The Myanmar Health Sciences Research Journal, Vol. 15, No. 1-3, 2003

Evaluation of pre hospital antivenom in management and outcome of Russell's viper (*Daboia russelii siamensis*) bite cases admitted to Taungdwingyi Hospital

*Tun Pe, *Aye Aye Myint, **Khin Aye Kyu & ***Sann Mya

*Venom Research Laboratory, Department of Medical Research (Lower Myanmar)
** Department of Railway, Taungdwingyi
***Institute of Medicine (2). Yangon

Evaluation of pre hospital antivenom in management and outcome of 61 Russell's viper (*Daboia russelii siamensis*) bite cases admitted to Taungdwingyi Hospital from August 1996 to October 1997 was carried out. The first dose of antivenom (1-4 ampoules) was given at rural health centers at 1.10h ± 13 min. after the bite and remaining 0-3 ampoules totaling 4 ampoules at admission 3h ± 23min. after the first dose. Majority of the cases (75%) received liquid antivenom. Venom antigen was not detected in admission post antivenom samples in 23% , moderate envenoming in 47% and severe envenoming in 30%. A venom level of 10-40ng/ml was detected at 5h in moderately envenomed cases given 1-2 ampoules of antivenom within 3h after the bite and 10-80ng/ml in severe envenomed cases within 6h after 1-5 ampoules of antivenom. Delay in venom clearance is probably related to quality and dose of liquid antivenom used. Five out of 24 moderately envenomed cases developed severe envenoming and complications. Systemic complications developed in 5 out of 9 severe envenomed cases (5 fatality) given 1-2 ampoules antivenom within 3h and second dose within 5h and in 3 out of 9 of the severe envenomed cases (3 fatality) given 3-5 ampoules antivenom. It is highlighted that a single early bolus dose of 4 ampoules of antivenom is more effective in preventing onset of systemic complications and fatality than giving the total in two divided doses. Since early administration of antivenom in the field plays an important role in management of snakebite, arrangement should be made for the availability of antivenom at rural health centers and local health workers should be trained and legislated to give intravenous antivenom according to the guidelines after assessing degree of envenoming by performing clotting test. Rapid quantitation of venom antigen by dipstick will be helpful in the field for selection and estimation of antivenom dose.

INTRODUCTION

Russell's viper (*Daboia russelii siamensis*) bite is an occupational hazard of our farmers. Most bites occur in the paddy field while at work. Because of delay in transporting victims to nearest health centers, some patients were severely envenomed by the time they seek medical treatment. Early and adequate administration of antivenom plays an important role in management of Russell's viper bite patients. Practice of giving antivenom in the villages of Taungdwingyi, Danuphyu and Yaekyi was reported [1]. Preliminary study on clinical significance of early antivenom on limited numbers of Russell's viper bite patients by our group indicated that early antivenom combined with local compression immobilization first-aid technique was found to prevent development of systemic complications [2].

Administration of 4-10 ampoules of monospecific antivenom within 4 h after Russell's viper bite did not prevent development of renal failure had been reported [3]. This study concerns with evaluation of pre hospital antivenom administered in villages in management and outcome of Russell's viper bite patients.

MATERIALS AND METHODS

While conducting snakebite research in different township hospitals [1], we came across a number of snakebite victims received pre hospital antivenom in the villages. We took the opportunity to evaluate the early intravenous antivenom in management and out come of Russell's viper bite cases. Since farmers are aware of the importance of receiving early antivenom in management of snakebite, they stock antivenom at room temperature in the villages for emergency use. Because of health education, local health workers are aware of using antivenom in management of snakebite and the role of clotting test in assessing degree of envenoming before giving antivenom. Snakebite cases given a variable dose of antivenom at the villages and then admitted to Taungdwingyi hospital during August 1996-October 1997 were studied.

