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IS THE CONCEPT OF "BIG 4" STILL RELEVANT IN INDIA? COMPARISON OF ENVENOMATION BY HUMP-NOSED PIT VIPER WITH RUSSELL'S VIPER

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ABSTRACT

Background: Hump-nosed pit viper *(Hypnale hypnale)* bites are common in the Indian subcontinent, especially in Kerala. In the past, Hump-nosed pit viper was considered as a mildly venomous snake; hence it was not included in the polyvalent anti snake venom manufactured in India. However, there is increasing number of reports of serious complications following envenomation by this species. **Aim of the study:** To study the complications following Hump-nosed pit viper envenomation and to compare it with Russell's viper envenomation. **Methods:** 29 cases of Hump-nosed pit viper envenomation and 15 cases of Russell's viper envenomation admitted in the Snake Bite Unit of Government Medical College Kozhikode from 1st January 2014 to 31st December 2014 were studied. Only cases in which the species of the biting snake was definitely identified were included. **Results:** Acute kidney injury was observed in 11 patients (6 cases required hemodialysis) with Hump-nosed pit viper envenomation and 14 patients (8 cases required hemodialysis) with Russell's viper envenomation. The difference between the number of dialysis-requiring cases in these two groups were statistically insignificant (P=0.058). One patient with Hump-nose pit viper bite and 2 patients with Russell's viper bite progressed to chronic kidney disease on follow up for 3 months. The renal biopsy of these patients showed cortical necrosis. There was no statistically significant difference in the incidence of coagulopathy and compartment syndrome between two groups. There was one death due to Hump-nosed pit viper bite and it was due to thrombotic thrombocytopenic purpura-like syndrome. **Conclusion:** Severe acute kidney injury, compartment syndrome and potential to cause renal cortical necrosis and even death following Hump-nosed pit viper envenomation are strong reasons to change the concept of the "Big 4" to "Big 5". Anti snake venom with activity against Hump-nosed pit viper venom need to be manufactured and be made available in India.

INTRODUCTION

The polyvalent anti snake venom (ASV) available in India has action only against the "Big 4" which includes common krait (*Bungarus caeruleus*), spectacled cobra (*Naja naja*), Russell's viper (*Daboia russelii*) and saw-scaled viper (*Echis carinatus*). Hump-nosed pit viper *(Hypnale hypnale)* was considered only as a mildly venomous snake; hence not included in the polyvalent anti snake venom. Hump-nosed pit viper (HNPV) is a common snake reported from the Western Ghats of South India and Sri Lanka.[1] Although formerly thought to result only in minor or local envenoming, HNPV bite is now known to cause serious systemic toxicity and even fatalities.[2-6] A study done in Kerala in 2003-04 identified HNPV as a common and dangerous source of envenoming, second to Russell's viper.[7] In subsequent years, cases of death following HNPV bites were reported.[5,8] Clinical manifestations of systemic envenoming by this snake include severe local reaction, acute kidney injury, haematological manifestations and sometimes, multi-organ involvement and death. As of now, there are only a very few case reports from India on HNPV bites causing serious complications, and there is a lack of proper understanding about the same among clinicians and toxicologists. Much of the work in the field of HNPV envenomation is from Sri Lanka. This data cannot be extrapolated to South India as the venom composition of the same species of snakes varies from region to region.

AIM

To study the complications following Hump-nosed pit viper envenomation and to compare it with Russell's viper envenomation.

