BRIEF COMMUNICATION

Antivenom Therapy for Crotaline Snakebites: Has the Poison Control Center Provided Effective Guidelines?

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Crotaline snakebites (*Protobothrops mucrosquamatus* and *Trimeresurus stejnegeri*) are a common medical emergency in Taiwan that can be effectively treated by a bivalent F(ab′)2 antivenom. We investigated the differences in the clinical outcomes of patients who received different therapeutic regimens of antivenom in a medical center where clinical toxicologists followed the poison control center (PCC) guidelines (medical group) and surgeons did not (surgical group). The medical records of inpatients with crotaline snakebites between 1991 and 2005 were reviewed and information on demographics, treatments, adverse effects of antivenom, and complications was abstracted and analyzed. A total of 179 patients (90 medical, 89 surgical) were eligible for study. There was no significant intergroup difference in baseline characteristics except that the dose of antivenom and the probability of antibiotic use were both higher in the surgical group (5.9 ± 4.2 vials *vs*. 2.7 ± 1.6 vials; 93% *vs*. 60%). Multiple logistic regression adjusting for age, gender, calendar year of envenomation, severity of envenomation, and antibiotic use did not disclose evidence of any difference in various clinical outcomes between medical and surgical patients. The lower dose of antivenom recommended by the PCC may be as effective and safe as the higher dose used in the surgical group for the treatment of crotaline snakebites. [*J Formos Med Assoc* 2007;106(12):1057–1062]

Key Words: antivenom, crotalid venom, poison control center, snake bite

Among the approximately 400 snakebites reported annually in Taiwan, snake envenomation is a common medical emergency.[1] Recent hospital-based studies showed that Taiwan habu (*Protobothrops mucrosquamatus*, formerly known as *Trimeresurus mucrosquamatus*) and green habu (*Trimeresurus stejnegeri stejnegeri*) accounted for the majority of venomous snakebites in northern Taiwan.[2,3] The Taiwan habu and green habu are from the crotaline (pit viper) subfamily, mainly producing the hemorrhagic type of venoms.[4]

Antivenom is the mainstay therapy for crotaline snakebites.[5] In Taiwan, a pepsin-digested F(ab′)2 fragment, bivalent antivenom produced from equine serum has been marketed by the National Institute of Preventive Medicine to treat crotaline snakebites since 1986. Based on laboratory neutralization studies and empirical experience, the Taiwan Poison Control Center (PCC) recommends the use of one vial of antivenom every 2 hours until clinical manifestations stabilize, or a total of four vials of antivenom.[6]

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However, the efficacy of the above approach remains undefined. In the absence of evidence-based guidelines, clinical toxicologists and other specialists (e.g. surgeons and emergency physicians) have adopted somewhat different approaches on antivenom therapy. In the study hospital, a major medical center in northern Taiwan, clinical toxicologists (medical group) follow the PCC guidelines, while surgeons (surgical group) tend to use higher doses of antivenom because they believe that more antivenom may be beneficial.[7] As a rule, both groups administered one vial of antivenom to snake-envenomed patients on initial presentation. Antivenom was then given in increments of one vial every 2 hours by toxicologists and two vials every 2 hours by surgeons until symptoms completely ceased to progress. The total dosage in the medical group was up to four vials according to PCC guidelines, but was unlimited in the surgical group.

Antivenom can neutralize crotaline snake venoms and reduce complication and mortality rates.[2,5,8,9] However, the limited data available on neurotoxic and *Bothrops* snake envenoming suggest that a higher dose of antivenom may not necessarily provide a better clinical outcome.[7,10] No previous study has evaluated the effects of the PCC-recommended approach versus an alternative antivenom regimen in treating crotaline snakebites. We investigated the differences in clinical outcomes between patients who received antivenom according to the PCC approach and patients who received antivenom according to a different therapeutic approach.

Methods

We conducted a retrospective cohort study by reviewing the medical records of patients with crotaline snakebite who were admitted to the study hospital from 1991 through 2005. The study protocol was approved by the hospital's institutional review board. All patients were followed from the time of envenomation till the date of discharge, complete recovery, having permanent sequelae, or envenomation-related death, whichever came last.

