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Hump-nosed Pit Viper Bite in Sri Lanka – Unravelling an Enigma

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Abstract

Lack of detailed studies on hump-nosed viper apart for a few isolated case reports had left a void of knowledge for centuries. Consequently, its precise clinical features and management remained an enigma. Detailed clinical studies initiated by me in 1990 and escalated by other investigators in the recent past have accurately identified the different species of *Hypnale*, and species specific clinical features. Coagulopathy and acute kidney injury (AKI), though rare, are the most important and potentially fatal systemic effects. The lack of efficacy and safety of the currently available antivenom is now well recognised. While haemodialysis can salvage patients developing AKI, use of fresh frozen plasma is an exciting management option to prevent AKI, when used early for selected patients at the inception of coagulopathy. An attempt to develop species specific safe and efficacious antivenom with international collaboration has been initiated.

Keywords: Acute kidney injury; Snake bite; Venomous snakebite; Naja Naja; *Bungarus caeruleus*; *Daboia russelii*

Introduction

Snake bite is a major problem and a medical emergency in Sri Lanka. Hump-nosed viper bite is the commonest venomous snakebite in Sri Lanka responsible for 22-77% of all snake bites [1,2]. It is a snake endemic to Sri Lanka and South West coastal region of India. Up to the latter part of the last century, it was considered to be a mildly venomous or moderately venomous snake. In that era, mortality from snakebite was associated with mainly three species of snakes, the Sri Lankan cobra (*Naja naja*), common krait (*Bungarus caeruleus*), and Russell's viper (*Daboia russelii*), which had accounted for 97% of all snakebite related deaths [3].

Consequently, clinicians and researchers alike paid scant regard to victims of hump-nosed viper bite, which was hitherto considered to be a relatively innocuous snake. This concept prevailed among the lay community as well, and tended to reinforce the overwhelming notion of innocence of the hump-nosed viper amidst the medical fraternity. Davy [4] was the first to report about swelling and bleeding due to bite by *H.hypnale*. Since then, apart for a few isolated case reports of renal injury and death, very little was known about the clinical features and the morbidity and mortality trends of hump-nosed viper bite in stark contrast to those of Russell's viper, Cobra and Krait [4-6]. *H. hypnale* which was referred to as Merrem's pit viper was the dominant species recognised with morbidity. However, clear detailed information about the different species of hump-nosed vipers and its clinical, toxinological and biological properties were not well studied, nor documented. It is against such a background that I embarked on a series of studies to fill this void of knowledge. I endeavoured to study first the clinical attributes of hump-nosed viper bite in greater detail and then its management.

Subjects and Methods

Over an 18 year period from 1990 to 2008, we carried out several prospective clinical studies, a randomized controlled trial, and also reviewed the updated information on the subject as it unfolded up to 2013. The studies were designed primarily to:

1. Determine the clinical effects of envenomation by the hump-nosed viper.
2. Identify the systemic effects of envenomation.
3. Test the efficacy of antivenom for local effects of envenomation.

4. Identify the primary underlying causes for mortality.
5. Review the prevailing modalities of management.
6. Test the efficacy of fresh frozen plasma in preventing acute kidney injury.

Clinical Features of Envenomation

We carried out a prospective clinical study from June to December 1993 at the Base Hospital Avissawella to determine the clinical features of envenomation by the hump-nosed viper (*Hypnale species*). All the included patients either brought the offending snake, which was personally identified by me as *Hypnale species*; or the patient pointed out accurately to hump-nosed vipers from jars containing preserved specimens of venomous and non-venomous snakes, when the offending snake was not available for identification. Among sixty-two consecutive adult patients, 63% were males and 37% females, with a median age of 30 years (age range 13-68 years). Most (85.5%) of the patients were bitten on the feet, while 14.5% of the patients were bitten either on the hands or forearms. Most (61.3%) of the patients were bitten during the evening hours (6:00-10:00 PM). The mean time for admission to the hospital following the bite was 1.5 hr (range 0.25-13 hr.). All patients had signs of local envenomation manifested by pain, swelling and induration at the site of the bite, which was occasionally associated with local haemorrhagic blister formation (11.3%) and tender regional lymphadenopathy (24.2%). None of the patients during this study period in this geographical location had signs of systemic envenomation [7].

