospitals, only 67 (4.34%) patients developed systemic effects with 2 (0.1%) deaths (Wijewantha & Sellahewa, 2010). The systemic effects varied from coagulopathy to nephropathy. Fatal events include pulmonary and intracerebral haemorrhage (which occur due to the complications of VICC) (Rathnayaka et al, 2019 and 2020a) and cardiotoxicity (Rathnayaka et al, 2021a).

Haemostatic dysfunction and acute kidney injury (AKI) are the commonest and most important systemic effects associated with mortality. Overt bleeding such as haematuria, hematemesis and bleeding per rectum is rare; coagulopathy is often NOT detected by the 20WBCT. The precise nature of the coagulopathy is poorly understood, it is most likely due to venom induced consumption coagulopathy.

Acute kidney injury

AKI is by far the commonest serious manifestation of hump-nosed pit viper envenoming and its incidence ranges from 1 to 10% (Ariaratnam et al, 2008; Maduwage *et al.*, 2013: Wijewickrama et al, 2021). The severity of AKI could range from mild, which usually resolves spontaneously to severe requiring dialysis sometimes ending up with chronic kidney disease (Herath et al, 2012a; Herath et al, 2012b). The exact mechanism of AKI in hump-nosed pit viper envenoming is not known. Direct venom nephrotoxicity, venom induced hemodynamic disturbances, intravascular haemolysis, rhabdomyolysis and more recently snakebite-associated thrombotic microangiopathy (Herath et al, 2012a; Karunatilake et al, 2012; Rathnayaka *et a*l, 2019a, 2019b; Wijewickrama et al, 2021) are some of the mechanisms which are postulated in the causation of AKI in these patients (Mohamed et al, 2015; Wijewickrama et al, 2021).

The primary cause for mortality following hump-nosed viper bite is either coagulopathy or acute kidney injury (AKI) (Sellahewa, 2013). Most victims who develop AKI have coagulopathy which can be detected before clinical and biochemical features of AKI become apparent.

The association of coagulopathy with AKI after hump-nosed viper bite is well recognised (Varugunam, 1970; Dharmaratne et al, 1988-89; de Silva et al, 1994; Premawardena et al, 1996 & 1998; Maduwage et al, 2011a; Herath et al, 2012; Rathnayaka et al, 2019a). It is likely that common pathophysiological mechanisms are responsible for both these important systemic complications of hump-nosed viper bite.

Histopathological changes in the kidney include acute tubular necrosis, focal segmental glomerulosclerosis, cortical necrosis, and interstitial nephritis associated with both acute kidney injury and chronic kidney disease.

Laboratory findings in hump-nosed viper bites

Eosinophilia (eosinophils > 500/µL in peripheral blood) is the predominant haematological manifestation of HNV bites (25%). In addition, leucocytosis (15%), neutrophilia (14 %), lymphocytosis (4%), thrombocytopenia (5%), microangiopathic haemolysis (7%), may occur (Rathnayaka et al, 2017c and 2021d). Blood urea and serum creatinine are elevated in patients with kidney injury. In patients with VICC, PT/INR, aPTT and 20WBCT are generally elevated/prolonged. Rarely, the 20WBCT is prolonged with normal PT/INR, aPTT (Rathnayaka et al, 2020a). Mild elevation (3 times normal) of serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) may

occur. Red cell indices are reduced (MCV (12%), MCH (18%) and MCHC (9%)). Hypokalaemia (7%), hyperkalaemia (4%) and hyponatraemia (5%) may occur following HNV bites (Rathnayaka et al, 2021d).

- **The currently available polyvalent snakebite antivenom is not effective in hump-nosed viper envenoming and should not be used.**
- **Expectant treatment is the only option to offer patients.**
- **Those who develop coagulopathy may progress to AKI and may require haemodialysis.**

Management of hump-nosed viper bites

As remarked earlier, dry bites are rare (Rathnayaka, 2017b). Patients with a history of being bitten by a hump-nosed pit viper with puncture marks should be admitted for observation. Most will develop pain and swelling at the bite site (94%) and possibly a haemorrhagic blister (11%). Observation for at least 48 hours is advocated owing to the possibility of delayed manifestations of coagulopathy that can have serious consequences.