In the study hospital, patients with snakebite were admitted to either the medical (clinical toxicology) ward or surgical ward after initial management in the emergency department. Ward assignment for a patient depended on which team was on duty and did not take into account the patient's clinical condition. We excluded 49 patients with non-crotaline snakebites (from *Naja naja atra*, *Bungarus multicinctus*, *Deinagkistrodon acutus*, and *Daboia russelli siamensis*) and 21 patients who were bitten by unidentifiable snakes. The species of culprit snake was documented through identification of the snake brought in by the patient or recognition of the snake's picture by the patient.

Two authors (YCC and CCY) independently retrieved the following information from the medical records: patients' age, gender, comorbidities, details of envenomation, clinical manifestations, laboratory data, treatments, clinical outcomes, complications, and length of hospital stay. Severity of envenomation was classified into mild, moderate, severe and very severe based on the number of swollen limb segments (one to three) and whether systemic effects were present.[11] Any dispute regarding data retrieval was resolved by the entire research team.

We considered the World Health Organization's guidelines for the clinical management of snakebites in the Southeast Asian region in the classification of clinical syndromes and complications of snake envenomation.[12] Definitions of various complications were as follows: (1) life-threatening complications, including severe rhabdomyolysis (creatine phosphokinase, CK, $> 10{,}000$ U/L)[13] and acute renal failure (creatinine > 3.0 mg/dL and oliguria);[8,9] (2) other complications, consisting of systemic complications (coagulopathy—prothrombin time with International Normalized Ratio > 1.25, rhabdomyolysis—CK > 1000 U/L and $\leq 10{,}000$ U/L, and acute renal impairment—creatinine > 1.4 mg/dL and ≤ 3.0 mg/dL)[14] and local complications (cellulitis, necrosis, compartment syndrome of bitten sites); (3) surgical treatment, including debridement,

dermatomy, fasciotomy, and skin graft; (4) permanent sequelae, defined as digit or limb amputation; (5) adverse effects of antivenom, i.e. presence of febrile and anaphylactoid reactions that immediately developed after antivenom therapy, and serum sickness. The primary outcome of study interest was any life-threatening complications; secondary outcomes included other complications. In the analysis of various outcomes, we also evaluated the potential confounding effects of major comorbidities (e.g. diabetes mellitus), transfer from other hospitals/clinics, prehospital management (e.g. use of tourniquet or wound incision), calendar year of envenomation, sites of the snakebites, route of antivenom use (either local plus intravenous injection or intravenous injection only), severity of envenomation, timing of initial antivenom therapy, and use of antibiotics.

We employed the t and χ^2 tests to compare intergroup differences in baseline characteristics and various outcomes. Possible secular trend of dose and initiation time of antivenom therapy was tested by ANOVA. We then used univariate and multivariate logistic regressions to estimate the crude and adjusted odds ratio (OR) of developing clinical outcomes by using patients in the medical group as the reference group. All analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). ORs are presented with point estimates and relevant 95% confidence intervals. All p values are two-sided.

Results

There were 249 inpatients whose records were available for review. After the application of various exclusion criteria, a total of 179 patients, including 136 patients with Taiwan habu envenomation and 43 patients with green habu envenomation, were eligible for study. The overwhelming majority (90%) of patients received antivenom therapy within 8 hours after being bitten. One-way ANOVA did not find any within-group secular trend in the initiation time or administered dose of antivenom during the study period (data not shown). The baseline characteristics of the 179 patients are summarized in Table 1.

Patients in the medical and surgical groups were similar in many of their baseline characteristics. Surgical group patients, however, received a higher dose of antivenom, were more frequently treated with antibiotics, and were more likely to be hospitalized before the year 2001 (Table 1).

