

EPIDEMIOLOGY AND CLINICAL PICTURE OF THE RUSSELL'S VIPER (*DABOIA RUSSELLII RUSSELLII*) BITE IN ANURADHAPURA, SRI LANKA: A PROSPECTIVE STUDY OF 336 PATIENTS

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Abstract. Russell's viper (*Daboia russelii russelii*) bite is associated with a high incidence of morbidity and mortality in Sri Lanka. Hence, this study enrolled all consecutive Russell's viper bite admissions to the 'Unit A' of General Hospital, Anuradhapura, over a two year period from January 1996, to describe the epidemiology, clinical picture, treatment and outcome. There were 336 cases which showed the following results. The male: female ratio was 5:1; 75% of patients were below the age of 40 years. Biting occurred mainly in paddy fields 41%, and on footpaths 29% at dusk or dawn. Envenoming manifested in 310 (92%) of patients as follows: local swelling 92%, local necrosis 8.9%, coagulopathy 77%, neurotoxicity 78%, nephrotoxicity 18%, cardiac effects 3-12% and myotoxicity 14%. Coagulopathy appeared within 30 minutes to 12 hours after the bite and was corrected within 1 hour to 48 hours (mode 20 hours). Neurotoxicity recovered spontaneously in 1 to 5 days (mode 3 days); however, eight patients needed mechanical ventilation. Thirteen (4%) of patients were managed with peritoneal dialysis because of hyperkalemia caused by a hypercatabolic state (7) and acute renal failure (6). The mortality rate of the series was 2.6% (9 patients). Rural dry zone paddy farmers are the common victims of Russell's viper bite in Sri Lanka and its' envenoming leads to diverse clinical manifestations. Therefore, practically feasible preventive measures should be developed to minimize the incidence of bite and an evidence based management guideline should be developed for hospital practice.

INTRODUCTION

The Russell's viper (*Daboia russelii russelii*), is a deadly poisonous snake with a well developed dentition and venom apparatus suitable for inflicting a deadly bite (De Silva, 1980). In Sri Lanka, this snake is known as the *thith polonga* and its bite is a common cause of severe and fatal envenoming. Out of the total snakebite admissions to the General Hospital, Anuradhapura, in the North Central province of Sri Lanka, 48% are due to Russell's viper bite (Kularatne, 2000). These snakes easily bite paddy farmers living in the dry zones of Sri Lanka and it appears to be an occupational hazard to this community.

The occurrence of snakebite is nothing new

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in the history of Sri Lanka. Relating back to the ancient era, the treatment modalities for snakebite are well established in traditional medicine. The most popular traditional methods of treatment include herbal preparations, the use of snakestones and reciting charms of secret holy phrases (*Manthras*) (De Silva and Urugoda, 1983). Nevertheless, a large number of patients succumbed to death (Sawai *et al*, 1983).

Current treatment methods for snakebite in Sri Lanka include administration of the polyvalent antivenom serum manufactured in India (Jeyarajah, 1984; Premawardene *et al*, 1999; Kularatne, 2000). A dramatic improvement in prognosis is achieved after treatment with the polyvalent antivenom. This has resulted in an increased demand for hospital care by the victims, without going to the traditional native practitioners. In the year 1996 alone, 27,082 victims of snakebite sought treatment in government hospitals in Sri Lanka with the mortality of 0.6% (De-

partment of Health Services, 1996). Consequently, the morbidity in hospitals has decreased.

Some aspects of the clinical manifestations of Russell's viper envenoming appear to be unique to cases in Sri Lanka as compared to those described elsewhere (Reid, 1968; Phillips *et al*, 1988). Thus, new monospecific bovine Fab fragment antivenom (*Polonga Tab*) against the local species of Russell's viper (*thith polonga*) was developed recently (Ariaratnam *et al*, 1999; 2001). The differences shown in the clinical picture of Russell's viper bite in Sri Lanka may have been due to the environmental and habitat changes of the snake.

This study therefore, aims to evaluate, in a sample of snakebite cases, the pattern of viper bite and the evolution of clinical manifestations following the bite; the responses to treatment procedures and the resulting complications; the relationship between the socio-economic status of the victim and the clinical manifestations as found in Sri Lanka. In addition, the efficacy of the Indian polyvalent antiserum in the treatment of viper bite in Sri Lanka is assessed with a view to recommending its continued use.

