Hump-nosed pit vipers and their bites in Sri Lanka

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

Kolitha H. Sellahewa

Introduction

The hump-nosed pit viper (*Hypnale hypnale*, Merrem's pit viper) is a snake widely distributed in Sri Lanka and the South Western 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 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).

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 up any possible variations (Maduwage et al, 2013; Rathnayaka et al, 2017b).

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

> The study demonstrates that the three *Hypnale* venoms are similar and cytotoxicity appears to be the most potent effect…
>
> Maduwage et al, 2011b

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 bite.

Clinical features of envenoming

The most consistent effects of envenoming are severe local pain and local swelling. Dry bites are not common: in the series of 152 bites (*H. hypnale* 122, *H. zara* 22 and *H. nepa* 8) reported by Rathnayaka (2017) 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 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 and nephropathy to neurological manifestations. Fifty-nine (3.8%) patients had only coagulopathy and they received either intravenous isotonic saline to ensure adequate urine output i.e. 0.5 ml/kg /hour or 15 ml/kg of fresh frozen plasma (FFP). None of the patients who had coagulopathy developed renal failure in this series.

- Bites commonly cause only local swelling
- Occasionally a haemorrhagic blister at the bite site
- Less frequently tender regional lymphadenopathy

Haemostatic dysfunction and acute kidney injury (AKI) are the commonest and most important systemic effects associated with mortality. Overt bleeding manifestations like haematuria, hematemesis and bleeding per rectum are rare but coagulopathy is often 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

The primary cause for mortality following hump-nosed viper bite is from complications associated with coagulopathy and acute kidney injury (AKI) (Sellahewa, 2013). All who develop AKI have coagulopathy which can be detected before clinical and biochemical features of AKI become apparent. It is possible that early correction of coagulopathy with FFP could prevent AKI and related adverse clinical outcomes.

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;). It is likely that common pathophysiological mechanisms are responsible for both these important systemic complications of hump-nosed viper bite. AKI is caused primarily by nephrotoxicity rather than myoglobinuria or haemoglobinuria. The procoagulant effects and venom induced consumption coagulopathy can also contribute to renal injury by the deposition of fibrin in the renal microcirculation and microvascular

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coagulation. Fibrinogen degradation products can perpetuate the bleeding tendency by its antihaemostatic effects. These pathogenic mechanisms associated with the haemostatic disturbances seen could be important contributors to AKI apart from the primary venom induced nephrotoxicity. It may even be more important than the direct nephrotoxicity unlike AKI after *D. russelii* bites.

Venom induced nephrotoxicity ranges from acute tubular necrosis, focal segmental glomerulosclerosis, and cortical necrosis to interstitial nephritis with the clinical manifestations of both acute and chronic renal failure. The mechanisms of renal injury have not been clearly elucidated. Both direct nephrotoxicity (Gunatilake et al, 2003) and adverse renal consequences of coagulopathy such as venom induced consumption coagulopathy and thrombotic microangiopathy (Herath et al, 2012; Karunatilake et al, 2012; Rathnayaka et al, 2017) are implicated. Interestingly coagulopathy was the earliest systemic manifestation among all patients who developed AKI. Arguably early correction of coagulopathy may prevent AKI.

Coma, external ophthalmoplegia, severe diarrhoea, and shock are some of the less commonly identified systemic effects of envenoming.

Management of a patient bitten by *Hypnale* spp.

As remarked earlier, dry bites are rare (Rathnayaka, 2017). 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 at the bite site and possibly a haemorrhagic blister. Observation for at least 48 hours is advocated owing to the possibility of delayed manifestations of coagulopathy that can have serious consequences.

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- Less frequently tender regional lymphadenopathy

➢ Rarely systemic effects such as coagulopathy, thrombotic microangiopathy (TMA), acute kidney injury and mild neurotoxicity.

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.

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 and aggressive therapy aimed at the early detection and treatment of venom induced consumption coagulopathy and thereby retard the onset 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.

