

**Russell's viper (*Daboia russelii siamensis*) bite:  
venom and antivenom clearance and outcome of antivenom therapy**

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Venom and antivenom clearance of 134 Russell's viper (*Daboia russelii siamensis*) bite cases treated with a variable dose of enzyme refined equine Fab<sub>2</sub> antivenom admitted to Taungdwingyi and Thayawady hospitals from 1994-96 were studied. In mild and moderate envenomed cases, neutralisation of venom by the antivenom was achieved within ½ to 2 hours following intravenous 2-4 ampoules of antivenom and in severe envenomed cases, 8 and 4 ampoules of antivenom in ½ and 4 hours and 4 ampoules of precipitated antivenom in 12 hours. Eight out of 22 severe envenoming cases were given an additional 4 ampoules of antivenom because of persistence of incoagulable state. A similar pattern of venom neutralisation by the antivenom was observed in prospective turns severe envenoming cases treated with 4 and 8 ampoules of the antivenom. Mean plasma half-life of the antivenom given to 17 systemic envenomed Russell's viper bite with a venom level more than 60 ng/ml is 15.0±3.58 hr (mean ±SD)(range 5.74 - 34.78 hours). Neutralisation of the venom by the antivenom depends on antivenom dose and the initial venom level. A bolus dose of 8 ampoules of antivenom given to severe envenomed cases within 4 hours after the bites did not confer better protection against development of renal failure compared to those given the total in two divided doses indicating that qualitative improvement of antivenom is necessary. Use of precipitated antivenom should be discouraged. Intravenous route is preferred to intramuscular because of slow absorption of antivenom in the latter.

## INTRODUCTION

Antivenom therapy is the mainstay in management of snakebite. Myanmar Pharmaceutical Factory manufactures monospecific antivenom for treating Russell's viper and Cobra bites. It is an enzyme refined equine F(ab<sub>2</sub>) antivenom and comes in liquid and lyophilised forms. Antivenom is used throughout the country for treating specific snake bite. Early neutralization of venom by an adequate dose of potent antivenom is the aim in management of snakebite. The guidelines for antivenom therapy in management of Russell's viper (*Daboia russelii siamensis*) bite patients will help in the selection of antivenom dose based

on clinical impression. Four ampoules of antivenom are recommended for treating severe envenoming cases [1, 2]. However, antivenom is given at the discretion of the medical officers in some township hospitals. There are few reports on study of antivenom kinetics of Malayan pit viper (MPV) bites [3] and bites following *Bothrops* species [4] and on suspected Russell's viper bites [5]. However, there is insufficient information on venom and antivenom clearance studies on Russell's viper bite patients. The purpose of the present study was to determine venom and antivenom clearance of Russell's viper bite cases treated with a variable dose of antivenom and its outcome.

## MATERIALS AND METHODS

Russell's viper bite cases admitted to Taungdwingyi and Thayawady hospitals treated with 1-4 ampoules of antivenom from 1994-96 were reviewed. Routinely, clotting test was carried out on admission sample and degree of envenoming was assessed clinically. Antivenom was given at the discretion of the medical officer, in-charge of the Thayawady Hospital. Routinely, 4 ampoules of antivenom (1 ml neutralises 2 mg of venom) were given to all snakebite patients on admission to Taungdwingyi Hospital.

Two milliliters of blood were needed for clotting test that is performed at 6 hours intervals after antivenom therapy until normal clot restoration occurred in severe envenoming cases and 6 hourly for 24 hours in suspected bites. Sera were saved for determination of venom antigen levels. One milliliter of blood was taken at admission, 30 min., hourly to 4 hours, 2 hourly to 12 hours, and then at 12,16,18,24,36,48,60 and 72 hours after antivenom. Serum was collected onto filter paper, air dried and transported to Venom Research Laboratory of the Department of Medical Research (LM), Yangon for determination of venom and antivenom levels by enzyme immunoassay techniques [6,7]. A total of 118 and 100 normal healthy adults from Thayawady and Taungdwingyi respectively who came from the same locality as the snakebite victims but had no history of snakebite were screened for venom antigen. The mean absorbance value  $\pm$  2 standard deviations were taken as normal cut-off value for respective snakebite cases. Plasma half-life ( $t_{1/2}$ ) of antivenom was calculated by using the trapezoidal method [8].

Arbitrary clinical grading was made according to degree of envenoming [8] and admission venom level into: no envenoming, mild, moderate and severe envenoming and prospective turns severe envenoming cases. Clinical details of the

cases were recorded in standard forms. Samples for determination of venom and antivenom levels following intramuscular injection of one ampoule (half ampoule to each buttock) of antivenom in suspected Russell's viper bite cases were also available for study. Liquid antivenom was used in Taungdwingyi and lyophilized antivenom in Thayawady study. Intramuscular antivenom study was carried out in Thayawady.

