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APPROPRIATE ANTIVENOM DOSES FOR SIX TYPES OF ENVENOMATIONS CAUSED BY SNAKES IN TAIWAN

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ABSTRACT: Six of the 15 species of venomous snakes found in Taiwan are responsible for most of the clinically significant envenomations in the country. These species are: *Trimeresurus mucrosquamatus*, *Trimeresurus stejnegeri*, *Naja atra*, *Bungarus multicinctus*, *Deinagkistrodon acutus* and *Daboia russelii siamensis*, which together can be subdivided into three groups based on their venom effects. Primary treatment consists of rapid administration of appropriate antivenoms. The present study aimed to identify a proper dose of antivenom for each snake group as well as to describe hemorrhagic, neurotoxic, and mixed effects of their venoms. A retrospective chart review identified 72 snakebite cases referred to an emergency department. Data on epidemiology, examination findings, snake identification, treatment, antivenom dose and complications were collected. After excluding 14 patients, data from 58 victims were analyzed. Most studied cases were male (86%). Significantly higher doses of antivenom were administered against neurotoxic envenomations (mean dose: three vials) compared with the other two ($p < 0.05$). Moreover, patients affected by neurotoxic bites were more likely to develop blurred vision and other complications ($p < 0.05$). Multivariate logistic regression analysis indicated that neurotoxic envenomation was a risk factor for complications (OR: 8.84, 95% CI: 1.06-73.73). Neurotoxic envenomations and complication occurrence were positively correlated with antivenom dosage. In conclusion, patients affected by neurotoxic envenomations received higher doses of antivenom than others whereas incidence of complications was associated with higher antivenom doses.

KEY WORDS: antivenom, venomous snakes, snake envenomation, neurotoxic venom, hemorrhagic venom.

CONFLICTS OF INTEREST: There is no conflict.

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INTRODUCTION

Taiwan, located in the South Pacific, has a subtropical environment with more than 40 snake species; 15 of these are venomous snakes. Six of these 15 are responsible for most of the clinically significant snakebites (1). Two of these six species belong to the Elapidae family that includes cobra, coral and sea snakes, while the other four belong to the Viperidae family, vipers and adders.

These six species can be divided into three groups based on local or systemic clinical effects produced by their venoms, namely hemorrhagic, neurotoxic or mixed symptoms. The hemorrhagic venom causes disorders of the clotting cascade such as prolonged bleeding, primary fibrinolysis and disseminated intravascular coagulopathy (2, 3). Snakes that present hemorrhagic venom are *Trimeresurus stejnegeri* (Taiwan bamboo viper), *Trimeresurus mucrosquamatus* (turtle-designed snake) and *Deinagkistrodon acutus*.

The neurotoxic venom provokes respiratory distress from weakened respiratory muscles, blurred vision, diplopia, dysarthria, dysphagia, dysphonia and paralysis of extremity muscles (2, 4). Snakes that produce neurotoxic venom are *Naja atra* (Chinese common or Formosa Island cobra) and *Bungarus multicinctus multicinctus* (Taiwan banded krait).

The mixed envenomation manifests as a combination of neurotoxic and hemorrhagic effects previously described, as well as rhabdomyolysis and acute renal failure (5). *Daboia russelii siamensis* can inoculate this type of venom.

There are six snake species more involved in accidents with humans in Taiwan: *Trimeresurus mucrosquamatus* (32.9%), *Trimeresurus stejnegeri* (24.2%), *Naja atra* (12.1%), *Bungarus multicinctus* (10.1%), *Deinagkistrodon acutus* (3.9%) and *Daboia russelii siamensis* (1.6%) (1). There are four types of antivenoms available against these six more frequent snake envenomations, specifically: antivenom against *T. stejnegeri* and *T. mucrosquamatus*; antivenom against *D. acutus*; antivenom against *N. atra* and *B. multicinctus multicinctus;* and antivenom against *D. russellii*. The present study particularly compares three types of envenomations regarding dosages of antivenom and complications.

PATIENTS AND METHODS

Our medical center has a standard protocol for treatment of snakebite patients. A retrospective review was conducted based on records of the emergency department

(ED) ranging from January 1993 to December 2002. Seventy-two patients who received medical treatment for snakebites were identified. Of them, 14 were unable to identify the snake species and were excluded. The following information of the remaining 58 patients was observed:

- basic epidemiological characteristics including age, gender, the time of the bite, bitten area of the body, season when the bite occurred and clinical manifestations;
- examination of snakebite evidence (fang marks);
- snake identification based on matching photographs, description, envenomation symptoms or the dead animal;
- associated therapy including laboratory tests, antivenom administration, supportive care, debridement, respiratory support;
- clinical outcomes.

This study was approved by the Institutional Review Board, Kaohsiung Medical University, protocol KMUH-IRB-960302.

