

Efficacy and safety of snake antivenom therapy: experience of a regional hospital

抗蛇毒血清療法的功效及安全度：一所區域性醫院的經驗

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Introduction: Snakebite is a commonly encountered envenomation emergency in the rural areas of Hong Kong. The majority of cases do not warrant antivenom therapy. We looked into those receiving antivenom to enhance the understanding of the results of antivenom therapy. **Methods:** This was a retrospective review of the snakebite cases treated with antivenom in Tuen Mun Hospital from 1st January 2000 to 31st August 2005, focusing on both the therapeutic and side effects of the antivenom. **Results:** Twelve patients were identified. All had local symptoms of swelling or numbness. Two of them subsequently developed skin necrosis requiring operative treatment. Thrombocytopenia was less amenable to correction than prolonged INR. No early or late allergic reactions were observed. **Conclusion:** Because of the small number of cases, the apparent safety of the antivenoms in the current review warrants larger trials in future. (*Hong Kong j.emerg. med.* 2006;13:70-78)

序言：蛇咬是香港鄉村地區常見的注毒急症。大部份的個案不需要抗毒血清治療。我們審查接受抗毒血清的個案，以增進對抗毒血清療法效果的理解。**方法：**這是一個回顧性的研究，覆查 2000 年一月一日至 2005 年八月三十一日在屯門醫院因蛇咬而接受抗毒血清治療的個案，並集中在抗毒血清的療效及其副作用方面。**結果：**共識別出十二名病者。全部有局部腫脹或麻痺的症狀。其中兩名病者隨後發展至皮膚壞死而需要手術治療。血小板減少比延長了的國際標準化比率（INR）較難矯正。察覺不到有早期或後期的過敏反應。**總結：**這次審查中抗毒血清表面上是安全，但因為個案數目太少，仍需要將來較大型的測試研究。

Keywords: Anaphylaxis, antivenins, blood coagulation disorders, snakebite, venoms

關鍵詞：過敏症、抗毒血清、凝血病、蛇咬、毒液

Introduction

Snakebite is a common medical problem in Hong Kong although the incidence appears falling due to the rapid urbanisation. According to our experience, local fatalities are rare nowadays especially if the victims

receive prompt medical care. However, morbidities such as local wound complications and haematological dysfunctions are not infrequent. Snake antivenom remains the most specific treatment for many decades but its precise therapeutic role is difficult to evaluate because of multiple confounding factors, including different venom load, venom potency, health status of the patients, timing and dosage of the antivenom, premedications for antivenom and concomitant medical treatments.

Tuen Mun Hospital (TMH) is an acute regional hospital of 1,600 beds with more than 200,000 emergency attendances a year from the approximately

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1,000,000 populations living in the northwestern part of the New Territories of Hong Kong. The number of emergency attendances in TMH has stayed the highest among all the hospitals in Hong Kong in the last few years. Coupled with the mixed rural and urbanised living settings of the populations it serves, it is not surprising that the numbers of snakebite victims and prescriptions of snake antivenom at TMH are more than those of the other hospitals. In the present review, we report and discuss the experience of snake antivenom usage in TMH.

Methods

The data of all snakebite victims attending the emergency department and/or admitted to the TMH for the period from 1st January 2000 to 31st August 2005 were retrieved. The medical records of the victims receiving snake antivenom were reviewed in details with respect to the age and sex of the victims, species of snake, time of bite, clinical and laboratory complications, dosage and timing of antivenom, premedications, places of antivenom administration and progress after antivenom therapy. The data of the cases with and without antivenom were entered into the computer software SPSS 12 for Windows and compared statistically. Mann-Whitney test was utilised for analysis of continuous variables, with $p < 0.05$ regarded as statistically significant.

Results

Within the study period, there were 192 cases of snakebite. Five types of antivenoms, the green pit viper, cobra and king cobra antivenoms from the Thai Red Cross Society in Thailand, the *Agkistrodon halys* and *Naja naja* antivenoms from the Shanghai Institute of Biological Products of the Ministry of Health of China, were given to 12 patients (Table 1).