Table 2 presents the frequency of developing various outcomes among the 179 patients. Eight patients (4 in each group) developed life-threatening complications, but none died. Two patients envenomed by Taiwan habu underwent digit amputation due to severe gangrenous change. The overall rate of positive skin test for antivenom was 10% (17 patients). All of them received antivenom after treatment with antihistamine and dexamethasone, and none developed allergic reactions. Antivenom-related allergic reactions were recorded in six (3%) patients who tested negative.

Table 2 also shows the results of both univariate and multivariate analyses. Using patients in the medical group as the reference group, the crude ORs of having life-threatening complications, other complications, and adverse effects of antivenom were all not different from unity. The ORs adjusted for age, gender, calendar year of envenomation, severity of envenomation, and use of antibiotics again revealed no differences between the two groups of inpatients. Further, none of the aforementioned potential confounders was significantly associated with the primary outcome. The length of hospital stay was longer for surgical group patients (7.7 ± 7.3 days) than for medical group patients (5.9 ± 5.8 days), but the difference was not significant ($p = 0.07$).

Discussion

In this study, both univariate and multivariate analyses failed to show that a higher dose of antivenom received by patients in the surgical group (5.9 ± 4.2 vials) was superior to the dose recommended by the PCC (2.7 ± 1.6 vials) in reducing the major complications of crotaline snakebites.

Table 1. Baseline demographic and clinical characteristics of 179 patients with crotaline snakebites*

	Surgical group ($n=89$)	Medical group ($n=90$)	p
Age (yr)	45.9 ± 20.5	44.4 ± 17.5	0.6
Male	64 (72)	59 (66)	0.4
Major comorbidities	2 (2)	1 (1)	0.6
Transfer from other hospitals	52 (58)	63 (70)	0.1
Prehospital management	12 (14)	17 (19)	0.4
Calendar year of envenomation			0.005
1991–1995	24 (27)	14 (16)	
1996–2000	37 (42)	26 (29)	
2001–2005	28 (32)	50 (56)	
Snake species			1.0
Protobothrops mucrosquamatus	68 (76)	68 (76)	
Trimeresurus stejnegeri stejnegeri	21 (24)	22 (24)	
Site of snakebite			0.9
Upper limb	41 (46)	43 (48)	
Lower limb	48 (54)	47 (52)	
Acute symptoms/signs			
Local pain	89 (100)	90 (100)	1.0
Inflammation	89 (100)	90 (100)	1.0
Local bleeding	20 (23)	19 (21)	0.9
Bruising	65 (73)	61 (68)	0.5
Blistering	15 (17)	12 (13)	0.5
Severity of envenomation†			0.5
Mild to moderate	49 (55)	48 (53)	
Severe to very severe	40 (45)	42 (47)	
Start of antivenom ≤ 8 hr	79 (89)	82 (91)	0.9
Antivenom dose (vials)	5.9 ± 4.2	2.7 ± 1.6	< 0.001
Route of antivenom			1.0
Intravenous infusion	84 (94)	84 (93)	
Local injection plus intravenous	5 (6)	6 (7)	
Use of antibiotics	83 (93)	54 (60)	< 0.001

**Data are presented as mean ± standard deviation or n (%); †the original four categories of severity of envenomation were reclassified into two categories of "mild to moderate" and "severe to very severe" because there were only two patients with mild envenomation and three with very severe envenomation.*

Our finding is consistent with previous studies on other snake antivenoms,[7,10] and supports the PCC approach for the management of Taiwan habu and green habu snakebites.

Some major complications of snake envenomation, such as coagulopathy, may be reversed by prompt administration of antivenom. A previous randomized trial demonstrated that compared to a high dose of antivenom, a lower dose can as effectively correct coagulopathy in patients with *Bothrops* envenomation.[10] In this study, both high-dose and low-dose antivenom therapy promptly corrected coagulopathy, suggesting a threshold effect of antivenom in the treatment of venom-related coagulopathy. On the contrary, current published data do not show any dose-related efficacy of antivenom in preventing or treating myotoxicity and nephrotoxicity from hemorrhagic snakebites.[15] In this study, the higher dose of antivenom seemed to be associated with a lower, albeit insignificant,