Definitions

Each complication was defined according to associated venom effects. Complications consisted of tissue necrosis, compartment syndrome, coagulopathy, respiratory failure and acute renal failure. Coagulopathy and compartment syndrome were consequences of hemorrhagic venoms. Respiratory failure and tissue necrosis or fasciitis requiring debridement or fasciotomy were complications of neurotoxic venoms. Coagulopathy and acute renal failure resulted from mixed venoms.

Coagulopathy was defined as a prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) or thrombocytopenia. Compartment syndrome comprised excessive pain with passive stretching, decreased sensation of pinprick or light touch, decreased discrimination of two points or necessity of fasciotomy. Measurement of intracompartmental pressure in affected limbs is required in an ideal situation; however, physical findings described above may substitute it in emergency circumstances. Acute renal failure was defined as a 50% decline in creatinine clearance or a 50% increase in serum creatinine from baseline. Acute respiratory failure was defined as arterial oxygen tension < 60 mmHg, arterial oxygen saturation

< 90%, or arterial carbon dioxide tension > 45 to 55 mmHg.

Antivenom

Antivenoms employed in the treatment were produced by the Center for Disease Control, Department of Health, Taipei, Taiwan. Antivenoms were prepared by immunizing horses after snake envenomations. Each vial of antivenom contains over 1,000 Tanaka units (mean, 1200 TU). Each unit can neutralize one minimum lethal dose (MLD) of 12 to 14 g of mouse body weight (6). A skin test dose of 0.1 mL of a 1:100 solution was intradermally injected in the forearm of the patient. Epinephrine was available prior to test dose injection. Patients were given diphenhydramine and corticosteroids for evidence of allergic reaction. Before the administration, the antivenom was diluted in 300 to 500 mL of normal saline and infused over 30 to 60 minutes.

Statistical Analysis

The Kruskal-Wallis test was used for baseline comparisons of continuous variables, i.e., age and antivenom dosage. Chi-square and Fisher's exact tests were employed for analyses of categorical variables between risk factors and venomous types. Logistic and linear regression analyses were employed to establish a model for predicting the probability of complications and dosage of antivenom, respectively. SAS 9.0® (SAS Institute Inc., USA) was utilized to perform statistical analysis; $p < 0.05$ was significant.

RESULTS

Epidemiological and demographic characteristics of patients bitten by venomous snakes are presented in Table 1. The majority of the victims were male (86%), which was statistically significant ($p < 0.05$). More than half of the patients bitten by Viperidae and Elapidae serpents were attacked near their homes, in suburban areas. Fingers and palms were more frequently affected by Viperidae (hemorrhagic venom) and Elapidae snakes (neurotoxic venom), while toes and the lower leg were more commonly bitten by Viperidae (mixed venom). However, the locations of bitten areas were no statistically significant difference among the three venomous groups (Table 1).

Local pain and swelling accounted for more than 50% of patients' complaints on the

arrival at the ED in the three groups. Blurred vision was predominantly found among persons bitten by Elapidae snakes (neurotoxic venom) ($p < 0.05$), otherwise, there was no significant difference in symptoms among the three groups (Table 1). Complication rates and the dosage of antivenom required were significantly different for the three groups. Patients bitten by Elapidae serpents (neurotoxic venom) had higher complication rates (9/22; 40.9%) and required larger antivenom dosages compared to Viperidae (median dose: three vials, range: 1.0 to 10.0) ($p < 0.05$) (Table 1).

Further analysis using a univariate logistic regression model indicated important correlations among venom complications and venomous types, respiratory distress and duration of treatment (Table 2). However, after adjusting for gender, multivariate logistic regression analysis indicated only a significant correlation between complication rate and neurotoxic venom (OR: 8.84, 95% CI: 1.06-73.73, Table 2), suggesting that patients bitten by Elapidae snakes (neurotoxic venom) had greater chance for complications even after antivenom therapy, which included respiratory failure and flaccidity (4/9; 44.4%) and fasciitis requiring fasciotomy and debridement (3/9; 33.3%).

Regression model results that analyzed the association among dose of antivenom and venom type, complications and blurred vision is presented in Table 3. After adjustment of age and gender, we found that patients affected by neurotoxic venom received a significantly greater dose of antivenom compared with those afflicted by hemorrhagic toxin ($p < 0.05$). Patients with complications received a considerably greater dose of antivenom compared with those who did not show any symptom ($p < 0.05$).