Local pain requires analgesia with paracetamol. NSAIDs should be avoided owing to the propensity for coagulopathy. Local swelling is due to a chemical inflammation and resolves spontaneously with time. Antibiotics are not indicated unless there is local sepsis. Hump-nosed pit vipers commonly inflict their bites on the extremities with the risk of severe local tissue destruction. Bites on the digits of the hand and foot if so affected may result in tapering of the fingers and toes, or even require amputation (Ariaratnam et al, 2008). Puncturing of the blisters early with prophylactic antibiotic administration and elevation of the limb have been found to improve recovery. Patients with severe local limb swelling are at risk of developing compartment syndrome, in which case prompt fasciotomy is needed. Therefore, patients with severe local swelling should be closely monitored and assessed by recording the distal pulse, oxygen saturation (SpO_2) and capillary refilling time of the affected limb.

The 20WBCT detects coagulopathy and can be used as an early predictor of systemic envenoming. Owing to the rarity and unpredictability of systemic manifestations and the recognized potential for a fatal outcome in patients with coagulopathy it is prudent that 20WBCT is monitored in all envenomed patients irrespective of the clinical status at presentation. Patients who develop coagulopathy as evidenced by a positive 20WBCT should be selected for intensive monitoring for bleeding and development of AKI.

The currently available snakebite antivenom is not effective in hump-nosed viper envenoming and should not be used (Maduwage et al, 2011b). Expectant treatment is the only option to offer patients. Those who develop coagulopathy may progress to AKI and would require haemodialysis. AKI without prior coagulopathy is a possibility.

Patients should be adequately hydrated to maintain urine output in order to prevent AKI resulting from hypotension and dehydration. The need, the amount and the rate of fluid administration will depend on the stage of the acute kidney injury and the volume status of the patient. Patients who develop severe AKI may require dialysis. Indications for urgent dialysis is the same as for any other AKI and include refractory pulmonary oedema, metabolic acidosis and hyperkalaemia, uremic encephalopathy, and pericarditis. However, the patient may be referred for dialysis before the development of these complications by the treating physician if the AKI is severe and is unlikely to recover soon.

Therapeutic plasma exchange (TPE) is commonly used in the treatment of snakebite-associated thrombotic micro-angiopathy (TMA) following hump-nosed pit viper bites. This practice is based on the evidence of beneficial effects of TPE in the setting of thrombotic thrombocytopenic purpura (TTP). Although case reports, case series and a few observational studies (Herath et al, 2012a; Rathnayaka et al, 2018b and 2021e) have suggested benefit of TPE, more recent larger cohort studies done in India, Sri Lanka, and Australia (Mohan et al, 2019; Wijewickrama et al, 2020; Noutsos et al, 2021) have not shown any benefit of TPE in the treatment of snakebite-associated TMA. Therefore, the decision to use TPE is best to be taken with caution after consultation with the experts in the field until more robust evidence is available.

Recommendations

- Observe all patients for 48 hours following hump-nosed viper bites, even if the initial presentation is innocuous.
- Paracetamol 1 g / 6 hourly is recommended for mild to moderate pain; for severe pain tramadol 50mg/bd should be added.
- Elevate the affected limb and monitor closely for the appearance of compartment syndrome with distal pulse, oxygen saturation (SpO_2) and capillary refilling time of the affected limb.
- If cellulitis or local sepsis is suspected intravenous or oral cloxacillin 500 mg/ 6 hourly and oral metronidazole 400 mg 8 hourly can be administered.
- Wound debridement should be performed for patients with local tissue necrosis and haemorrh-agic blistering at the site of bite.
- Perform 20WBCT 6 hourly for 48 hrs.
- Ensure adequate hydration based on the volume status of the patient.
- Haemodialysis should be considered in patients with severe AKI having the following indications: refractory pulmonary oedema, refractory hyperkalemia, refractory metabolic acidosis, uremic encephalopathy, uremic pericarditis, established AKI with anuria/ oliguria not showing any signs of recovery.
- Currently available Indian polyvalent antivenom is ineffective for hump-nosed viper and should not be used.
- Intramuscular tetanus toxoid should be given when the patient is discharged.
- For chronic musculoskeletal disabilities physiotherapy is recommended.

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