In a series of 1543 patients we studied from 1990 to 2008, all complained of pain at the bite site and 1535 (99.5%) patients complained of swelling at the bite site. All the included patients in this series brought either the dead or the live snake to hospital, which was identified as *Hypnale species* personally by me as the attending

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Number of patients = 1543		
Variable	Frequency	%
Coagulopathy	59	3.8
Shock	1	0.06
Diarrhea	1	0.06
Abdominal pain & vomiting	1	0.06
Oliguria/Anuria	0	0
Ptosis	0	0
Muscle paresis	0	0
Ophthalmoplegia	3	0.2
Coma	2	0.1
Deaths	2	0.1
Total	67	4.3

Table 1: Systemic effects of envenomation.

physician. A Hemorrhagic blister was present in 230 (14.9%) patients and 413(26.8%) had painful regional lymphadenopathy. Out of the 1543 patients studied, 67 patients developed systemic effects. There were two deaths in this series [8] (Table 1).

The patient who developed shock had coagulopathy, but the patients with diarrhea, abdominal pain, vomiting, ophthalmoplegia and coma did not have coagulopathy. Out of the 59 patients who had only coagulopathy, 58 developed coagulopathy within 24 hours of the bite, and one patient developed hematuria after 48 hours with prolonged clotting tests, despite having serial normal 20 minute whole blood clotting tests (20WBCTs) within the first 24 hours after the bite.

The two patients who died due to envenomation had the following clinical manifestations. The first death in this series was a twenty eight year-old male in Anuradhapura, who developed a profuse watery diarrhea and died on the same day of the bite. He remained in the hospital only for one day and the diarrhea was not investigated. Clinical evaluation did not reveal any other cause for the diarrhea. He had not received any traditional medication prior to admission. His 20WBCTs were negative. The second was a 35 year-old female who had incoagulable blood 2 hours after the bite. She was treated with 100 ml of polyvalent antivenom from the Serum Institute of India diluted in 400 ml of isotonic saline as an intravenous infusion over one hour. She had persistent coagulopathy, developed shock, and died within 6 hours of admission. We were not sure whether death was due to a reaction to antivenom or to the effects of envenomation; the former was probably the more likely cause [8].

Since the turn of the century, many have independently recognized the propensity of hump-nosed viper to give rise to coagulopathy and acute kidney injury (AKI) [9-17]. Several deaths due to systemic envenomation have also been reported [13,18]. All these findings have caused a resurgence of interest in this small innocent looking neglected species of snake. Recent work by other investigators has led to an accurate identification of the different species of hypnale, better documentation of species specific clinical features from different geographical locations, and also paved the way for identification of pathologically important venom constituents.

The completion in 2009 of a taxonomic revision of the genus *Hypnale* by Maduwage et al. [13] has identified four species of hypnale, namely, *H. hypnale*, *H. nepa*, *H. zara* and one specimen of a novel species *H. amal*. *H. walli* is synonymous with *H. nepa* and *H. zara* is different from *H. hypnale* [19]. It is evident from a review of recent data that hemostatic dysfunction and AKI are important systemic effects of envenomation, and responsible for most deaths with a reported mortality rate of 1.7%

[18]. In a series of 302 cases by Ariyaratnam et al. [18], Coagulopathy and AKI were reported among 39% and 10%, respectively. Among 13 patients who had AKI after hump-nosed viper bite, 6 developed chronic renal failure within 1 year, which was attributed to focal segmental glomerulosclerosis, cortical necrosis and interstitial nephritis [19,20]. A case of coagulopathy and AKI due to *H. zara* has been reported [13]. Precise mechanism of AKI however remains unclear. Mild local pain and swelling due to *H. nepa* has also been reported [18]. Reverse phase high performance liquid chromatography and SDS-PAGE by Maduwage et al. [13] have revealed that all three Hypnale venoms had potent cytotoxicity, mild procoagulant activity and weak neurotoxic, myotoxic and phospholipase A2 activity [21].