MATERIALS AND METHODS

This prospective study was conducted between 1 January 1996 and 31 December 1997. All admissions known to be due to Russell's viper bite, to Unit A, General Hospital, Anuradhapura were included in this study. Firstly, measures were taken to confirm that the bite was due to a Russell's viper. Secondly, the patients were treated with polyvalent serum and then kept under observation. Several assessments and laboratory investigations were done as mentioned below.

To confirm the bite was by a Russell's viper by using one of the following criteria:

1. If the dead snake was produced (it is customary for passers by to kill the offending snake), previous knowledge of physical characteristics of Russell's viper enabled identification.
2. By showing specimens of formalin preserved snakes to the patient and/or accompanying persons who witnessed the bite.
3. If both failed, definitive clinical features guided identification. Definitive clinical features mean presence of local swelling, coagulation de-

fect and neurotoxicity together in a given patient.

4. By exclusion of the other poisonous snakes in Sri Lanka: common krait and Ceylon krait (purely neurotoxic), cobra (neurotoxicity and severe local necrosis) and Merrum's hump-nosed viper (severe local swelling, coagulation defect and rarely renal damage).

Patient assessment took place at the time of the admission and thereafter, periodically until the outcome. Clinical assessment included taking down a detailed history, followed by examination for spontaneous bleeding, neurotoxicity, local swelling, and evaluation of the renal and cardiac status. Various sites, including the gingival sulci and nose were examined for spontaneous bleeding. Observations of hematuria and hemoptysis were the other two criteria for spontaneous bleeding. Criteria for the diagnosis of neurotoxicity included ptosis, ophthalmoplegia, weakness of neck and limb muscles and low tidal volume. Observations of urine output, blood pressure and pulse rate were used to estimate the renal and cardiac status. Observations of local swelling were graded as mild, moderate or severe, depending on the extent of the swelling and the severity of involvement. Swelling confined only to the bite site was graded mild; extension to more than half the limb was graded moderate; and extensive swelling with tissue necrosis was graded severe.

Similarly, neurotoxicity was graded as mild, moderate or severe. The mild group consisted of patients showing only ptosis and external ophthalmoplegia; the moderate group consisted of patients with generalized muscle weakness, including weakness of the bulbar and neck muscles, but were managed without the use of a mechanical ventilator; and the severe group consisted of patients who needed mechanical ventilation due to paralysis of the respiratory muscles assessed by measurement of Tidal Volume using a Wright respirometer at frequent intervals.

Laboratory assessment included estimations of "whole blood clotting time taking 20 minutes as a cutoff point (WBCT 20), which was measured using the bedside test by assessing the time required to clot 3ml of whole blood collected in to a clean glass tube. Additional investigations included blood urea, serum creatinine, serum electrolytes, Hb percentage, platelet count, and an ECG.

Patient management was according to the routine procedure adopted in the Unit, without any modifications. This is as follows: at the earliest sign of envenoming, both systemic effects and moderate to severe local swelling, 5 to 10 vials of Haffkine polyvalent antivenom serum (AVS) were infused over a period of one hour; repeated six hourly until the coagulation defect recovered, as measured by the WBCT20.

Resuscitation, monitoring of vital organs, and management of complications, were additional measures taken. Details including occupation, socio-economical background, age and sex of the patient; the time, place and site of the bite and the first aid measures used were recorded. All these results were recorded in a pre-designed data sheet and the recovered patients were regularly followed up after discharge to detect late sequelae.

RESULTS

Identification of the snake and biting pattern

Twenty-one percent (70 patients) made available the dead snake. The remaining 79%,

showed definitive a clinical picture supported by descriptive evidence and recognition of the responsible snake using formalin preserved specimens. In 2.7% (8 patients), the bite showed no signs of envenoming despite the presence of fang marks and the produced dead specimens of the offending snakes. The rest (97.3% of patients) had definitive envenoming.

