Cardiotoxicity of Russell's Viper venom; an overview

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Abstract

Snake bite is an important health problem and an occupational hazard in Sri Lanka. The most recent data available from the Registrar General's Office in Sri Lanka reveal that there are over 800 deaths due to bites and stings of venemous animals and insects under which snake bite is classified. Of these about 40% of deaths are due to Sri Lankan Russell's viper bites, which may be due to complications such as renal failure, neurotoxicity and respiratory failure, disseminated intravascular coagulation as well as heart failure and other cardiotoxic effects.

Very little information is available about the cardiotoxicity of Russell's viper venom or the properties of venom components, which are responsible for cardiotoxicity. This brief review attempts to present the current knowledge about Russell's viper venom and is cardiotoxic effects and also attempts to identify what additional key information needs to be obtained through research into viper venom and its cardiotoxicity in order to develop an effective antivenom.

Introduction

Sri Lanka has one of the worlds highest death rates due to snake bite. [1]. There are 92 species of snakes in Sri Lanka and only five of them are considered deadly and they are common cobra *(Naja)*, common krait *(Bangus caeruleus)*, ceylon Krait *(Bangarus ceylonicus)*, Russells viper *(Vipera russelli)* and saw scaled viper *(Echis carinatus)*[2].

Deaths from snake bites in Sri Lanka have been on the increase and the fatality rate of 5-7 per 100,000 population per year is one of the highest recorded. At present, there are more than 800 deaths recorded from snake bite every year and 26% of bites in Sri Lanka are in children under 15 years.

The Russels viper is distributed throughout the island except at extremely high altitudes and is second only to cobra in the number of deaths it causes. Majority of these bites occur in rural areas during seasonal agricultural activities or are inflicted inside or near human habitations[3]. Russell's viper bites are common and cause much morbidity and mortality and north central province in Sri Lanka including Anuradhapura[4] and mahaveli settlement areas[5]. It is found that the species of snake that caused the most number of deaths in Sri Lanka were Russell's viper accounting for nearly 40% of deaths[6].

Though toxicity wise, it is less potent than the cobra and krait, Russell's viper is the most dreaded reptile in the island[6]. It has a triangular shaped head with small scales and a distinct 'Y' shaped mark (apex pointing to the front) on it. Its nostrils are as large as the eyes and has twenty nine to thirty costal rows in the body[6]. It is nocturnal in habit and found throughout the island except in the highest altitudes. It could reach a length of about 1500mm.

Russell's viper venom and cardiotoxicity

Its venom is of great interest to laboratory scientists and clinicians. The coagulant activity of the venom was used by Warrell and others to elucidate the human clotting cascade[7]. Russell's viper venom contains many different components – toxic and non toxic, enzymatic and non enzymatic. About 90% of the dry weight of venom is made up of proteins. In some, 70% is phospholipase A_2 and other enzymes including L-aminoacid oxidase, endonuclease, phosphodiesterase, hyaluronidase and phosphomonoesterase[8]. Possible clinical effects of the enzyme include rhabdomyolysis, neurotoxicity, cardiotoxicity and vasodilation[7]. The enzyme effects of venom of some south east asian vipers vary with a certain geographical pattern[8].

Russell's viper venom is mainly vasculotoxic but neurotoxic effects have also been reported[9]. It is likely that viper toxins affect the myocardium adversely, which may cause deaths directly due to cardiotoxicity[10]. Viper bites have shown to cause myocardial infarction or myocarditis in other countries too[11]. However, some studies have not shown any pathological changes in the heart muscle following deaths from viper bites[12]. That may be because these investigators may have failed to identify them as Russell's viper or because only light microscopic studies were done.

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The cardiovascular effects of Russell's viper venom are varied. The action of Russell's viper venom on the cardiovascular system was studied by Chopra and Chowhan (1934)[13]. A small dose of the venom (0.05–0.1 mg Kg^{-1}), when injected intravenously into a cat produced a slight initial rise in blood pressure followed by a gradual fall amounting to 20-30 mmHg. With larger dose (0.2–0.5 Kg^{-1}), the fall was more pronounced and the blood pressure remained permanantly at a lower level[13].

Vick et al (1967) reported that a lethal dose (0.5 mg Kg^{-1} iv) of Russell's viper venom produced an immediate and irreversible decline in arterial pressure. There was a reduction in pluse pressure and heart rate accompained by a fall in blood pressure. The respiration was not affected during the initial post injection period. However, about 10 min after the injection, respiratory movements ceased abruptly and profound bradycardia was noted. Progressive hypoxia induced ECG changes were noted and cardiac arrest followed electrical disassociation of the heart. They also concluded that Russell's viper venom produces a pooling of blood in the hepato-splanchnic bed of the dog. Apparently, these authors did not consider the possiblity of intravascular clotting by this venom[14].

