Bungarus multicinctus multicinctus Snakebite in Taiwan

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Abstract. Although specific antivenom is available in Taiwan, respiratory failure and general pain frequently accompany *Bungarus multicinctus* envenomation and there have been few reports on the management of *B. multicinctus* envenomation. We retrospectively analyzed 44 cases of *B. multicinctus* bite admitted to Taichung Veterans General Hospital (VGH) or to Taipei VGH. Demographic data, treatment, and outcome of patients with and without respiratory failure were compared. In this study, 20.5% patients had bites without noticeable signs or symptoms of significant envenoming, 27.3% developed respiratory failure, and 27.3% experienced general pain. Bivalent specific antivenom for *B. multicinctus* and *N. atra* was administered in all envenomed cases. Respiratory failure occurred 1.5–6.5 hours post-bite and general pain occurred 1–12 hours post-bite. Specific antivenom for *B. multicinctus* and *N. atra* at the recommended dose (i.e., 2–4 vials) might not effectively prevent respiratory failure and pain. Respiratory failure, general pain, and autonomic effects after *B. multicinctus* bite were probably caused, at least partly, by β -bungarotoxin. Although general weakness, ptosis, dysarthria, and dilated pupils were significantly associated with respiratory failure, their predictive value could not be accurately determined in such a retrospective study. Due to the rapid onset of respiratory failure, every suspected envenomed case thus should be closely monitored in the first few hours. We recommend the initial administration of four vials of antivenom in all envenomation cases, and a subsequent four vials be considered if the patient's condition is deteriorating. Prospective evaluation of the antivenom dosing regimen is urgently needed to improve *B. multicinctus* envenomation treatment.

INTRODUCTION

Six venomous land snakes are considered medically important in Taiwan, including *Bungarus multicinctus multicinctus* (*B. multicinctus*) and *Naja atra* in family Elapidae and *Trimeresurus stejnegeri*, *Protobothrops mucrosquamatus*, *Deinagkistrodon acutus*, and *Daboia siamensis* in family Viperidae.^{1,2} *Bungarus multicinctus*, also known as the many-banded krait or umbrella snake, is the only krait species in Taiwan. Its inhabited area extends throughout south China, Myanmar, Laos, north Vietnam, and Thailand.³ *Bungarus multicinctus* bites are rare and account for only 7.5% (range: 0–17.1%) of all snakebites in Taiwan.¹ However, the bite of *B. multicinctus* was ranked as second in lethality only to that of *D. acutus*.¹ The case-fatality rate is reported as 7–50%, with death occurring 6–30 hours post-bite if no antivenom therapy was provided.^{4–7} Although the Taiwan government produces specific antivenoms against the six major venomous snakes, published recommendations on managing *B. multicinctus* bites are scarce.^{6,8} We conducted a retrospective case series study to better understand the clinical outcome and risk factors associated with respiratory failure after *B. multicinctus* envenomation at two medical centers, Taichung Veterans General Hospital (VGH-TC) in central Taiwan and Taipei Veterans General Hospital (VGH-TP) in northern Taiwan in an attempt to provide

better management guidelines and foster further studies on *B. multicinctus* snakebites.

MATERIALS AND METHODS

Study population. This retrospective observational study was approved by the Institutional Review Board (CE15098A) and the study protocol followed the Principles of the Declaration of Helsinki. All *B. multicinctus* bite cases were admitted to VGH-TC or VGH-TP between July 1995 and July 2014. The patients were initially identified by searching the computerized database of both hospitals using the keywords “snake,” “many-banded snake,” “umbrella snake,” “*B. multicinctus*,” and “*B. multicinctus multicinctus*” in both English and Chinese. A “definite case” was diagnosed by examining the culprit snake, whereas a “suspected case” was diagnosed by having the patient to identify the snake in a picture. Patients with typical manifestation as determined through physical examination, serial wound inspection, and a relevant history were included as “clinical case.” After careful review of the medical records, snakebites other than *B. multicinctus* were excluded (e.g., *N. atra*, *T. stejnegeri*, *P. mucrosquamatus*, *D. acutus*, *D. siamensis*, as well as bites of other, less toxic, nonvenomous, or unknown species).