On admission, routinely a total dose of 4 ampoules of antivenom was given to all snakebite cases. Twenty minute clotting test was performed on admission post antivenom samples in order to assess the clotting status and degree of envenoming. Serum was saved onto filter paper strips, air dried, sealed in a plastic bag and transported to the Venom Research Laboratory, Department of Medical Research (Lower Myanmar), Yangon for determination of venom antigen level by Enzyme immunoassay technique [4]. Clinical details of the patients were recorded in standard proforma.

Serum venom antigen levels were determined by double antibody sandwich enzyme immunoassay technique (EIA) method described by Voller *et al.* (1979) [5]. One hundred normal healthy adults from the same locality as the snakebite victims but had no recollection of snakebite were screened for venom antigen by EIA. The mean absorbance value ± 2 Standard deviations was taken as normal cut-off value. Details were described in our earlier paper [4].

RESULTS

A total of 61 snakebite cases given 1-5 ampoules of antivenom in the villages were available for the study. Majority of the victims (74%) were males of 31 years old (14-60yr) who were bitten while at work (54%) and walking home or in the field (46%). The victims received 1-5 ampoules of antivenom at 1.10h ± 13min (010-430h) after the bites and remaining 0-3 ampoules (totaling 4 ampoules) on admission 3h ±23min (045-1020h excluding one in 25h) after the first dose. Two severe envenomed cases treated with 4 ampoules antivenom received an additional 4 ampoules of it at the hospital.

Venom antigen levels after the first dose of antivenom

Determination of admission post ASV venom antigen levels of 61 snake bite patients showed no antigen was detected in 23% (n14), 16.4ng/ml (10-40ng/ml) in 47% (n29) of the patients presented with clottable blood ("local") and 47.2ng/ml (10-80ng/ml) in 30% (n18) of severe envenomed cases.

A venom level of 10-40ng/ml was detected up to 5h in "local" envenomed cases given 1-2 ampoules of antivenom within 3h after the bite (Table 1) and 10-20ng/ml in the cases given 3-4 ampoules of antivenom within 4h. Venom antigen 10-80ng/ml was detected up to 11h in severe envenomed cases (n18) given 1-5 ampoules of antivenom within 5h after the bites.

Table 1. Clinical details, antivenom timing and development of systemic complications of 61* Russell's viper bite cases

Degree of envenoming	ASV 1st dose (h)	Timing 2nd dose (h)	No: of Subjects	ASV 1st dose (amp)	ASV 1st dose (h)	ASV 2nd dose (h)	Venom level after 1st dose ASV (ng/ml)	Systemic envenoming (n)	Systemic complications	Fatality
Clotted (local)	3	5	25	1-2	052 (010-230)	2.12 (045-445)	17.4 (10-40)	5	S-1 SA-2 SAB-1	0
	4	4	4	3-4	1.21 (015-330)	2.55 (105-400)	12.5 (10-20)	1	SA-1	0
Nonclot (Systemic)	3	5	9	1-2	1.27 (030-300)	4.06 (230-440)	51.2 (10-80)	9	SA-2 SAB-2 SAR-2	5
	5	11	9	3-5	3.27h (030-430)	6.14 (210-1020)	48.8 (40-70)	9	S-2 SA-1 SAR-1	3

* No venom antigen was detected in 14 admission post antivenom cases.
ASV=antivenom, S=shock, SA=shock+albuminuria,
SAB=shock+albuminuria+haemorrhagic manifestations, SAR=shock+albuminuria+renal failure

Clotting test and antivenom therapy at the villages

Clotting test was carried out on only 19 out of 61 cases (31%) in rural health centres before giving antivenom. Eleven were "locally" envenomed and 8 were severely envenomed. Of 11 "local" envenomed cases, nine received 2 ampoules and the remaining 3 ampoules. Of eight severe envenomed cases, one ampoule was given to one, two ampoules to 3, four ampoules to 3 and five ampoules to one.

Forty-six cases (75%) received liquid, 14 (23%) lyophilised and one (2%) mixed (liquid and lyophilized) antivenoms. The antivenom was administered intravenously at rural health center (60, 98%) and at home (1, 2%).