Fresh frozen plasma (FFP) is an accepted modality of intervention for consumption coagulopathy in a variety of clinical situations (Maduwage & Isbister, 2014). FFP could be useful in correcting coagulopathy by replenishing depleted clotting factors. The immunoglobulins in FFP could potentially prevent nephrotoxin-induced primary renal injury by immunomodulation. In a similar way FFP could reverse venom induced consumption coagulopathy and arrest the cascading adverse consequences by replenishing clotting factors. Any added benefit in the prevention of AKI could be related to the impact of FFP on the haematopathogenic mechanisms implicated in AKI.

In the absence of a safe and effective antivenom, or any other specific therapy for hump-nosed viper bite in Sri Lanka, a non-randomised observational study was carried out to test the hypothesis that FFP, by immunomodulation, could prevent venom mediated renal injury by acting at a site lower down the cascade of events that eventually lead to tissue injury. FFP, by replenishing depleted clotting factors, may also be useful in correcting the coagulopathy (Sellahewa, 2013). Of 42 patients receiving FFP none developed acute renal failure—neither did 18 patients who received isotonic saline. During the same period 32 patients with hump-nosed viper bites who developed coagulopathy and did not receive FFP (in other institutions) progressed to acute renal failure and required haemodialysis in the unit where the study was carried out.

Fresh frozen plasma is a safe, and probably effective, option to reduce morbidity and mortality from hump-nosed viper bites in Sri Lanka, in the absence of other treatment options. It is therefore recommended for selected patients — i.e. ONLY for patients with COAGULOPATHY, not for patients with only local effects or any other systemic effect. FFP should be given by infusion at a dose of 15ml/kg body weight and can be repeated every 6 hours until the coagulopathy has normalised. The 20WBCT should be repeated 6 hourly up to 24 hours after the intervention.

Maintaining adequate urine output is important in preventing the development of AKI. Saline infusion is recommended to ensure a urine output of 0.5 ml/kg/hour (Wijewantha & Sellahewa, 2010). Any patient developing AKI should be managed with haemodialysis.

Recommendations

- Observe all patients for 48 hrs after hump-nosed viper bites even if the initial presentation is innocuous
- Perform 20WBCT 6 hrly for 48 hrs
- Select those with positive 20WBCT for specific therapy with FFP
    - The objective of FFP is the prevention of AKI as early correction of coagulopathy can prevent AKI
- Hydrate adequately with isotonic saline and ensure adequate urine output of 0.5ml/kg body weight/hour
- Currently available antivenom is ineffective for hump-nosed viper and should not be used

Kolitha H. Sellahewa MBBS, MD, FCCP, FRACP(Hon)
Consultant Physician
Neville Fernando Teaching Hospital
Chair Professor of Medicine
South Asian Institute of Technology and Medicine

Bibliography

Ariaratnam CA, Thuraisingam V, Kularatne SAM, Sheriff MHR, Theakston RDG, de Silva A, Warrell DA (2008). Frequent and potentially fatal envenoming by hump-nosed pit vipers *(Hypnale hypnale and H. nepa)* in Sri Lanka*:* lack of effective antivenom, *Trans R Soc Trop Med Hyg*, **101**, 2008, 1120-6.

Davy J (1821). *An account of the interior of Ceylon*, Longman, Hurst, Rees and Brown, London.

de Silva A (1981). Snakebites in Anuradhapura district, *The Snake,* **13**, 1981, 117–130.

de Siva A, Ranasinghe L (1983). Epidemiology of snake-bite in Sri Lanka: a review, *CMJ*, 1983, **28**, 144-154.

de Silva A, Wijekoon ASB, Jayasena L, Abeysekara CK, Bao C-X, Hutton RA, Warrell DA (1994). Haemostatic dysfunction and acute renal failure following envenoming by Merrem's hump-nosed viper (*Hypnale hypnale*) in Sri Lanka: the first authenticated case, *Trans R Soc Trop Med Hyg*, **88**,1994, 209-12.

de Silva HJ, Fonseka MMD, Gunatilake SB, Kularatne SAM, Sellahewa KH (2002. Anti-venom for snakebite in Sri Lanka, *CMJ*, 2002, **47** (2), 43---45.