The clinical features of the patients before and after antivenom administration are listed in Table 2. All the bites were on the limbs and the bamboo snake (*Trimeresurus albolabris*) and the Chinese cobra (*Naja*

naja atra) were the culprits of 7 and 5 cases respectively. The proximal extent of limb swelling, which was present in 11 patients, was particularly marked in cases of bamboo snakebite. Ecchymosis occurred early in three cases of bamboo snakebite but late after antivenom treatment in one case of Chinese cobra bite. Paraesthesia around the wound was noticed in all cases soon after the Chinese cobra bite. The victim in case 5, a case of bamboo snakebite with green pit viper antivenom therapy, developed compartment syndrome of the right hand and small areas of gangrene over the right middle finger, requiring fasciotomy, debridement and skin graft. Another case of gangrene (case 11) involving the dorsum of the foot and the lower leg despite antivenom therapy, was due to Chinese cobra bite. Initially, king cobra antivenom was administered basing on the result of identification by the patient with the help of the snake photo guidebook. However, the dead snake specimen was available later and proved to be a Chinese cobra. Cobra antivenom was then infused at 11 hours after the bite. Even with different surface areas involved, the depth of gangrene in these two cases was limited to the dermal layer only, sparing the muscles beneath the fascial plane. Another Chinese cobra bite victim was found to have the onset and progress of ecchymosis after antivenom treatment and he later discharged himself against medical advice. The rest of the cases showed gradual resolution of the limb symptoms after antivenom treatment. In case 7, the result of antivenom therapy was very impressive. Within several minutes of completing the infusion, the progress of the swelling, which had been spreading quickly from the hand to above the elbow in three hours, stopped. In the Chinese cobra bite cases showing proximal extension of paraesthesia, no deterioration

Table 1. Number of patients receiving the different types of antivenom

Type of antivenom	Number of patients
Green pit viper	4
<i>Agkistrodon halys</i>	4
Cobra	4
<i>Naja naja</i>	1
King cobra	1

Table 2. Treatment response, premedication, skin test and place of giving antivenom in the 12 antivenom-treated cases

No.	Sex	Age	Snake	Site of bite	Complications before antivenom		Type, dose, & post-bite time of antivenom	Progress at post-antivenom time		Premedication	Skin test	Place of giving antivenom
					Local	Haematological		Local	Haematological			
1	M	47	B	R arm	R arm swelling	Nil	AH 1 vial at 5 h	Swelling improved after 16 h	Not applicable	H, A	Negative	GW
2	M	51	B	L ankle	Swelling up to leg, local ecchymosis	INR >4.5	AH 1 vial at 24 h	Swelling improved after 6 h	INR 1.6 after 5 h	H1, H, A	Nil	GW
3	M	46	B	R hand	Swelling up to axilla	INR 1.2, Plt 37	AH 3 vials at 24 h	Swelling improved after 49 h	INR 1.3, Plt 66 after 6 days	H1, H, A	Negative	ICU
4	F	5	B	R foot	Swelling up to thigh, local ecchymosis	INR 1.1	AH 1 vial at 3 h, 1 more at 92 h, GPV 5 vials at 137 h	Swelling improved after 56 h	INR >4.5 after AH, 1.2 18 h after GPV	H1	Borderline	GW
5	M	2	B	R middle finger	Swelling up to hand, local ecchymosis	INR >4.5	GPV 2 vials at 13h, FFP at 15 h	Swelling progressed, R middle finger gangrene after 12 h	INR 1.2 after 5 h	H1	Nil	ICU
6	M	47	B	L ankle	L ankle swelling	INR 1.1, Plt 52	GPV 2 vials at 25 h	Swelling improved after 41 h	INR 1 & Plt 82 after 18 h	H1, H	Nil	GW
7	M	43	B	L hand	Swelling up to elbow	Nil	GPV 4 vials at 3 h	Swelling progress halted in minutes	Plt 68 after 13 h	H1, H	Nil	ED
8	M	20	CC	L big toe	Foot swelling, numbness up to leg	Nil	C 2 vials at 2 h	Swelling & numbness improved after 18 h	Not applicable	H, A	Nil	GW
9	M	34	CC	R ankle	Swelling & numbness of R ankle & foot	Nil	C 2 vials at 4 h	Ecchymosis after 19 h	Not applicable	H1, H	Nil	ED
10	F	44	CC	R index finger	Numbness up to forearm	Nil	C 2 vials at 3 h	Numbness subsided after 10 h	Not applicable	H1, H	Nil	ED
11	F	15	CC	L foot	L foot swelling & numbness	Nil	KC 3 vials at 3 h, C 2 vials at 11 h	Swelling progressed, L foot gangrene 13 h after C	Not applicable	H1	Nil	ICU
12	M	44	CC	L thumb	Swelling & numbness up to forearm	Nil	NN 1 vial at 6 h	Swelling & numbness improved after 2 h	Not applicable	Nil	Nil	GW