Thirty-nine percent (24) received the first dose of antivenom within 30 minutes following the bite, 57% (35) in one hour, 87% (53) in 2 hours, 93% (57) in 3 hours, 98% (60) in 4 hours and 100% (61) in 430 hr.

Venom neutralization following liquid and lyophilized antivenom

Since venom antigen could be detected in 4 "local" and 4 severe envenomed cases following 1-4 ampoules of lyophilized antivenom, no attempt was made to compare its neutralizing efficacy with that of liquid antivenom.

Clinical details of the cases

Clinical details, antivenom timing and development of systemic complications of the cases are presented in Table 1.

"Local" envenoming cases

In 29 "local" envenoming cases treated with 1-4 ampoules of antivenom, 6 developed severe envenoming (5 with complications) during the course of treatment (Table 1). Shock developed in one, shock plus albuminuria (n3) and shock plus albuminuria plus haemorrhagic manifestations (n1) such as haematemesis, malena, haematuria and shock on day 2. All recovered from shock.

Severe envenomed cases

Of 18 severe envenomed cases, 9 received first dose of antivenom (1-2 ampoules) within 3h and second dose in 5h. From this group, 6 developed systemic complications such as shock plus albuminuria (n2), shock plus albuminuria and renal failure (n2), shock plus albuminuria plus haemorrhagic manifestations (n2) such as gingival bleeding (n2), haematemesis, malena, haematuria, epistaxis (n1) and sub-conjunctival haemorrhage (n2). Five died of shock and renal failure.

In the remaining 9 severe envenomed cases treated with 3-5 ampoules of antivenom within 5h, four developed systemic complications. Shock (n2), shock plus albuminuria (n1), shock plus albuminuria and renal failure (n1), of which 3 died of shock and renal failure.

Systemic complications developed in the latter group were milder and less in number than the former. It is noteworthy that a patient given three ampoules of antivenom 30 minutes after the bite and second dose one ampoule 240h after the first could not prevent development of systemic complications, shock, albuminuria, renal failure and death.

Clot restoration time of systemic cases treated with 4 ampoules was 16.8h (6-30h).

DISCUSSION

The study highlights the value of early antivenom in management and prevention of development of complications of Russell's viper bite cases. It is learnt that 39% of the victims received antivenom within 30 minutes after the bite and twenty minute whole blood clotting test could be carried out in the rural health centre. Four severe envenomed cases were given 1- 2 ampoules of antivenom instead of 4 ampoules and more than 4 ampoules of antivenom should have been given to severe envenomed cases with complications where only 2 cases received an additional 4 ampoules of antivenom. It is probable that the dispensers were giving antivenom as an first aid to the snakebite victims rather than rendering treatment to them. It is highlighted that these cases should be treated early with adequate dose of antivenom in order to prevent development of systemic complications.

The incidence of "local" envenoming in the present study (based on post antivenom levels) (47%) is high compared to other studies (based on pre antivenom levels) (23-26%) [3, 6]. Venom antigen of local envenoming (10-20ng/ml) cases are usually cleared in 2h after antivenom [7] whereas in the present study, a venom level of 10-40ng/ml was still detectable 5h after antivenom suggesting that degree of envenoming in these "local" envenomed cases amount to **moderate envenoming** since 5 cases from this group later developed severe envenoming and complications. It is suggested that a proportion of these moderately envenomed cases could be detected early if clotting test and rapid quantitation of venom antigen by dipstick [8] (if available) could be performed in the field on all snakebite cases in order to assess degree of envenoming and early institution of appropriate dose of antivenom.

Failure of venom clearance in systemic cases up to 11h after 4 ampoules of antivenom and poor clot restoration of antivenom treated systemic cases suggested that liquid antivenom used have poor neutralizing efficacy of procoagulant activity of the venom. Use of lyophilized preparation of antivenom or proper storage of antivenom in the absence of cold chain [9] in the villages should be practiced.