Treatment of Envenomation

In Sri Lanka, the usual treatment of patients envenomed after snakebite is with polyspecific snake antivenom. We carried out a prospective, randomized, placebo-controlled, single-blind clinical trial to determine the efficacy and safety of polyspecific snake antivenom in the treatment of severe local envenomation by the hump-nosed viper. Inclusion criteria required the patients to present within 24 hours after a confirmed hump-nosed viper bite who had not received any medication prior to admission. Confirmation of the biting snake as hump-nosed viper was made by me by visual examination of the dead or live snake that was brought to hospital. They also required to have local pain and swelling >15 cm. Sixty-three patients with signs and symptoms of local envenomation by the hump-nosed viper were randomized to receive either polyspecific snake antivenom (100 ml in 400 ml of isotonic saline), or 500 ml of normal saline. The two groups were similar in age, sex, time of presentation to hospital and degree of envenomation. There was no significant difference between the antivenom and placebo groups in the time taken for complete resolution of the local envenomation (5.52 days versus 4.77 days; P=0.53, by the Mann-Whitney U test). There was a 44.8% incidence of adverse reactions associated with treatment with antivenom. We excluded two patients from the treatment group, owing to the development of a severe anaphylactic reaction with bronchospasm and respiratory distress, which necessitated the discontinuation of antivenom. One patient from the control group was also excluded owing to a concomitant infection with *Plasmodium falciparum*. We concluded that polyspecific snake antivenom is not indicated for the treatment of severe local envenomation by the hump-nosed viper [22].

My initial assertion of the lack of efficacy of antivenom in Sri Lanka for hump-nosed viper bites, and the need for antivenom with specific activity against hump-nosed viper has been further supported by other investigators in recent studies [2,18,22-24]. Tan et al. [25] have shown that Thai Red Cross Malayan Pit Viper antivenom because of the close phylogenetic relationship between *H. hypnale* and *C. rhodostoma* could be useful in the treatment of hump nosed viper bite [25]. This antivenom however is not available in Sri Lanka.

Owing to the lack of safety and efficacy of the currently available antivenom in Sri Lanka for envenomation by hump-nosed viper I searched for therapeutic options, and conceptualized that fresh frozen plasma (FFP) by replenishing depleted clotting factors could be useful in correcting the coagulopathy. It was also hypothesized that Fresh frozen plasma (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. Immunomodulating effects of intravenous immunoglobulin are well recognised, and it is possible that FFP could also exert Immunomodulatory effects in a similar way. These benefits of FFP transcending beyond normalisation of

coagulopathy have been recognised by independent investigators who have used FFP for other disorders like shock and dengue, where complex immunological mechanisms are implicated in the pathogenesis [26-32].

To test this hypothesis, we carried out an observational study at the National Hospital of Sri Lanka from March 2005 to June 2008. All patients admitted to one adult medical unit with a diagnosis of having been bitten by hump-nosed vipers that developed coagulopathy were studied. Only those patients who brought the dead or live snakes that were identified as hump-nosed vipers by me were included in the study. However, species identification as *H. hypnale*, *H. nepa*, or *H. zara* was not done. Coagulopathy was inferred by the detection of a positive 20WBCT, which was performed in all patients on admission, and then every 4 hours up to 24 hours. The patients who developed coagulopathy received either an infusion of FFP at a dose of 15 ml/kg body weight or isotonic Saline. 20WBCTs were then repeated 4 hourly up to 24 hours after the intervention. FFP was repeated every 4 hours, until the coagulopathy was normalised. During this study period, 60 patients developed coagulopathy, 42 of whom were treated with FFP and 18 with isotonic Saline.

The mean times for normalization of coagulopathy in the treatment and control groups were 4.7 hours and 6.2 hours, respectively. In both these groups, none developed AKI as evidenced by oliguria, elevated blood urea and a rise in the serum creatinine. Mean duration of hospital stay was also similar at 89.3 and 89.3 hours. None of the 42 patients treated with FFP developed any adverse sensitivity reactions. During this study period, 32 patients who had developed AKI were transferred from the regional base hospital to this same unit for haemodialysis. All 32 patients were bitten by hump nosed vipers (*Hypnale spp.*), and were identified as such by the physician in the base hospital. Perusal of case records from the transferring base hospital revealed that all the 32 transferred patients had developed coagulopathy within the first 24 hours after the bite, but none had received FFP [33].