A: adrenaline; AH: *Agkistrodon halys*; B: bamboo snake; C: cobra; CC: Chinese cobra; ED: emergency department; FFP: fresh frozen plasma; GPV: green pit viper; GW: general ward; H: hydrocortisone; H1: H₁ antihistamine; ICU: intensive care unit; INR: international normalised ratio; KC: king cobra; L: left; NN: *Naja naja*; Plt: platelet count (unit: x 10⁹/L); R: right.

occurred after antivenom treatment and none of them had neurotoxicity affecting the respiratory muscles or cranial nerves.

Coagulation dysfunctions or thrombocytopenia, all without causing systemic haemorrhage, were present in 6 out of the 7 cases of bamboo snakebite, and none of those of Chinese cobra bite. Fibrinogen level was not consistently checked so its results were not presented. *Agkistrodon halys* antivenom was delivered to counteract the clotting defects in three cases. It significantly improved the INR after 5 hours in one case, but it failed to correct the prolonged INR and thrombocytopenia in one case, and the prolonged INR in another. In the last case, infusion of five vials of green pit viper antivenom resulted in nearly normal INR after 18 hours. The prolonged INR in case 5 was significantly improved after the use of green pit viper antivenom immediately followed by fresh frozen plasma (FFP). The green pit viper antivenom, however, did not affect the persistence or development of thrombocytopenia in two patients. After excluding the inconclusive case 5, five cases received antivenom and

one of them received both *Agkistrodon halys* and green pit viper antivenoms. The successful rate of *Agkistrodon halys* and green pit viper antivenoms in normalising INR was 33% (1 out of 3 cases) and 100% (1 case only) respectively, while all the 3 cases of thrombocytopenia were antivenom resistant.

Clotting (including INR, APTT and platelet count) dysfunction was present in 11 cases (4 bamboo snakebite and 7 unknown snakebite) not given antivenom (Table 3) compared with 6 cases given antivenom (Table 4). Both groups were compared for the impact of antivenom on the restoration of normal clotting. In the group without antivenom treatment, cases excluded for analysis were case 1, 8 and 9 because of inadequate follow up for normalised clotting, as well as case 10 and 11 because of possible FFP effect. Within the antivenom group, case 3, 6 and 7 were considered treatment failure and the resolution of prolonged INR in case 5 was probably partially contributed by FFP. Case 2 and 4 of the antivenom group were used to calculate the effect of successful antivenom therapy on the normalisation time of the

Table 3. Progress of clotting dysfunction in cases not given antivenom

Case no	Clotting dysfunction onset at post-bite time	Normal or latest known clotting at post-bite time	Time for clotting normalisation
1	7 h Plt 128 64 h INR 1.2	64 h Plt 75 88 h INR 1.1	24 h (INR only), Plt not further checked
2	18 h INR 1.1 45 h Plt 89	103 h INR 1.1 117 h Plt 146	72 h
3	5 h APTT 50.3	41 h APTT 30.3	36 h
4	74 h Plt 52	434 h Plt 200	360 h
5	4 h INR 1.1 APTT 71	11 h INR 1 APTT 29.2	7 h
6	93 h Plt 91	1068 h Plt 163	975 h
7	37 h Plt 110	229 h Plt 272	192 h
8	6 h INR 1.1	95 h INR 1.2	Prolonged INR up to 89 h
9	4 h INR 1.1	29 h INR 1.2	Prolonged INR up to 25 h
10	5 h INR >4.5 APTT >150 36 h Plt 37	34 h INR 1.3 APTT 30.3 FFP at 30 h	4 h (INR) after FFP, Plt not further checked
11	6 h Plt 113 INR >4.5	69 h Plt 40 114 h INR 1 FFP at 103 h	11 h (INR) after FFP, Plt not further checked