The admissions contained 80% (267 patients) males and 20% (69 patients) females with a sex ratio of 5:1 (Table 1). Seventy-seven percent (259 patients) were between the ages of 10 and 40 with the majority 29% (97 patients) in the 4th decade of life. Russell's viper bites occurred throughout the year with two peaks corresponding to the agricultural activities of the farmers. The highest peak was seen in March-April (28%) during the paddy harvesting time and the next peak in October- November (19%) at the time of cultivation. All the bites except three occurred outdoors. These three took place when the victims were asleep (specimens of the offending snakes were available).

Forty-one percent (139 patients) of bites occurred in paddy field while the victims were engaged in agricultural work, 29% (98 patients) in

Table 1
Characteristics of patients, biting pattern and treatment.

Description	Number	%	
Sex	Male	267	80
	Female	69	20
Age- years	10 - 40	259	77
Seasonal incidence	March- April	94	28
	Oct - Nov	64	19
Place of bite	Paddy field	139	41
	Footpath	98	29
	Home garden	64	19
	Inside house at night	3	0.8
Site of bite	Foot	281	84
	Ankle-leg	41	9
	Hand-arm	10	3
Time of bite	08 00-12 00h	70	21
	18 00-22 00h	133	40
First-aid received	Washing-site	146	43
	Tourniquet	159	47
Pre-admission indigenous treatment		12	3.5
Mode of admission: direct/transfer	55/281		16/84
Direct admissions within 1 hour	28		51 (out of 55)

Table 2
Clinical and biochemical manifestations of 336 patients.

Manifestation	No. of patients (%)	Manifestation in isolation	Manifestations in combinations	No. of patients (%)
Local swelling	310 (92)	20	Local+Hem	36 (11)
Hematotoxicity	261 (77)	3	Local+Neurotoxicity	40 (12)
Neurotoxicity	262 (78)	3		
Nephrotoxicity	61 (18)		Local+Hem+Neurotoxicity	176 (52)
^a Established ARF	26 (8)	1		
Myotoxicity	47 (14)		Local+Hem+Neuro+Nephro	24 (7)
^b Cardiac effects	12-42 (3-12)			
Hyperkalemia	21 (6.5)		Hematotoxicity+Neurotoxicity	7 (2)
Fetal loss	1 patient			

(ARF- Acute renal failure; Hem-Hematotoxicity, Neuro-Neurotoxicity, Nephro-Nephrotoxicity, Local – Local swelling, n-Number of patients)

^aEstablished ARF: oliguria persisting more than 24 hours, rising serum creatinine and blood urea, enlarged or swollen kidneys demonstrated by ultrasound examination.

^bCardiac effects: reversible T wave inversion or tall T wave in anterior leads.

foot paths at dusk or dawn, 19% (64 patients) in home garden and 5% (18 patients) while trekking in forests. In 84% (281 patients), the bite was on the foot below the ankle, 3% (10 patients) at the ankle joint, 7% (25 patients) on the leg, 5% (16 patients) on the arm while harvesting paddy.

As regards the time of bite, four definitive peaks were observed, 7% (23 patients) at 08.00 to 10.00 hours, 14% (47 patients) at 10.00 hours to 12.00 noon, 24% (79 patients) at 18.00 to 20.00 hours and 16% (54 patients) at 20.00 to 22.00 hours. Daytime bites occurred mainly in the paddy fields and at dusk, the bites occurred on footpaths and roads.

All, except 20% (67 patients), have had some form of first aid before coming to hospital. Forty-three percent (146 patients) washed the site of bite with water. Tourniquets have been applied, above the site of bite without significant arterial occlusion to distal limb in 47% (159 patients). However, five patients developed rapid systemic envenoming after removing the tourniquet in hospital. Three percent (12 patients) had sought native treatment before admission to hospital. Sixteen percent (55 patients) was admitted to the General Hospital, Anuradhapura directly and the rest (67%) were transferred from a peripheral hospital after the initial treatment. Out of the direct admissions, 51% (28 patients) were admit-

ted within one hour and 81% (45 patients) within two hours after the bite respectively. Among the transfers, 27% (91 patients) reached the hospital five hours after the bite.

Clinical picture: local and systemic effects

Multisystem involvement, in the frequency given in Table 2, was evident. Local effects at the bite site occurred in 92%, hematotoxicity (coagulation-defect) in 77%, neurotoxicity in 78%, nephrotoxicity in 18%, cardiac involvement in 3-12%, myotoxicity in 14% and hyperkalemia in 6.5%.