Dharmaratne L, Gunawardena U (1988-89). Generalised bleeding tendency and acute renal failure following Merrem's hump-nosed viper bite, *J Cey Col P*,1988-1989, 21–22.

Gunatilake M, Jayakody RL, Angunawela P, de Tissera A (2003). Direct Nephrotoxic Effects Produced by Venoms of Sri Lankan Cobra, Russell's Viper and Hump Nosed Viper, *Cey J Med Sci*, **46**, 2003, 61-66.

Herath N, Wazil A, Kularatne S, Ratnatunga N, Weerakoon K, Badurdeen S, Rajakrishna P, Nanayakkara N, Dharmagunawardane D (2012). Thrombotic microangiopathy and acute kidney injury in hump-nosed viper (Hypnale species) envenoming: A descriptive study in Sri Lanka, *Toxicon*, 2012, 61–65.

Herath HMNJ, Wazil AWM, Abeysekara DTDJ, Jeewani NDC, Weerakoon KGAD, Ratnatunga NVI, Bandara EHCK, Kularatne SAM (2012b). Chronic kidney disease in snake envenomed patients with acute kidney injury in Sri Lanka: a descriptive study. *Postgrad. Med. J*. 2012, **88** (1037), 138–142.

Isbister GK, Maduwage K, Shahmy S, Mohamed F, Abeysinghe C, Karunathilake H, Ariaratnam CA, Buckley NA (2013). Diagnostic 20-min whole blood clotting test in Russell's viper envenoming delays antivenom administration, QJM, 2013 Oct, 106 (10), 925-32, doi:10.1093/ q.j.med/hct102.

Joseph JK, Simpson ID, Menon NCS, Jose MP, Kulkarni KJ, Raghavendra GB, Warrell DA (2007). First authenticated cases of life–threatening envenoming by the hump–nosed pit viper (*Hypnale hypnale*) in India, *Trans R Soc Trop Med Hyg,* **10**, 2007, 85–90.

Karunatilake H, Nayakarathna T, Atapattu S, Saparamadu T, Dharmasena S (2012). Thrombotic microangiopathy and fibrinolysis after hump nosed viper envenomation, *CMJ*, 2012, **57**, 45-46.

Keyler DE, Gawarammana I, Gutiérrez JM, Sellahewa KH, McWhorter K, Malleappah R (2013). Antivenom for snakebite envenoming in Sri Lanka: The need for geographically specific antivenom and improved efficacy, *Toxicon* (**69**) 2013, 90-97.

Kularatne SA, Ratnatunga N (1999). Severe systemic effects of Merrem's hump-nosed viper bite, *CMJ*, 1999, **44**, 169–170.

Maduwage K, Silva A, Manamendra-Arachchi K, Pethiyagoda R (2009). A taxonomic revision of the South Asian pit viper genus Hypnale (Fitzinger), *Zootaxa*, 2009, **2232**, 1–28.

Maduwage K, Kularatne K, Wazil A, Gawarammana I (2011a). Coagulopathy, acute kidney injury and death following Hypnale zara envenoming – The first case report from Sri Lanka, *Toxicon*, **58**, 2011, 641-643.

Maduwage K, Hodgson WC, Konstantakopoulos N, O'Leary MA, Gawarammana I, Isbister GK (2011b). The in-vitro toxicity of venoms from South Asian Hump-nosed pit vipers (Viperidae: Hypnale). *J. Venom Res*. **2**, 17–23.

Maduwage K, Isbister GK, Silva A, Bowatta S, Mendis S, Gawarammana I (2013). Epidemiology and clinical effects of Hump-nosed pit viper (Genus: *Hypnale*) envenoming in Sri Lanka, *Toxicon*, 2013, **61**, 11---15.