Table 1. Epidemiological characteristics of 58 patients bitten by venomous snakes who received antivenom treatment in the medical center of Taiwan, from January 1993 to December 2002

Demographics/ other variables	Viperidae Family[a] hemorrhagic venom (n = 28)	Elapidae Family[a] neurotoxic venom (n = 22)	Viperidae Family[a] mixed venom (n = 8)	*p* value[b,c]
Age (years)	51.5 (15.0-93.0)	44.5 (22.0-67.0)	55.5 (19.0-78.0)	0.37
Median dose (vials)	1 (1.0-2.7)	3 (1.0-10.0)	2 (1.0-2.0)	0.005*
Gender				
Male	22 (78.6)	22 (100)	6 (75.0)	0.03*
Female	6 (21.4)	0 (0.0)	2 (25.0)	
Location				
Near house	15 (55.5)	15 (68.1)	3 (37.5)	0.29
Suburban	12 (44.4)	7 (31.82)	5 (62.5)	
Bitten area				
Fingers	9 (32.1)	12 (54.5)	1 (12.5)	0.13
Palms	8 (28.6)	4 (18.2)	1 (12.5)	
Toes	4 (14.3)	0 (0.0)	2 (25.0)	
Lower legs	6 (21.4)	4 (18.2)	3 (37.5)	
Others	1 (3.6)	2 (9.1)	1 (12.5)	
Symptoms[d]				
Local swelling	23 (46.9)	14 (28.0)	7 (36.9)	0.22
Pain	18 (36.7)	12 (24.0)	5 (26.3)	0.82
Local paralysis	2 (4.1)	9 (18.0)	3 (15.8)	2.00
Blurred vision	0 (0.0)	4 (8.0)	0 (0.0)	0.04*
Respiratory distress	1 (2.0)	4 (8.0)	0 (0.0)	0.21
Others	5 (17.9)	7 (31.9)	4 (50.0)	0.17
Complications	2 (7.1)	9 (40.9)	3 (37.5)	0.015*

Data are presented as mean for age and dosage of antivenom and number (percentage) for other variables.

[a]Viperidae family with hemorrhagic venom: *T. stejnegeri, T. mucrosquamatus, D. acutus*; Elapidae family with neurotoxic venom: *N. atra, B. multicinctusmulticinctus*; and Viperidae family with mixed venom: *V. russellii*.

[b]Kruskal-Wallis for age and dosage of antivenom.

[c]Chi-square test for gender, location, biting position, complaint and complications.

[d]Number of subjects for data analysis of variables does not correspond to the total number of subjects because of more than one complaint from each subject.

* $p < 0.05$.

Table 2. Logistic regression analysis of complications derived from 58 cases of venomous snake bites, the medical center of Taiwan, January 1993 to December 2002

	Univariate logistic regression		Multivariate logistic regression[a]	
Complication rate	**Crude OR**	**95% CI**	**Adjusted OR**	**95% CI**
Venom type				
Hemorrhagic	Ref.	[b]	Ref.	
Neurotoxic	7.29*	1.31-40.54	8.84*	1.06-73.73
Mixed	7.50	0.98-57.14	3.53	0.28-45.26
Respiratory distress				
No	Ref.		Ref.	
Yes	13.67*	1.27-146.98	20.19	0.77-526.98
Treatment duration (hours)				
< 1	Ref.		Ref.	
< 2	2.17	0.24-19.28	4.42	0.25-77.80
< 4	0.65	0.05-8.23	1.34	0.06-32.93
< 10	8.13*	1.12-59.21	16.99	0.90-320.65
> 10	1.44	0.17-12.23	1.55	0.10-24.80

OR: odds ratio; CI: confidence interval; Ref.: reference group.
[a]Adjusted for sex and age.
[b]Dashes represent no 95% CI for reference groups.
*$p < 0.05$.

Table 3. Linear regression analysis of the association between antivenom dose and effectors in 58 patients who received treatment in the medical center of Taiwan, from January 1993 to December 2002

Variable	Beta	*p* value[a]
Venom type		
Hemorrhagic	Ref.	[b]
Neurotoxic	1.33241	0.05*
Mixed	0.27685	0.75
Complications		
No	Ref.	
Yes	1.57634	0.05*
Blurred vision		
No	Ref.	
Yes	1.42317	0.34

Ref.: reference group.
[a]Adjusted for sex and age.
[b]Dashes represent no *p* value for the reference groups.
* $p < 0.05$.

DISCUSSION

Roughly, one quarter of all the snake bite patients could not confirm the species of snake that had attacked them. Hung (1) found that of the 282 cases he studied, 50 patients were unable to identify the snake species that bite them. This may have clinical significance, as it could delay the antivenom administration. Based on this retrospective review, patients bitten by snakes of the family Elapidae (neurotoxic venom) required higher antivenom doses and had greater chances for complications, even after antivenom therapy. We found similar epidemiological patterns in previous studies including male predominance (86%), bites on distal extremities of the body (98%) and a large incidence of attacks occurring near the individual residence (57%) (3, 4, 7-9). Correct antivenom administration remains the mainstay of therapy, with a suggested elapsed time from the moment of the bite to the antivenom administration of six to eight hours (10). Most patients (72%) in our study received antivenom therapy within six hours from the time they were bitten.