APTT: activated partial thromboplastin time; FFP: fresh frozen plasma; INR: international normalised ratio; Plt: platelet count

clotting parameters, but the effect was statistically insignificant ($P=0.096$) (Table 5).

There was one case of Chinese cobra bite causing skin necrosis in the absence of antivenom therapy. The magnitude and time course of local swelling in the antivenom and non-antivenom groups were generally

not precisely documented, hence comparison was not attempted.

Antivenom was given in the general ward in 6 cases, in the intensive care unit in 3 cases and in the resuscitation room of the emergency department in 3 cases. Hypersensitivity test of the *Agkistrodon halys*

Table 4. Progress of clotting dysfunction in cases given antivenom

Case no*	Clotting dysfunction at post-bite time	Antivenom at post-bite time	Time (post-antivenom) for any clotting normalisation
2	22 h INR >4.5 ← 24 h AH 28 h INR 1.6	24 h AH	4 h
3	5 h Plt 91 10 h INR 1.2 23 h Plt 37 ← 24, 42, 43 h AH 165 h INR 1.3 Plt 66	24, 42, 43 h AH	Abnormal Plt & INR 122 h after antivenom
4	2 h INR 1.1 ← 3, 92 h AH 131 h INR >4.5 ← 137 h GPV 155 h INR 1.2	3, 92 h AH 137 h GPV	18 h after GPV
5	12 h INR >4.5 ← 15 h FFP 18 h INR 1.2	13 h GPV 15 h FFP	5 h but uncertain concomitant FFP effect
6	3 h Plt 32 21 h INR 1.1 24 h Plt 52 ← 25 h GPV 43 h INR <1 Plt 82	25 h GPV	Persistent thrombocytopenia 18 h after antivenom
7	1 h Plt 211 ← 3 h GPV 16 h Plt 68 206 h Plt 165	3 h GPV	Thrombocytopenia developed after antivenom

*The case numbers correspond to those in Table 2

AH: *Agkistrodon halys*; FFP: fresh frozen plasma; GPV: green pit viper; INR: international normalised ratio; Plt: platelet count

Table 5. Clotting normalisation time in cases successfully corrected by antivenom vs. cases having no antivenom or FFP

	Total no.	Minimum (h)	Maximum (h)	Mean (h)	Median (h)	Standard deviation	P-value Mann-Whitney test
No antivenom or FFP	6	7.0	975.0	273.7	132.0	367.2	0.096
Antivenom	2	4.0	18.0	11.0	11.0	9.9	

FFP: fresh frozen plasma

antivenom was performed in three cases, two turned out to be negative and one revealed borderline result. All patients except one were pre-treated with various combinations of intravenous H₁ antihistamine, intravenous hydrocortisone and subcutaneous adrenaline (Table 2). There were no cases of anaphylaxis, and among the eight patients attending follow up, none had delayed serum sickness.

Discussion

Bamboo snake followed by Chinese cobra, account for most of the snakebites in Hong Kong.^{1,2} Bamboo snake, as with other species of the family Viperidae, causes local wound complications and coagulopathy. The family Elapidae includes cobra (*Naja*) as one of the genus. The clinical features of cobra bite range from profound neurotoxicity with little local reaction e.g. *Naja philippinensis*³ to severe tissue necrosis in the absence of neurotoxicity e.g. *Naja nigricollis*.⁴ In cases of Chinese cobra bite, local tissue injury appears more prominent than neurological defect⁵ as the relative amounts of the cytotoxic and neurotoxic venoms are 50 and 10% respectively.⁶