The association of coagulopathy with AKI after hump-nosed viper bite is now well recognised, and has been independently reported by many investigators. It is likely that common pathophysiological mechanisms are responsible for both these important systemic complications of hump-nosed viper bite. Hump-nosed viper venom contains procoagulant, nephrotoxic, myotoxic and cytotoxic properties. 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 coagulation [14]. Fibrinogen degradation products can perpetuate the bleeding tendency by its antihemostatic effects. These pathogenic mechanisms associated with the haemostatic disturbances seen could be important contributors to AKI apart for the primary venom induced nephrotoxicity. It may even be more important than the direct nephrotoxicity, unlike AKI after *Daboia russelii* bites [34]. Interestingly, coagulopathy was the earliest systemic manifestation among all the patients who developed AKI in all the cases studied. Arguably, early correction of coagulopathy may prevent AKI in view of the observation that none of the 42 patients with coagulopathy who received FFP developed AKI; while all the 32 patients with coagulopathy who had not received FFP developed AKI. Whether this observation was a chance occurrence or was causally related to the intervention needs to be ascertained. However, all the 18 patients with coagulopathy who were treated with only isotonic saline also recovered completely none of whom developed AKI, even though it took a longer time for correction of coagulopathy (mean 6.2 hours), when compared with the group treated with FFP (mean 4.7 hours).

The immunoglobulins in FFP could potentially by immunomodulation prevent nephrotoxin-induced primary renal injury. FFP is an accepted modality of intervention for consumption coagulopathy in a variety of clinical situations. In a similar way, FFP by replenishing clotting factors could reverse venom induced consumption coagulopathy and arrest the cascading adverse consequences. Any added benefit in the prevention of AKI could be related to the impact of FFP on the haematopathogenic mechanisms implicated in AKI. In this study, coagulopathy normalised earlier in those treated with FFP when compared with the patients who received only isotonic Saline [33].

Management Concerns

The mysteries that shrouded this little known snake for several centuries have now been unravelled. A taxonomic revision by Maduwage et al. [13] has clarified errors and overlap in terminology pertaining to the different species. Ever since Davy [4] first studied the pathological effects of hump-nosed viper as far back as 1821, and the yawning gap of knowledge that existed for centuries has now been bridged by research commenced by me in 1990 and escalated by many other independent investigators in the recent past. The effects of envenomation are no longer a mystery, nor the recognition of hump-nosed viper as a highly venomous snake capable of inflicting AKI and death. However, how best to manage victims of hump-nosed viper bite remains a dilemma for both clinicians and researchers alike, as the only known antidote for snakebite is antivenom; which is not effective for hump-nosed viper bite. Currently available antivenom in Sri Lanka is raised against the venom of *N. naja*, *D. russelli*, *B. caeruleus* and *E. Carinatus*, but not hump-nosed viper. Its use for patients after hump-nosed viper bite was associated with an incidence of adverse reactions ranging from 45% to 53% [22,23]. These issues leave the clinician in a dilemma of whether to use the available antivenom (the only antidote for snake bite) of dubious efficacy and high tendency for adverse effects, or avoid specific interventions and offer dialysis for those with AKI; the development of which is sporadic and unpredictable.

In the absence of safe and effective antivenom or any other specific therapy for hump-nosed viper bite to date in Sri Lanka, I would advocate the use of FFP for selected patients as a safe and probably effective option to reduce morbidity and mortality from hump nosed viper bite in the Sri Lankan setting. Patient selection is based on the 20WBCTs. The 20WBCT detects coagulopathy, and can be used as an early predictor of systemic envenomation. It can easily be done at the bedside, without depending on laboratories in resource poor settings where snake bite is common. 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. Observation for at least 48 hours is advocated, owing to the possibility of delayed manifestations of coagulopathy. Patients, who develop coagulopathy, as evidenced by a positive 20WBCT, should be selected for intensive monitoring and aggressive therapy aimed in the early detection, and treatment of venom induced consumption coagulopathy, and thereby, retards the advent of acute renal failure. This has been my personal management preference, and is what I have practiced [33,35].

Conclusions

1. Hump-nosed viper bite is the commonest venomous snake bite in Sri Lanka, which is an important medical problem. Owing to well recognised and reported fatal outcomes, both in Sri Lanka and India,

it is now considered a venomous snake with the capacity to develop severe envenoming.