METHODS

All patients admitted in the Snake Bite Unit of Government Medical College Kozhikode, with envenomation (local/systemic) due to Hump-nosed pit viper and Russell's viper from 1st January 2014 to 31st

December 2014 were included in the study. The species of the biting snake was identified by three experts independently. Cases were excluded if:

- Any disagreement between the experts in species identification of the snake
- Pre-existing kidney disease (as evidenced by a serum creatinine of more than 1.4mg/ dL before the snake bite or ultrasonography of abdomen showing bilateral contracted kidneys / impaired cortico-medullary gradient / obstructive nephropathy / any other renal pathology)
- Patients with systemic hypertension and/or diabetes mellitus
- Recent (within 2 weeks) exposure to nephrotoxic drugs

As per the hospital protocol, all cases of Russell's viper bite received 10 vials of ASV (VINS Bioproduct Limited) within 15 minutes of reaching the hospital, if they have features of envenomation. If they do not have features of envenomation at presentation, ASV was administered when the first sign of envenomation appeared. The requirement for further doses of ASV was decided by the 20 minute whole blood clotting time which was repeated 6 hours after the first dose. No patients with hump-nosed pit viper bite received ASV. Symptoms, signs, laboratory investigations and various complications of all the study subjects were noted. All subjects with acute kidney injury were followed up for three months to assess their renal recovery. Renal biopsy was done in all the cases where renal function did not normalise in 3 months. Statistical analysis was done on the data thus obtained. P value of less than 0.05 was considered significant.

RESULTS

During the one year study period (1st January 2014-31st December 2014) there were 363 cases of snake bite envenomation, of which 44 cases satisfied the inclusion and exclusion criteria. Among them, 29 bites were due to Hump-nosed pit viper and 15 were due to Russell's viper. Mean age of the study population was 47.3 years (SD 14.4 years, min 15 years, max 70 years) of which 25 (56.8%) were males. 32 bites (77.3%) were in the lower limb, 19 bites (43.3%) occurred in setting of poor illumination and 11 bites (25%) occurred while the subjects were engaged in agricultural work. Time delay to reach the hospital was less than 2 hours in 27 patients (61.4%), 2-4 hours in 7 patients (15.7%) and more than 4 hours in 10 patients (22.7%). 19 patients (43.3%) received indigenous treatment (sucking, incising and local applications) before reaching the hospital. 33 patients (75%) had applied tourniquet immediately after the bite and 27 of them had used improper technique. Indigenous treatment received after the bite was significantly associated with delayed presentation to the hospital. Only 6 out of the 19 patients who received indigenous reached the hospital in less than 2 hours, whereas 21 out of the 25 patients who did not receive indigenous treatment aid reached the hospital in less than 2 hours (P <0.001). Delayed administration of ASV was associated with increased mortality, with 3 out of 4 deaths due to Russell's viper envenomation occurring in patients who presented to the hospital after 4 hours of bite (P=0.077). The differences between the clinical profile of HNPV bite and Russell's viper bite is tabulated in the table 1 and 2.

Table 1 : Symptoms and signs

	Hump-nosed pit viper (n=29)	Russell's viper (n=15)	P value
Head ache	8	9	0.039
Vomiting	13	14	0.002
Flank pain	1	8	<0.001
Local pain and swelling	29	15	---
Regional lymphadenopathy	23	13	0.552
Bleeding from the bite site	23	15	0.067
Ptosis and ophthalmoplegia	0	4	0.01
Bleeding manifestations	1	5	0.013
Coagulopathy	21	15	0.024
Mean time taken for resolution of coagulopathy	6.19 ± 2.06	1.4 ± 0.5	<0.001
Hematuria	6	14	<0.001
Albuminuria	11	14	<0.001
Urine output Anuria Oliguria Normal	 6 4 19	 9 5 1	<0.001
Acute kidney Injury Stage I Stage II Stage III	 2 1 8	 1 1 12	<0.001

Dialysis requiring AKI	6	8	0.058
Progression to CKD	1	2	0.264
Compartment syndrome	2	4	0.092
Capillary leak syndrome	0	6	0.001
Deaths	1	4	0.039

Table 2. Comparison of means blood counts and biochemical parameters done on the first day

TYPE OF SNAKE		TOTAL WBC COUNT (per mm^3 of blood)	PLATELET COUNT (per mm^3 of blood)	LDH* (in IU/litre)	CPK** (in IU/litre)
Pit Viper N=29	Mean	11340	199170	376	442
	Std. Deviation	4980	60670	325	471
Russell's Viper N=29	Mean	20910	60530	2103	1760
	Std. Deviation	6810	48620	1439	2247
P value (Independent samples T test)		<0.001	<0.001	<0.001	0.004

* Lactate dehydrogenase.
**Creatine phosphokinase.