Local effects

Out of 336 patients, local effects were seen in 92% (310 patients). The commonest was mild local swelling in 49% (166 patients), moderate in 33.7% (113 patients) and severe in 8.9% (30 patients).

Mild and moderate local swellings recovered in 4 to 7 days time. Ten patients with severe effects needed surgical intervention and four of them ended up with skin grafts. Two patients who had bites on toes were left with excruciating pain and numbness on their toes more than six months after recovery. One patient with pure local envenoming developed a deep venous thrombosis of the leg where the bite mark was found which was confirmed by Doppler ultrasound examination.

Table 3
Severity grading and complications of
envenoming local and systemic toxicity.

Parameter	Number of patients	%
Local swelling		
Mild	166	49
Moderate	133	33.7
Severe (Necrosis)	30	8.9
Hematotoxicity		
Positive WBCT20	261	77
Hematuria	81	24
Spontaneous bleeding	24	7
DIC	7	2
Intracranial bleeding	3	0.8
Neurotoxicity		
Mild	56	17
Moderate	197	58
Severe (ventilated)	8	2.4
Nephrotoxicity		
Conservatively treated	49	14.5
Peritoneal dialyzed	12	3.5
Hyperkalemia		
Hypercatabolic	9	2.6
Cardiac		
Tall T effect	42	12.5
T inversion	12	3.5
Myocardial infarction	1	0.3
Hepatotoxicity	4	1.2

Hematotoxicity

Positive WBCT20 (coagulopathy) was observed in 77% (261 patients). Out of these, 24% (81 patients) passed red urine with proved to be hematuria and hemoglobinuria. Spontaneous bleeding, such as bleeding gums, hematemesis, melena, and ecchymosis were manifested in 7% (24 patients). Development of coagulopathy occurred within 30 minutes to 12 hours after the bite. Among these, 78% (203 patients) developed coagulopathy within the first six hours.

It was observed that coagulopathy was corrected over a range of 1 hour to 48 hours (mode 20 hours) with polyvalent antivenom therapy in 94% (246 patients), as follows: 31% (81 patients) in 18 hours and 78% (203 patients) in 24 hours. Six percent (15 patients) did not respond to antivenom therapy, and the blood coagulation de-

fect lasted more than 48 hours. Three patients with severe spontaneous bleeding (hematemesis, hematuria, hemoptysis) and hypotension were treated with repetitive doses of antivenom amounting to 30 vials within six hours. Their coagulopathy was resolved in eight hours and they recovered fully.

Neurotoxicity

Neurological manifestations were observed in 78% (262 patients) in this series. The commonest manifestation was ptosis (78%) and the rest were external ophthalmoplegia in 215 (64%) and weakness of the bulbar group of muscles, and neck flexors in 22% (73 patients). Weakness of limb muscles was not a significant feature and paralysis of respiratory muscles was rare. Grades of neurotoxicity were (Table 3): mild in 17% (56 patients), moderate in 58%, (197 patients) and severe in 2.4% (8 patients). Antivenom serum was not effective in reversing neurotoxicity and the recovery was spontaneous and slow over one to five days (mode 3 days). In five days 90% (302 patients) were completely free of neurological effects.

Renal and metabolic effects

Sixty-one (18%) patients had some evidence of renal involvement and 26 (8%) had definitive acute renal failure as suggested by oliguria, high blood urea and elevated serum creatinine levels (Table 3). Twenty-one (6.5%) of patients developed hyperkalemia caused by a hypercatabolic state with normal renal function in 9 patients and established acute renal failure in 12 patients. Development of silent hyperkalemia was a problem and it was recognized as the cause of sudden deterioration in three clinically stable patients on 2nd and 3rd days after envenoming. Out of the patients with hyperkalemia, 13 (4%) needed peritoneal dialysis and the rest were managed with total restriction of potassium containing fluids, insulin-dextrose infusion and 8.4% sodium bicarbonate infusion to correct the acidosis.