2. Taxonomic revision by Maduwage et al. [13] recognises 3 medically important species of the genus *Hypnale* viz. *H. hypnale*, *H. nepa*, and *H. zara*, with all three having the capability of inflicting serious morbidity and potential for a fatal outcome owing to common toxinological attributes demonstrated by venom analysis.

3. Bites are seen mainly in the extremities, feet, ankles, fingers, hands and forearms. There is a male preponderance, with most bites taking place outdoors in the evening hours. This information is useful in the planning and education of preventive strategies.

4. Local pain and swelling are the most consistent effects of envenomation. A haemorrhagic blister at the bite site and regional tender lymphadenopathy are seen in some patients; 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 among many other viperid bites, as well.

5. Systemic effects and even deaths do occur after hump-nosed viper bite. However, these are rare and unpredictable. Coma, ophthalmoplegia, shock and profuse diarrhoea with abdominal pain are all recognised systemic effects. However, coagulopathy is the commonest and the most important systemic effect, as it is often associated with AKI, which has the potential for a fatal outcome. The primary cause for mortality is from complications associated with coagulopathy and AKI. All who developed AKI had coagulopathy, which was evident before the advent of clinical and biochemical features of AKI. It is possible that early correction of coagulopathy with FFP could prevent AKI and related adverse clinical outcomes. This assertion is based on a consideration of the recognized pathogenic mechanisms implicated in hump-nosed viper venom induced AKI and coagulopathy, and application of the known pharmacological benefits of FFP for immunomodulation and consumption coagulopathy to offset these adverse consequences. Personal experience and the observation that none of the patients in this series developed AKI, when FFP was used early at the inception of coagulopathy tend to support this contention. A well designed large double blind randomized controlled trial is recommended to test this hypothesis further.

6. Overt bleeding manifestations like haematuria, hematemesis and bleeding per rectum are rare, and coagulopathy is often detected by the 20WBCT. The recent demonstration by Maduwage et al. [17] of the low sensitivity of the 20WBCT in detecting coagulopathy after envenomation by *D. russelli* may compromise the utility of this bedside test [36]. The precise nature of the coagulopathy is poorly understood, and is most likely due to venom induced consumption coagulopathy.

7. 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 and adverse renal consequences of coagulopathy, such as venom induced consumption coagulopathy and thrombotic microangiopathy are implicated [14,15].

8. Paracetamol is sufficient for the symptomatic relief of pain. Aspirin and nonsteroidal antiinflammatory agents are best avoided, owing to the potential for coagulopathy in envenomed patients.

9. Local swelling is a chemical inflammation and resolves spontaneously without the use of antibiotics. Antibiotics are not

indicated routinely for local swelling, except in the presence of secondary sepsis or prophylactically after surgical interventions. Hemorrhagic blisters, when present, can be left alone or punctured with a sterile needle when local pressure is an issue, particularly in the fingers and toes in children. Inappropriate surgical interventions with the misdiagnosis of gangrene can lead to unnecessary extensive surgical debridement of tissue. This diagnostic pitfall can easily be avoided by careful examination of the bite site and attention to detail. It will then be clearly discernible that it is the black color imparted by altered blood underlying the thin layer of skin epithelium that has given a wrong notion of gangrene.

10. Currently available antivenom is not effective for hump-nosed viper bite and should not be used, whatever the severity of envenomation. Supportive and symptomatic therapy is what is usually available, apart from hemodialysis for those with AKI.

11. FFP used early at the inception of coagulopathy for all those few who develop coagulopathy could be a useful option to save lives, prevent AKI and obviate the need for hemodialysis.

Future Research

1. Determine the precise mechanisms implicated in AKI. Such insight could provide targeted interventions to prevent renal injury.

2. Our understanding of the haemostatic disturbances after hump-nosed viper bite is rather nebulous. Detailed investigations directed at all points of the clotting cascade could yield accurate information with therapeutic implications.

3. Antivenom with specific activity against hump-nosed viper is urgently needed. This need was first highlighted by me in 1997, but sadly to date, no such antivenom exists [24]. Many futile attempts have been made by independent investigators over the years to meet this need. Progress had been hampered not only by the poor venom yield of this small snake, but also by bureaucracy and red tape attendant with the export of venom to centres outside Sri Lanka, with the technological capabilities of antivenom manufacture. Current attempts to develop species specific antivenom by international collaboration needs to be pursued vigorously [37].

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