The amount of tissue injury produced by Russell's viper envenomation was significantly more when compared with HNPV as evidenced by higher mean values of LDH and CPK (Table 2). AKI was observed in 11 patients with HNPV envenomation and 14 patients with Russell's viper envenomation. This difference was statistically significant with a P value <0.001. Dialysis requiring AKI was observed in 6 patients with HNPV bite and 8 patients with Russell's viper bite, the difference being statistically insignificant (P=0.058). One patient with HNPV bite and 2 patients with Russell's viper bite progressed to CKD on follow up for 3 months (P=0.264). All patients in this study had some degree of local reaction but compartment syndrome was observed only in 2 patients with HNPV bite and 4 patients with Russell's viper bite (P=0.092).

It took more number days for complete resolution of coagulopathy in HNPV bites (6.2±2.1 days) when compared with Russell's viper bites (1.4 + 0.5 days) and this difference was statistically significant with P value <0.001. Number of days taken for the resolution of coagulopathy in HNPV bite had a significant association with the development of AKI; odds ratio 2.71 (95% CI 1.18-6.20). The mean platelet count in the first 24 hours in patients with coagulopathy due to HNPV envenomation (199500 ± 62300 per mm^3) did not statistically differ from the mean platelet count of patients without coagulopathy (198300 ± 60100 per mm^3). All patients with Russell's viper envenomation had coagulopathy and their mean platelet count was 60500 ± 48600 per mm^3.

Snake venom induced capillary leak syndrome was defined for the purpose of our study as a combination of hypotension, hypoalbuminemia and third space fluid collection. There were 6 cases of capillary leak syndrome, all of them due to Russell's viper bite, out of which there were 4 deaths. One death occurred due to HNPV bite and it was due to thrombotic thrombocytopenic purpura (TTP) - like clinical picture.

DISCUSSION

The mean age of the subjects in our study was 47.3 years. A study on snake bite envenomation conducted in our centre in 2003-04 had a mean age of 32.8 among its study subjects.[7] This difference may be explained by the declining trend among youngsters to engage in agriculture related work, which is a potential risk factor for snake bites. Only 61.4% of the subjects reached the hospital in less than 2 hours. Many patients (43.2%) had initially resorted to indigenous treatments and the majority of them reached the hospital later than 4 hours after the bite, revealing the dismal lack of awareness regarding timely and proper treatment for snake bite in the community. Delayed administration of ASV was the most important predictor of bad outcome as evidenced by the fact that, 3 out of the 4 deaths due to Russell's viper bite occurred in patients who received ASV after a delay of 4 hours.

Even though the toxicity profile of HNPV envenomation is less when compared with Russell's viper, a fair number of patients developed renal failure (37.9%), of which more than half required hemodialysis. Serum creatinine did not normalise in one patient even after 3 months and renal biposy revealed cortical necrosis. One patient with HNPV bite developed a lethal TTP-like syndrome, which is a very rarely reported complication in literature.[9] A significant number of patients with HNPV bite had coagulopathy (72.4%). The venom induced coagulopathy seen in HNPV envenomation is different from disseminated intravascular coagulation (DIC) as these patients had normal platelet count.[9] An interesting observation was that these patients had incoagulable blood for a mean of 6.2 days, but none of them had any major or minor bleeding except one patient who had minor oozing from the fasciotomy site. The peculiar component of HNPV venom that could make blood incoagulable without clinical bleeding, if isolated and characterised could be of major therapeutic importance in the field of anticoagulation. The coagulopathy observed in Russell's viper envenomation

is different from HNPV envenomation as it was significantly associated with low platelet count and clinical bleeding, suggesting venom induced DIC as the etiology.