Maduwage K, Isbister GK (2014). Current treatment for venom-induced consumption coagulopathy resulting from snakebite, PLOS Neglected Tropical Diseases, https://doi.org/10.1371/journal.pntd.0003220.

Premawardena A, Seneviratne SL, Jayanthi S, Gunathilake SB, de Silva HJ (1996). Coagulopathy and fibrinolysis following the bite of a hump-nosed viper (*Hypnale hypnale*), *Trans R Soc Trop Med Hyg,* **90**, 1996, 290- 293.

Premawardena AP, Seneviratne SL, Gunatilake SB, De Silva HJ (1998). Excessive fibrinolysis: the coagulopathy following Merrem's hump-nosed viper (*Hypnale hypnale*) bites, *Am J Trop Med Hyg*, **58**,1998, 821-3.

Rathnayaka RMMKN, Kularatne SAM, Ranatunga N, Kumarasinghe M, Rajapakse J (2017). Prolonged coagulopathy, ecchymoses and microangiopathic haemolytic anaemia following hump-nosed pit viper (Hypnale hypnale) bite in Sri Lanka, Case report, *Wilderness & Environmental Medicine*, **28**, Issue 3, 253-258.

Rathnayaka RMMKN, Kularatne SAM, Ranathunga PEAN, Rajapakse RPVJ, Ranasinghe JGS (2017b). Species specific clinical manifestations following hump nosed pit viper (genus: Hypnale) envenoming in Sri Lanka, Abstract: oral presentation, SLMA 130th Anniversary International Medical Congress, Colombo.

Sellahewa KH, Kumararatne MP (1994). Envenomation by the Hump-nosed viper (*Hypnale hypnale*), *Am J Trop Med Hyg*, **51**, 1994, 823–825.

Sellahewa KH, Gunawardena G, Kumararatne MP (1995). Efficacy of antivenom in the treatment of severe local envenomation by the hump-nosed viper (*Hypnale hypnale*), *Am J Trop Med Hyg*, **53**, 1995, 260—262.

Sellahewa KH (1997). Lessons from four studies on the management of snake bite in Sri Lanka, *CMJ*, 1997, **42**, 8-15.

Sellahewa KH (2008). Management of Hump nosed viper in Sri Lanka, *The Sri Lankan Prescriber*, June 2008, **16**, No. 2.

Sellahewa KH (2013). Can Fresh Frozen Plasma Prevent Acute Kidney Injury after Hump-Nosed Viper Bite? *Open Journal of Nephrology*, 2013, 3, 70-74 Doi:10.4236/ojneph.2013.31012 Published Online March 2013 (http://www.scirp.org/journal/ojneph).

Seneviratne S, Opanayaka CJ, Ratnayake NS, Kumara KE, Sugathadasa AM, Weerasuriya N, Wickrama WA, Gunatilake SB, de Silva HJ (2000). Use of antivenom serum in snake bite: a prospective study of hospital practice in the Gampaha district, *CMJ*, **45**, 2000, 65–68.

Tan CH, Leong PK, Fung SY, Sim SM, Ponnudurai G, Ariaratnam C, Khomvilai S, Sitprija V, Tan NH (2011). Cross neutralization of *Hypnale hypnale* (hump–nosed pit viper) venom by polyvalent and monovalent Malayan pit viper antivenom in vitro and in a rodent model, *Acta Trop*, **117**, 2011, 119–124.

Varagunam T, Panabokke RG (1970). Bilateral necrosis of the kidneys following snakebite, *Postgrad. Med. J*., **46**, 1970, 449–451.

Wijewantha HS, Sellahewa KH (2010). Hump-nosed viper bite in Sri Lanka — a descriptive observational study of 1543 cases, *Asian Pac. J. Trop. Med*. 2010, 902–90.

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