The exact antivenom dose required remains a matter of discussion. Yeung *et al*. (11) in a study of 35 brown snake envenomations in Australia found that initial antivenom doses were very small, leading to a continued circulation of venom. Paul *et al*. (2) conducted a study with 100 patients bitten by snakes from three venom groups (hemorrhagic, neurotoxic and mixed). They further divided the patients into two groups; the first was treated with high doses of antivenom and the other group with low doses. There was no statistical difference in clinical outcomes between the two groups (2).

Antivenom can present adverse effects ranging from local skin reactions to severe anaphylaxis and death. Additionally, delayed reactions that include serum sickness may occur. Therefore, the goals of antivenom treatment comprise administration of an appropriate dose of antivenom to neutralize the toxin, avoidance of complications related to the envenomation and prevention of additional complications (12, 13).

In our study, the median dose of antivenom administered for the family Viperidae (hemorrhagic venom) was one vial and the complication rate was 7.14% (2/28), suggesting that the dose of antivenom may be suitable for most patients. Two of these victims had coagulopathy with compartment syndrome and required fasciotomies. Three victims were bitten by *D. acutus* and received antivenom for *T. stejnegeri* and *T. mucrosquamatus* since the antivenom against these two species presents weak cross-reactivity with *D. acutus*.

The median dose of antivenom administered for the family Elapidae (neurotoxic venom) was three vials, and the complication rate was 40.91%. This rate is consistent with the fact that neurotoxins cause paralysis that may not be reversible by antivenom. Pre-synaptic neurotoxins damage nerve endings at the neuromuscular junction while post-synaptic neurotoxins are short or long and bind to nicotinic acetylcholine receptors (14). Antivenom doses required in the Elapidae group were higher, although the suggested dose was one vial. Our findings suggest that the recommended dose of antivenom for treating these bites is insufficient.

Hung (7), in his work on neurotoxic envenomations, suggested that the level of serum venom detected by ELISA was connected with the severity of local tissue damage, with higher levels indicating higher damage. This author indicated that when this type of envenomation is suspected, patients may require ELISA tests in order to determine the correct dose of antivenom. Similarly, Agarwal *et al*. (4) analyzed low doses of antivenom for treating patients with neurotoxic envenomations. Patients were divided into two groups, one treated with high doses of antivenom, and the other treated with low doses. While there are apparent problems with the study design, they found a similar outcome between groups that received low or high doses of antivenom. Even though there were three deaths in the high dose group and none in the low dose group, the deaths were attributed to late presentation and complications related to pneumonia and sepsis (4).

The median dose of antivenom administered for envenomations provoked by Viperidae snakes (mixed venom) in our study was two vials, and the complication rate was 37.5% (3/8). The toxin from this family commonly causes coagulopathy with bleeding diathesis due to procoagulants contained in the venom that activate factor X, factor IX, and factor V leading to thrombosis and disseminated intravascular coagulation (6, 8, 9). In another study by Hung *et al.* (5), 13 patients received a mean dose of 3.3 vials. Among those patients, the mortality rate was 0% in 12 patients who received prompt treatment, compared to three deaths out of 19 cases in which treatment was delayed (5, 8). We found that antivenom may prevent hemorrhage, but appears to have no effect on progression to acute renal failure. Dialysis remains the preferred conduct for acute tubular necrosis in these patients.

Although improvements in the production and standardization of antivenom have occurred over the years, and resulted in highly efficient treatments, these changes have increased production costs, and several authors believe that the overall quality

is similar to those from older methods when properly conducted (13). Additionally, new assay systems allow a very accurate assessment of antivenom efficacy, apart from changes in a patient clinical status (15). Though we may agree that improvements in quality, efficacy and consistency have resulted from enhanced methods of antivenom production, appropriate dosage and treatment duration are still decisive, and are based on clinician assessment of the patient condition.

There are some limitations to this study, specially being a retrospective chart review rather than a double blind, placebo-controlled trial of the antivenoms. Patients could have incorrectly identified the snakes that bit them and victims excluded from the present study due to the inability to identify the snake may have affected the results. Despite these limitations, important information regarding appropriate antivenom dosage and complication of envenomations caused by snake bites has been obtained.

CONCLUSION

Based on the present findings, patients affected by neurotoxic envenomation received higher doses of antivenom than other types of envenomation. However, they still presented higher rate of complication after antivenom therapy, suggesting that the dosage of antiserum may not be appropriate for them. Our study also indicated that the dosage of antivenom used for neutralizing venom may positively be connected with the occurrence of complications.

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INSTITUTION APPROVAL

The present study has been approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-960302).

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