The circulatory action of the venom *Vipera russelli formosensis*, a subspecies of Russell's viper was studied in rabbits[15]. When a sublethal dose (0.05–1 mg Kg^{-1}) of the venom was injected into rabbits intravenously, an immediate fall in mean blood pressure and an increase in heart rate were observed. However, after a dose of 0.5 mg Kg^{-1}, the blood pressure fell to zero and could not be restored by adrenaline or artificial cardiopulmonary resuscitation. The haemodynamic effects of this venom were further studied after heat treatment (80° for 30 min), which destroyed the enzyme and other activities of venom[15]. The heated venom did not produce sudden death even at large doses (5-10 mg Kg^{-1}), but produced an irreversible fall in blood pressure and animals died of circulatory failure within several hours. Therefore, the hypotensive action of the venom was not affected by heat treatment. It was concluded that the cause of death is at least due to the effects of (i) the coagulant enzymes, leading to death due to intravascular clotting and (ii) the thermostable vasculotoxin producing sustained hypotension leading to delayed circulatory shock produced by peripheral vasodilation[15].

Composition and structure of cardiotoxins

Snake venoms have different types of toxins and of these, cardiotoxins are one group of toxins, which have toxic effects on many organs in the body including the heart and blood vessels[16]. Cardiotoxins are a group of very basic polypeptides present in some snake venoms and that of the cobras have been well documented[16,17]. It is believed that most snake venom cardiotoxins causes cardiomyocyte degeneration by acting on the extracellular surface of cardiomyocytes to increase cytosolic free Calcium ions[18]. The subsequent cell degeneration may result from the activities of a Ca^{+2} dependant non lysosomal proteolytic system[18]. These cardiotoxins also have effects on the skeletal muscles[19,20]. The degeneration of rat and mouse and rabbit skeletal muscles by cobra cardiotoxin has been established[21]. However, it is yet to be established whether similar effects are seen with the Russell's viper venom. However, some studies have shown that Victims of Russell's viper bites in Sri Lanka commonly develop features of generalysed rhabdomyolysis[20], and cardiac arrythmias, electrocardiographic abnormalities seen with concurrent hypotension in acutely envenomed patients with Sri Lankan Russell's viper bite suggest myocardial damage due to the toxin[21].

Previous workers, who studied the biochemical structure of many cardiotoxins[22,23,24]. Hung et al[24] separated the cobra cardiotoxins and isolated and purified these using high performance liquid chromatography. It has helped to obtain the complete sequence of the cardiotoxin analogues in the venom. Some subtle differences among these isotoxins lie in the intrinsic differences of the surface hydrophobicity of these analogues[24]. Nuclear Magnetic resonance studies of these cobra cardiotoxins show the presence of a triple and a double stranded antiparallel beta sheet[23]. However, the structural properties of cardiotoxins of Russell's viper venom has not been studied or is not documented.

Mechanism of the cardiovascular depressor action of viper venom

Viperid venoms in general have a pronounced haemodynamic activity and some of them are also blood coagulating agents[15]. The fall in blood pressure produced by most viper venoms is not central in origin since in decerebrated animals[13], exactly the same results were achieved suggesting

a peripheral effect. So far, no purified toxin responsible for the hypotensive action has been isolated from viper venoms except viperotoxin from vipera Palestnae venom[16]. A heat stable toxin acting on the splanchnic vascular bed is suggested to be the cause of circulatory failure with Russell's viper bites[17]. However, very little has been found about the cardiotoxicity of Russell's viper venom in humans and its implications in morbidity and mortality following Russell's viper bites.

Electrocardiographic studies on the effect of cobra venom were made by several workers[25,26,27], who observed that intravenous injection of cobra venom in the dogs, rabbits and guinea pigs in non lethal doses ranging from 0.2-2 mg Kg^{-1} produced ST segment depression, atrial flutter, extrasystoles, ventricular bigeminy, A-V dissociation and sinus bradycardia following iv injection. Such extensive studies on the cardiotoxicity of Russell's Viper venoms has not been undertaken and in the case of Sri Lankan Russell's viper, whose venom composition appears to be different and unique from the rest of the south asian Russell's vipers[17], much need to be researched in this area.

It is likely that similar to the cobra cardiotoxins, viper cardiotoxins are responsible for the effects on the cardiovascular system including the heart. Although disseminated intravascular clotting is rarely found in viper bites, intravascular clotting has been proved to be the cause of sudden death of animals following injection of high doses of venom. After the initial stages, viper venom shock is characterized by prolonged hypotension and heart failure. The auto pharmacologic substances such as bradykinins, histamine, serotonin, prostaglandins etc, which are released by venom enzymes such as proteinase and phospholipase A could contribute towards circulatory changes produced by viper venoms[15]. However, to what extent each of these substances may be responsible for the circulatory changes is yet to be solved. Therefore, much needs to be studied with regard to the cardiotoxicity of Russell's viper venom on the cardiovascular system.

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