Systemic complications developed in 67% of severe envenomed cases treated with 4 ampoules of antivenom in two divided doses within 440h with 56% mortality whereas

38% of severe envenomed cases treated with a bolus dose of 4 ampoules within 4h developed complications with 25% fatality. Our observation is in agreement with hospital based study carried out in Tharawaddy [3] and Taungdwingyi [6] where 38% (8/21) and 44% (7/16) severe envenomed cases treated with a bolus dose of 4 ampoules of antivenom developed complications respectively. It is highlighted that early administration of a single bolus dose of 4 ampoules of intravenous antivenom to severe envenomed cases (within 4h after the bite) in the field will have a better chance of preventing development of systemic complications and fatality compared to those given the total in two divided doses. Moreover, if antivenom therapy is combined with local compression immobilization technique [2] it will further proved to be effective in preventing development of complications.

Since early and adequate administration of antivenom to snakebite patients plays an important role in management of snakebite, arrangement should be made for the availability of antivenom at the rural health centers and local health workers should be legislated to give intravenous antivenom in the field after giving them a full comprehensive training course on first aid management of snakebite in the field including indication for antivenom therapy and management of its untoward effects, method of assessment of degree of envenoming by performing clotting test and (if available) use of quantitation of venom antigen by dip stick [8] and storage of antivenom in the absence of cold chain in the villages [9] and promotion of wearing protective boots and gloves [10] by the farmers.

REFERENCES

1. Tun Pe, Aye Aye Myint, Sann Mya, Khin Aye Kyu, Kyaw Than, Aung Myint, Tint Lwin, Myint Soe and Min Than. A study of Russell's viper (*Daboia russelii siamensis*) bites from six township hospitals. Myanmar Health Research Congress 2000 abstract p 74.
2. Tun Pe, Khin Aye Kyu, Aye Aye Myint, Nu Nu Aung, Sann Mya and Tin Oo. Clinical significance of early intravenous antivenom in Russell's viper bite cases in Taungdwingyi district: a preliminary study. *Myanmar Health Science Research Journal* 1998; 10: 22-25.
3. Myint Lwin, Warrell, DA., Phillips, RE., Tin Nu Swe, Tun Pe, and Maung Maung Lay. Bites by Russell's viper (*V.russelli siamensis*) in Burma: Haemostatic, vascular and renal disturbances and response to treatment. Lancet, 1985; ii:1259-1264.
4. Tun Pe, Ba Aye, Aye Aye Myint, Tin Nu Swe and Warrell, DA. Bites by Russell's vipers (*Daboia russelii siamensis*) in Myanmar: effect of the snake's length and recent feeding on venom antigenaemia and severity of envenoming. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1991; 85: 804-808.
5. Voller, A., Bidwell,D. & Bartlett, A. Enzyme-linked immunosorbent Assay (ELISA). A guide with Abstracts of Microplate Applications. 1979. Dynatech Europe.
6. Sann Mya, Tun Pe, Aye Aye Myint, Nu Nu Aung, Khin Aye Kyu and Tin Oo. Russell's viper bites in Taungdwingyi hospital: clinical features and response to antivenom. *Myanmar Health Sciences Research Journal.* 1998;10: 26-30.
7. Tun Pe, Aye Aye Myint, and Nu Nu Aung. Antivenom abuse: a review of antivenom policy in management of Russell's viper bite cases of six township hospitals. *Myanmar Health Sciences Research Journal.* 1999; 11(1-3) : 33-37.
8. Aye Aye Myint, Tun Pe, and Tin Zar Maw. Development of a rapid dipstick dot blot immunoassay for detection of Russell's viper (*Daboia russelii siamensis*) venom. Myanmar Health Research Congress 2000 abstract p 83.
9. Aye Aye Myint, Tun Pe, Kyi May Htwe and Khin Aye Kyu. Potency assay of the liquid Russell's viper (*Daboia russelii siamensis*) antivenom stored at different environment. *Myanmar Health Sciences Research Journal* 1998; 10: 131-134.
10. Tun Pe, Aye Aye Myint, Khin Aye Kyu and Maung Maung Toe. Acceptability study of the fang proof protective boots among farmers of Taungdwingyi town ship. *Myanmar Health Sciences Research Journal* 1998; 10:57-60.