Cardiac effects

Reversible repolarization abnormalities in ECG were seen in a significant number of patients. Tall 'T' waves in anterior leads were a feature in 42 (12%) of patients and inversion of the 'T' wave was seen in 12 (3%) of patients. A young girl developed a non-Q wave myocardial infarc-

tion with typical chest pain and elevated cardiac enzymes and the offending dead specimen of snake was recognized as a Russell's viper. She was treated only with AVS which she tolerated without any allergic reactions. Ten patients with 'T' wave inversion developed hypotension and were treated with inotrope (dopamine) infusion.

Myotoxicity

Forty-seven (14%) patients had generalized severe muscle pain and tenderness suggestive of a myotoxic effect of the venom. Testing for myoglobin in the blood and urine to confirm myotoxicity was not done due to lack of facilities. Myotoxicity could also have been the cause of hyperkalemia in nine patients who had no evidence of acute renal damage.

Effects on pregnancy

A 32 year old pregnant mother with a period of amenorrhea of 18 weeks developed local swelling, positive WBCT20 and mild neurotoxicity after an authenticated Russell's viper bite. She was treated with the standard dose of 10 vials of polyvalent antivenom and she made a gradual recovery. She did not developed allergic or anaphylactic reactions to antivenom. However, on 4th day she went into premature labor and delivered a dead fetus.

Complications and outcome

A total of 38 (11%) patients developed complications: profuse persistent spontaneous bleeding, thrombocytopenia and multiorgan dysfunction suggestive of severe disseminated intravascular coagulation (DIC) in 7 patients; hypercatabolic hyperkalemia in 9 patients; acute renal failure in 14 patients; intracranial bleeding leading to coma in 2 patients; hemiplegia in one; acute respiratory distress syndrome (ARDS) in association with DIC in 2 patients; hepatic failure in 4 patients and surgical emphysema in one patient. Patients with hepatic dysfunction developed icterus with tender hepatomegaly and elevated ALT, AST, alkaline phosphatase and bilirubin levels. All of them developed early encephalopathy, but recovered with appropriate treatment.

In the years 1996/1997 respectively, six (4%) and three (1.6%) patients died. Five patients died due to acute severe DIC leading to multiorgan failure, two patients died due to cardiac arrest be-

cause of silent hyperkalemia and two died due to intracranial bleeding. The duration of hospital stay of the patients ranged from one to more than five days (mode 4 days) and 79% of the patients were able to leave the hospital before six days.

DISCUSSION

Russell's viper, (*Daboia russellii russellii*) is a nocturnally active snake. It encounters man mainly on footpaths, roads and in home gardens, at dusk and early hours of night. This behavior is responsible for the regular biting pattern seen throughout the year. Daytime bites take place in paddy fields where the Russell's viper finds a secure home for sleep.

Existence of a subspecies of Russell's viper based on their morphology and the composition of the venom has been established. This fact is testified by the absence of neurotoxicity in the Indian species of Russell's viper (*Daboia russellii russellii*) (Reid, 1968; Phillips, 1988). Similarly, the Burmese Russell's viper (*Vipera russellii siamensis*) is free of neurotoxicity, but it produces fatal coagulopathy, vascular damage, shock and disseminated intravascular coagulation (Warrell, 1989; Myint-Lwin, 1985; Than-Than *et al*, 1988). Old native texts in Sri Lanka describe 15 subspecies of vipers (Pereira, 1871). A study done in 1988 described the clinical picture and detailed laboratory investigations in a series of 22 patients after Russell's viper bite in Anuradhapura, Sri Lanka, where the current study was also conducted, has reported myoglobinemia in 19 and myoglobinuria in 14 patients as a result of myotoxicity of the venom (Phillips, 1988). A similar study reported that 72.7% of patients in a series of 22 patients had generalized myalgia and some of them passed dark colored urine suspected of myoglobinuria in Sri Lanka (Jeyarajah, 1984). As a general observation, tenderness of muscles was common in our patients and only 14% had definitive severe myalgia which is far below the results of former studies. However, laboratory investigations to detect myoglobinemia were not done in the present study.

Hyperkalemia in nine patients without renal failure could have been caused by myotoxicity and a hypercatabolic state in this series of patients. Rapid development of hyperkalemia, undetected

despite a daily serum electrolyte measurement, led to two deaths in our patients. Hence, regular ECG recording is recommended to detect early hyperkalemia enabling implementation of treatment before irreversible cardiac decompensation.