Local tissue damage was the commonest manifestation in our case series. Antivenom was usually capable of arresting or slowing the deterioration of the wound condition but in some cases the swelling progressed and gangrene subsequently developed. Snake venoms comprise multiple enzymes, metals and peptides. Once injected into the human tissues, they trigger the activities of neutrophils and macrophages, and release numerous inflammatory mediators. Viper venoms are rich in zinc metalloproteinases, converting tumour necrosis factor- α (TNF- α) from pro-TNF- α . The TNF- α mediates the action of inflammatory cells, and stimulates the production of endogenous matrix metalloproteinases, which release more TNF- α , thus amplifying the tissue inflammation and resulting in necrosis in severe cases. Antivenom injected up to 15 minutes after envenomation reduces tissue necrosis by inhibiting the venom metalloproteinases from initiating the TNF- α positive feedback cascade.⁷ Isolation of the haemorrhagic metalloproteinases from

many viperid snakes, as well as the king cobra (*Ophiophagus hannah*), helps further clarify the mechanism of local toxicity. Subcutaneous injection of this haemorrhagic toxin in rabbits induces swelling of the capillary endothelial cells, followed by complete lysis of their cytoplasmic organelles eight minutes post-injection and finally disruption of the basement membrane. The extravasated plasma and erythrocytes manifest clinically as oedema, ecchymosis and blistering. The capillary damage attracts local platelet aggregation, occluding the capillaries and aggravating the injury through ischaemia.⁸ Animal study on the mouse utilising intradermal *Naja nigricollis* venom demonstrated myonecrosis beginning after 30 minutes and intravascular fibrin deposition after one hour.⁹ Owing to the underlying structural changes in the local envenomation process, antivenom administration is not expected to quickly reverse the established oedema and haemorrhage at the injury site. The neutralisation power of the antiserum against myotoxicity induced by the myotoxin of *Crotalus viridis viridis* (rattlesnake) is time dependent, best if injected immediately after the toxin, with effect falling considerably after the initial 30 minutes.¹⁰

A rat study of *Crotalus atrox* envenomation followed by various therapies 30 minutes later revealed that antivenom alone was superior to fasciotomy and debridement, as well as the combination of antivenom and surgical treatment in the survival and muscle function preservation.¹¹ The reasons behind might be that fasciotomy reduces compartmental pressure and soft tissue oedema but does not directly address the envenomation process, and debridement performed too early may remove or injure viable muscles. Therefore surgical intervention should not be the sole therapy in snakebite but at the appropriate setting is definitely a useful adjunct to antivenom administration, which should be prescribed early to achieve optimal results.

Besides the impact on the severity of local tissue injury, early antivenom therapy is also beneficial in improving survival. The use of *Agkistrodon halys* antivenom in 665 patients resulted in the survival of all but three who presented later than 24 hours.¹² In a rabbit study, the survival rate after receiving *Agkistrodon halys* antivenom

at 15 minutes, 2, 6 and 12 hours post envenomation was 100, 50, 25 and 0% respectively.¹³ Positive correlation of increased mortality with delay in antivenom administration was also observed in rats given *Crotalus viridis helleri* venom, showing antivenom started beyond one hour carried no survival benefit.¹⁴

In order to reduce irreversible tissue damage and mortality, snake antivenom administration should be as early as possible. Its protective effect against tissue necrosis is likely to be greatly diminished after 15 to 30 minutes. Antivenom is recommended to be instituted in the first four hours,^{15,16} Although the latest time limit is unknown, its effect is supposed to decline over time.