Russell's viper envenomation, even after anti venom administration produced more frequent and severe complications and death than HNPV bite. Capillary leak syndrome was a unique complication that occurred only in Russell's viper bite, and it had a very high mortality rate (66.7%). In our study, all the deaths due to Russell's viper bites were due to capillary leak syndrome. Previous reports of this rare and under-recognised complication were mainly from southern India. Capillary leak syndrome was also noted in a study done in our centre in 2003-04 with high mortality rate.[7] It has been postulated that a vascular apoptosis producing component of Russell's viper venom that is not neutralised by the available ASV is responsible for this complication as it occurs even after adequate doses of anti venom administration in most cases.[10] The lack of neutralisation of such lethal constituents of Russell's viper venom by the currently available anti venom questions its efficacy. The venom obtained from a single source, the Madras Crocodile Bank situated in the state of Tamil Nadu is being used for manufacturing ASV supplied all over India and Sri Lanka. The regional differences in the venom composition of the same snake species being well known, it is highly likely that this currently used antivenom is inadequate to fully neutralise all the components of the snake venom and prevent all the complications across the different regions of the Indian subcontinent. This alarming possibility of inadequacy of the currently used antivenom could also explain the high incidence of severe acute kidney injury (KDIGO stage III), which developed in 12 out of 15 cases with envenoming due to Russell's viper even after administration of the antivenom. Out of the 14 cases of acute kidney injury following Russell's viper envenomation, 8 required hemodialysis, and 2 patients progressed to CKD. Renal biopsy done in these 2 patients revealed acute cortical necrosis. However, it was reassuring to note that the antivenom was very effective for correcting the coagulopathy in Russell's viper envenomation as the mean time taken for the normalisation of coagulopathy was only 1.4 days.

This study strongly points towards the need for developing antivenom against Hump-nosed pit viper in view of a significant number of patients developing acute kidney injury and the potential of the venom to cause renal cortical necrosis and even death. The results of various studies on HNPV from Sri Lanka also point in a similar direction.[4,11,12,13,14] This study further strengthens the already raised concern about the design of the presently used antivenom in India, due in part to recognition that many more species of venomous snakes are implicated in envenoming across India and to the low effectiveness in certain published clinical studies.[8,15]

CONCLUSION

Hump-nosed pit viper bite is an important yet under-recognized cause of morbidity and mortality in Kerala, a state in southern India. Severe acute kidney injury, compartment syndrome, potential to cause renal cortical necrosis and even death following Hump-nosed pit viper envenomation are strong reasons to change the concept of the "Big 4" to "Big 5". Anti snake venom with activity against Hump-nosed pit viper venom need to be manufactured and be made available in India, especially in southern India where these snakes are highly endemic.

List of abbreviations

AKI: Acute kidney injury
ASV: Anti snake venom
CKD: Chronic kidney disease
CPK: Creatine phosphokinase
DIC: Disseminated intravascular coagulation
KDIGO: Kidney Disease Improving Global Outcome
LDH: Lactate dehydrogenase
HNPV: Hump-nosed pit viper

Ethics approval

Ethics Committee, Government Medical College Kozhikode (Reg.No.ECR/395/inst.KL/2013) - Ref no. GMCKKD/RP/2014/31/7.

Availability of data and material

The datasets used during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

E. T. Arun Thomas and Bhagya. S have done the monitoring of the enrolled patients, data collection, analysis and prepared the manuscript. Udayabhaskaran. V and K. G. Sajeeth Kumar were the physicians who treated the enrolled patients. N. K. Thulaseedharan monitored the entire study.

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Authors' information

E. T. Arun Thomas and Bhagya. S were Junior Residents in the Department of Internal Medicine, Government Medical College Kozhikode at the time of study. Udyabhaskaran. V was the head of the Snake Bite Unit of Government Medical College Kozhikode and K. G. Sajeeth Kumar was his first assistant.

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