## RESULTS

Venom and antivenom clearance of 134 Russell's viper bite cases (including 11 cases given intramuscular first aid antivenom) were available for the study.

### *Venom and antivenom neutralization following intravenous antivenom therapy*

In non-envenomed cases (n=21), antivenom was cleared from the circulation in 36-60 hours after intravenous injection of one to four ampoules of antivenom. In mild envenomed cases (n=11), (mean admission venom level 21 ng/ml, range 10-30 ng/ml) given 2-3 ampoules of antivenom took half an hour to neutralize venom antigen. In moderate envenomed cases (n=38) (venom level 44 ng/ml, range 10-65 ng/ml) venom antigen was neutralized in 1 hour after injection of 4 ampoules and half an hour in 8 ampoules of antivenom that was detectable at 36 hours after injection.

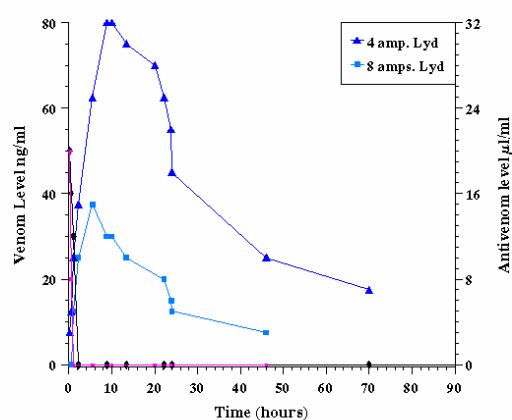


Fig.1. Venom (.....) and antivenom (—) clearance of severe envenomed Russell's viper bite cases treated with 4 and 8 amp of antivenom

In severe envenoming cases (n=35) (venom level 79 ng/ml, range 50-100 ng/ml) neutralisation of venom was faster in cases treated with 8 ampoules (1 hour) compared to 4 ampoules (4 hours) of antivenom (Figure 1).

An additional 4 ampoules of antivenom was given at 2-6 hours after the first dose in 8/22 cases because of the persistence of incoagulable state. Two from the former and one from the latter developed renal failure and one case succumbed. Mean plasma half-life ( $t_{1/2}$ ) of intravenous enzyme refined equine F(ab<sub>2</sub>) antivenom given to 17 severe envenomed Russell's viper bite cases with venom level of more than 60 ng/ml was 15.0 ± 3.58 hours (range 5.74 -34.78 hours).

It took 3 hours to clear the venom antigen by 4 ampoules of precipitated antivenom given to 3 moderate envenomed cases (venom level 44 ng/ml, range 10-65 ng/ml) and 12 hours in four severe envenomed cases (95 ng/ml)(range 80-100 ng/ml).

Intramuscular antivenom given to 8 non-envenomed and 3 mild envenomed (20 ng/ml, range 10-30 ng/ml) cases (half ampoule of intramuscular antivenom at each buttock) peaked at 8-11 hours after the injection and was detectable at 48 hours. It took 4 hours (when next measured) to clear venom.

#### *Development of renal failure*

Renal failure developed in 4/17 severe envenomed cases treated with 4 ampoules of antivenom and 5/14 cases treated with 8 ampoules of antivenom within 4 hours after the bites with 3 fatalities in the former and one in the latter. Development of renal failure could not be prevented in a severe envenomed case given 4 ampoules of antivenom as early as 50 minutes after the bite and an additional 4 ampoules of antivenom 6 hours after the first. Retrospective study of the case showed that venom antigen was cleared in 2 hours after the first dose of antivenom.

#### *Prospective turns severe envenoming group*

Mean venom level 70 ng/ml (50-90 ng/ml) was found when prospective Russell's viper bite cases turn into severe envenoming (n=22) detected by development of incoagulable state. An additional 4 ampoules of antivenom was given in 3/15 cases who still presented with incoagulable blood 6 hours after the first dose. A fatal renal failure developed in a prospective patient admitted to the hospital thirty five minutes after the bite which later turned to severe envenoming nearly 12 hours after the bite in spite of treatment with 8 ampoules of antivenom. Venom and antivenom clearance of two prospective turns severe envenoming cases given subsequent second dose of antivenom at 2 and 6 hours after the first (4 ampoules) was shown in Figure 2.