Table 2. Outcomes of the 179 patients with crotaline snakebites and their association with treatment group

	Surgical group ($n=89$)	Medical group* ($n=90$)	OR (95% CI)	
			Crude	Adjusted†
Life-threatening complications‡	4 (5)	4 (5)	1.0 (0.2–4.2)	1.4 (0.2–7.7)
Other complications	28 (32)	35 (39)	0.7 (0.4–1.3)	0.5 (0.2–1.0)
Coagulopathy	4 (5)	5 (6)	0.8 (0.2–3.1)	0.8 (0.2–4.2)
Rhabdomyolysis	3 (3)	10 (11)	0.3 (0.1–1.1)	0.3 (0.1–1.2)
Acute renal impairment	1 (1)	4 (4)	0.2 (0–2.2)	0.1 (0–1.2)
Cellulitis/necrosis	17 (19)	21 (23)	0.8 (0.4–1.6)	0.5 (0.2–1.1)
Compartment syndrome	4 (5)	6 (7)	0.7 (0.2–2.4)	0.5 (0.1–1.9)
Dermatomy/fasciotomy	4 (5)	3 (3)	1.4 (0.3–6.3)	0.7 (0.1–4.2)
Skin graft	8 (9)	5 (6)	1.7 (0.5–5.3)	0.9 (0.2–3.2)
Digit amputation	1 (1)	1 (1)	1.0 (0.1–16.4)	0.4 (0–6.7)
Adverse effects of antivenom	3 (3)	3 (3)	1.0 (0.2–5.2)	1.3 (0.2–8.1)

**Reference group; †adjusted for age, gender, calendar year of envenomation, severity of envenomation and use of antibiotics; ‡including severe rhabdomyolysis (creatine phosphokinase ≥ 10,000 U/L) and acute renal failure (creatinine ≥ 3 mg/dL). OR = odds ratio; CI = confidence interval.*

risk of mild-to-moderate rhabdomyolysis and acute renal impairment. However, that treatment was not more effective in preventing severe rhabdomyolysis or renal failure. The length of hospital stay was also not shortened among patients in the surgical group. Therefore, although a higher dose of antivenom may be beneficial in preventing milder myotoxicity and renal impairment, its clinical importance is probably limited.

Envenomation by Taiwan habu and green habu can result in severe tissue damage, such as compartment syndrome. Antivenom is thus frequently administered in the hope of ameliorating local toxicity. However, limited published data are controversial on what constitutes an efficacious dosage of antivenom in preventing local edema and tissue necrosis.[15] The results of this study suggested that a higher dose of antivenom was not more effective in abolishing local complications or reducing the need for surgical treatment, a finding consistent with a previous trial on equine F(ab′)2 antivenoms in Brazil.[16]

The incidence of adverse effects of antivenom is likely to be an important factor in deciding whether and how antivenom should be administered. Equine-derived F(ab′)2 antivenoms produced in other countries have various incidences of adverse reactions, ranging from 4.3% in the French FAV-African (highly purified equine F(ab′)2) antivenom to 53% in the Brazilian equine F(ab′)2 antivenom.[17,18] Severe life-threatening reactions, however, are rare.[15] In this study, the incidence of adverse effects of antivenom was 3%, a result consistent with previous reports in Taiwan.[19,20] We also did not observe any patient who experienced severe allergic reactions or serum sickness. Moreover, a positive skin test did not predict the occurrence of allergic reactions. The safety profile and the discrepancy between skin test and allergic reaction to the F(ab′)2 antivenom agrees with Malasit et al's proposition of possible obviation of routine sensitivity test before antivenom therapy.[21]

This was a retrospective study. Therefore, the identification and ascertainment of minor study

outcomes may be incomplete. This could result in an underestimation of the true incidence of certain effects. However, the findings on major and life-threatening complications were unlikely to be biased. Nevertheless, because the number of patients with life-threatening complications was small in this study and because we did not measure circulating venom levels, it remains possible that for a few severely envenomed patients, a dose of antivenom that is higher than the PCC-recommended dose may be beneficial.

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