Thrombocytopenia was less correctable than INR prolongation in this study. Apart from intravascular platelet destruction by the snake venom¹⁷ and platelet membrane damage by snake venom causing subsequent platelet sequestration and destruction in the reticuloendothelial system,¹⁸ other causes of thrombocytopenia like the platelet aggregating factors in the venom and sequestration of platelets at the bite wound might explain the unfavourable antivenom response.¹⁹⁻²¹ Five ampoules of the green pit viper antivenom manufactured by the Thai Red Cross Society had been reported to restore the blood coagulation after a median of five hours but the recovery of thrombocytopenia and hypofibrinogenaemia were slower.²² Resumption of normal coagulation occurred as late as 139 hours post-envenomation in our cases, suggesting coagulopathy, unlike local injury, is more amenable to correction even late after envenomation.¹⁶ This is probably because the intravascular venom reactions are more accessible by the antivenom. Albeit none of our cases had systemic bleeding and life-threatening haemorrhage after snakebite, which is uncommon, there are reports of intracranial haemorrhage causing death.^{4,23,24} A definite safe threshold of the clotting parameters for bleeding does not exist. Data suggest a relative risk for major bleeding of 2.1 and 3.1 for INR ≥ 1.5 and ≥ 2.0 respectively,²⁵ and a rise of the percentage of days with gross haemorrhage from 5% to 33% corresponding with the decrease of platelet count from $>100 \times 10^9/L$

to $<10 \times 10^9/L$.²⁶ The actual bleeding risk for any individual is certainly modified by other variables such as the age, hypertension, history of gastrointestinal haemorrhage and aspirin use.

The incidence of anaphylaxis and delayed serum sickness for green pit viper antivenom was described as 45 and 5% respectively in a report in 1990,²² whereas 2.3% of the patients undergoing *Agkistrodon halys* antivenom treatment develop serum sickness.¹² No single case of anaphylaxis or serum sickness was detected in our study. This discrepancy with the older reports could be partially attributed by the use of prophylactic medications for anaphylaxis in most of our cases, the possible purification of the antivenom in recent years and the small case number in our series. The hypersensitivity skin test has no predictive value for anaphylaxis. The skin test results of the green pit viper and *Agkistrodon halys* antivenoms have been proved unreliable in predicting the occurrence and severity of early reactions.^{12,27} Anaphylaxis generally responds well to treatment and is frequently anaphylactoid in nature, therefore antivenom can usually be restarted at a slower rate and in a more diluted solution after control of the allergy.¹⁶ Anaphylaxis is rarely fatal although there are anecdotal reports of asthmatics developing bronchospasm and death after snake antivenom infusion.^{28,29} Randomised controlled trials demonstrated that subcutaneous adrenaline, not intravenous antihistamine like promethazine, is effective in preventing anaphylaxis.^{30,31} It should be noted that the exclusion criteria in the adrenaline study included age over 70 years, hypertension, ischaemic heart disease, strokes, wheezing etc. The failure of promethazine might be because it does not block the H₂ histamine receptor and histamine is only one of the chemical mediators in anaphylaxis.³² Delayed reaction in the form of serum sickness may occur after high doses of antivenom therapy. It commonly manifests as fever, urticaria and arthralgia, and very rarely peripheral neuritis or other neurological symptoms. Antihistamines and a course of steroid readily produce good clinical response.^{16,33}

In light of the good safety records of antivenom usage in our cases, snake antivenom administration, if

deemed necessary, should not be restricted to the intensive care unit. Instead it should be initiated with minimal delay, provided personnel experienced in resuscitation and resuscitation equipment are available, and appropriate prophylaxis for anaphylaxis adopted. Though antivenom is the antidote for snakebite, the importance of supportive measures should not be overlooked as 94% of all our 192 cases had not been prescribed antivenom.

Because of the limited number of 12 and 11 cases in the antivenom and non-antivenom groups respectively, the inconsistent venom and antivenom doses, the time lag between actual clotting recovery and its detection, the imprecise record of swelling progress and the exclusion of several cases during the assessment of the haematological benefits of antivenom, reliable statistical measurement as well as comparison of the efficacy among the different antivenoms would be difficult. In case 4 of the antivenom group, the INR did not shorten after two vials of *Agkistrodon halys* antivenom, but considerably improved after five vials of green pit viper antivenom. The apparently poor result of the former antivenom is not completely understood, but could simply be due to inadequate dose although one vial of it has been reported sufficient for the majority of cases.¹²

Conclusion

In order to minimise local wound complications, snake antivenom should be given early in adequate doses. The reversal of coagulopathy is however less time dependent. The results in the present study may reduce the concern on the side effects of snake antivenom but this should be confirmed by larger studies.

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