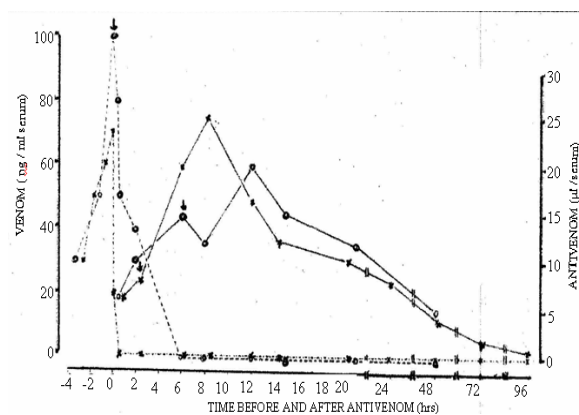


Fig. 2. Venom(----) and antivenom (—) clearance of 2 prospective turns severe envenoming Russell's viper bite cases given 2nd dose of antivenom at 2 and 6 hours after the first dose of 4 amps. antivenom

## **DISCUSSION**

Time taken for neutralisation of venom by antivenom depends on antivenom dose and the initial venom level. Rapid venom neutralisation is achieved in moderate and severe envenoming cases given 8 ampoules of antivenom compared to that of four. Mild envenoming cases could be managed with 2-3 ampoules, moderate with 4 ampoules and severe with 4 to 8 ampoules of antivenom. The elimination half-life

of the three commercial monospecific antivenom in 26 patients systemically envenomed by Malayan pit viper (*Calloselasma rhodostoma*) in southern Thailand [3] ranged from 45.5 to 96 hours. An earlier study on antivenom clearance of 4 ampoules of lyophilized antivenom on six suspected Russell's viper bite cases using radio-immunoassay technique was 36 hours (26-50 hours) [5]. Mean plasma half-life ( $t_{1/2}$ ) of 17 severe envenomed Russell's viper bite cases with venom level more than 60 ng/ml given 4 ampoules of enzyme refined equine antivenom was  $15.0 \pm 3.58$  hours (range 5.74 -34.78 hours). The difference could be attributed to the use of data based on a few sampling points in the former.

Neutralisation of venom by 4 and 8 ampoules of antivenom in severe envenomed cases show that 4 ampoules of antivenom is sufficient for treating these cases, since venom is cleared in 2-4 hours after therapy with no resurgence of the venom. It is assumed to be adequate for most severe envenoming cases if given in the early hours after the bite except in some cases [11]. However, giving additional antivenom in cases who still have incoagulable blood after 4 ampoules of antivenom is justified in the sense that venom-induced effects are not completely neutralized yet. Failure in clot restoration after 2 doses of 4 ampoules of antivenom in severe envenoming cases has also been reported [12]. The observation calls for improvement in quality of antivenom. It is suggested that in order to achieve early neutralization of venom-induced effects in severe envenoming cases with systemic complications, a bolus dose of 8 ampoules should be given rather than giving the total in divided doses.

An earlier study showed that a bolus dose of 4 ampoules of antivenom given to severe envenoming Russell's viper cases in the field soon after bite has a better chance of preventing development of renal failure than

giving the total in divided doses [10]. In the present hospital-based study, no difference in preventing development of renal failure was observed in severe envenomed cases treated with a bolus dose of 8 ampoules or the total given in two divided doses within 4 hours after the bite. However, fatality rate was higher in the latter compared to the former. The difference between the two studies could be due to the fact that 57% of the earlier study cases received antivenom within 1 hour after the bites in the field. A severe envenoming case treated with 4 ampoules of antivenom as early as 50 minutes after the bite plus another 4 ampoules of antivenom after 6 hours failed to prevent onset of renal failure. It has been documented that administration of 4-10 ampoules of antivenom within 4 hours after Russell's viper bite to the victims did not prevent development of renal failure [9]. It is speculated that antivenom raised with potent anti procoagulant and nephrotoxic factors may be more effective.

A slow build-up of incoming venom released from venom depot in prospective turns severe envenoming cases should be neutralized rapidly and early with an adequate amount of antivenom in order to minimize prolonged exposure of venom-induced effects on vital organs. Development of systemic complications, renal failure and death has been reported from this group. Quantitation of venom antigen using dipstick [13] will be of value in monitoring the trend of venom level in these cases along with the clotting test [14] and antivenom could be given early or before clotting test detected incoagulable state.

Since local health workers (midwives) are permitted to give antivenom intravenously, this route is preferred to intramuscular since rapid neutralisation of venom by antivenom is vital in management of snakebite. However, intramuscular anti-venom could be used as first aid in bites occurring at a distance from the health centre where giving

intravenous route of antivenom is not available. It should be given in antero lateral aspect of the thigh instead of buttock where absorption is delayed. Again poor or lack of venom neutralizing efficacy of precipitated antivenom was documented and its use should be discouraged since it gives a false sense of security [15]. Moreover, it is unethical to give precipitated antivenom. Proper storage of liquid antivenom in the absence of cold chain should be promoted [16].

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