This study shows the development and recovery of hematotoxicity and neurotoxicity on a detailed time scale and these facts should be useful in producing a management guideline for envenoming. In comparison to the study done in 1988, which reported hematotoxicity in 57% and neurotoxicity in 82% in a series of 22 patients (Phillips, 1988), the present study shows 77% hematotoxicity, and 78% neurotoxicity. The observation of the development of a blood coagulation defect over 1-12 hours from the time of bite highlights the importance of frequent measurements of the WBCT20, at least within the first 12 hours for early detection of envenoming. Commencement of antivenom therapy based on the earliest sign of coagulation defect (WBCT20) and neurotoxicity (ptosis or external ophthalmoplegia) is the current practice. Onset of hematotoxicity preceded the neurotoxicity in the majority of patients. Restoration of blood coagulability was permanent and occurred within one to 48 hours, after polyvalent antivenom therapy (78% in the first 24 hours). The study done in 1988 showed that the restoration of blood coagulability took place from one to 25 hours, which is comparable to our findings (Phillips, 1988). It was reported that Haffkine polyvalent antivenom was more effective in restoring a clotting defect in comparison to the newly developed monovalent (Polonga TAB) antivenom against the local species of Russell's viper (Ariaratnam *et al*, 2001). Adverse reactions to the Indian polyvalent antisera were more than those due to Polonga TAB. Furthermore, a recent study described the pattern, severity and management of reactions to Indian polyvalent antivenom in a series of 60 patients and observed that 68% showed a reaction (Kularatne, 2000).

Identifying counter measures for antivenom reactions will be a major task in future. Recent research shows a significant reduction of reactions with prophylactic administration of a low dose of subcutaneous adrenaline. However, further assurance is needed about the safety of the free use of adrenaline (Premawardene, 1999).

The onset of neurotoxicity was rapid and lasted one to five days without any obvious response to polyvalent antivenom. Similar observations have been made by previous workers (Phillips, 1988). Eight patients in our series needed mechanical ventilation.

The rate of peritoneal dialysis due to established renal failure was 3.5%, which was far below the results of a former study done in 1984 where 55% patients needed peritoneal dialysis (Jeyarajah, 1984). The reduction of severe renal failure shown in this study could be due to the early administration of antivenom, complimented by early hospital admission.

The venom effects on kidney, myocardium, liver, cerebral vessels, pregnancy and bite site are highlighted in this study clinically. Complications, such as severe disseminated intravascular coagulation lead to high mortality. A case of middle cerebral artery occlusion following Russell's viper bite was reported in 1972 (Ameratunga, 1972). A necropsy study in 1971, reported pathological changes in organs including heart, gut, adrenal gland and kidney and found extensive hemorrhage and necrosis in those organs (Karunanayake, 1971). Renal biopsies in 19 patients following snake bite in south India showed acute tubular and cortical necrosis (Shastri, 1977).

It is known that hematotoxins in snake venom consisted of procoagulants, anticoagulants, fibrinolysins, platelet factors and vessel wall factors and up to 70% of the protein content of Russell's viper venom is a mixture of isoenzymes of phospholipase A2 (Theakston and Reld, 1983; Warrell, 1989; Hutton and Warrell, 1993; Ariaratnam *et al*, 2001) The possible clinical effects of these enzymes include hemolysis, rhabdomyolysis, pre-synaptic neurotoxicity, vasodilatation and shock.

This study shows that, rural Sri Lankan folk prefer hospital based treatment rather than traditional medicine, for snakebite. First-aid methods like, washing the bite site and applying a tourniquet are practiced frequently, though the safety and reliability of the tourniquet is questionable.

In conclusion, this study showed the pattern of Russell's viper bite and the practices of a population of rural Sri Lankan folk after a bite. Clinical manifestations were documented in detail such

as severity and development in a time scale. Complications and causes of death were identified and possible remedies were suggested such as early administration of polyvalent antivenom, close monitoring of vital parameters and providing intensive care management in severe cases. Farmers should be educated to practice practically feasible simple preventive measures such as wearing shoes during paddy harvesting and avoiding walking in the dark to avoid the Russell's viper bite.

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