Demographic data and definition of variables. Patient sex, age, bite location, and place of the snakebite were abstracted. Because wound site reactions are minimal in *B. multicinctus* envenomation, the signs and symptoms were arbitrarily organized by motor or sensory effects. “Local” (pain or numbness) describes effects that did not extend beyond the affected limb. “General” (pain or numbness) describes effects spreading to the head/neck, trunk, and/or contralateral limbs. “Numbness” was defined as a feeling of

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decreased sensation, tingling, but might have included subtle weakness. "Pain" was defined as muscle soreness, ache, pain, or their combination. The duration of pain was abstracted from the medical chart that recorded every 2 hours in the first 48 hours post-bite. "Motor effects" included general weakness, respiratory failure, ptosis, diplopia, difficulty in opening the mouth, chewing, or swallowing, and dysarthria. "Sensory effects" included numbness or pain (including eye, throat, head, facial, neck, abdomen, back, or general pain). Miscellaneous effects included dilated pupils (≥ 5 mm without light reflex), abnormal taste, nausea or vomiting, urinary retention, sweating, hypertension ($> 140/90$ mm of Hg), tachycardia (> 100 beats/minute), and bradycardia (< 60 beats/minute). Laboratory findings were recorded on arrival in the emergency department and included hyponatremia (≤ 135 mEq/L), hyperglycemia (≥ 200 mg/dL), and rhabdomyolysis (creatinine kinase [CK] ≥ 1000 U/L). If no abnormalities were mentioned in the medical records, it was assumed that none was present.

Treatment and outcome. Treatments administered, details of specific antivenom administration, complications during hospitalization (e.g., skin allergy or anaphylaxis to antivenom, serum sickness, delirium, or pneumonia), length of hospital stay, residual neurological (e.g., numbness, pain, soreness, or weakness), or gastrointestinal (GI) (e.g., GI upset or constipation) effects reported in the 2 weeks after discharge were abstracted by reviewing the medical records or contacting the patients if necessary. Because this is a retrospective study, a specific follow-up period was not predetermined.

Statistical analysis. Demographic data including signs and symptoms were compared between definite, suspected, and clinical case groups, and in patients with and without respiratory failure using the Mann-Whitney test for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. All data were analyzed with SPSS version 22.0 software (2013 release; IBM Corporation, Armonk, NY). A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Demographic data. No significant differences were found in the demographic data between definite, suspected, and clinical case groups; therefore, the data were combined to facilitate comparison of patients with and without respiratory failure (Table 1). Forty-four patients (33 from VGH-TC and 11 from VGH-TP) were identified, including six patients identified with snake specimen, 27 by a picture, and 11 by typical manifestation; 39 (88.6%) were men and the median age was 41.5 years (range, 19–80). Most bites were on the upper limbs ($N = 29$, 65.9%), in the home or yard (space surrounding a home), at a farm, or on a road. Nine patients (20.5%) experienced a bite without noticeable signs or symptoms of significant envenoming.

Signs and symptoms of envenoming appeared 0.5–6 hours post-bite. Motor effects were identified in 33 (75%) patients, sensory effects in 38 (86.4%), and miscellaneous effects in 35 (79.5%). Twelve patients (27.3%) developed respiratory failure 1.5–6.5 hours post-bite. Moreover, 12 patients experienced severe general pain 1–12 hours post-bite, causing disability, such as inability to get out of bed, cough without distress, or turn the head. The estimated duration of

general pain was 3.5–24 hours. Three patients developed pain in spite of 4–6 vials of antivenom administration before its onset. The median CK levels in patients with and without general pain were significantly different: 273.5 U/L (interquartile range: 182–778.75 U/L) versus 102 U/L (interquartile range: 82.5–174.5 U/L) with a P value of 0.002 by Mann-Whitney U test. Abnormal taste was noted in two patients. General weakness, ptosis, dysarthria, and dilated pupils were significantly associated with respiratory failure. Abnormal laboratory findings included transient hyponatremia in three patients (125, 128, and 134 mEq/L), hyperglycemia in seven (one was subsequently diagnosed with diabetes mellitus), and rhabdomyolysis in one (peak CK level of 1,389 U/L).

Treatment and outcome. All the envenomed patients ($N = 35$) received specific antivenom and the majority of them received antivenom within 4 hours post-bite (Table 2). Twenty-four cases (68.6%, 24/35) received more than four vials of antivenom. An antivenom skin test was performed prior to antivenom administration in all cases. Four of them had positive skin tests. A skin allergic reaction occurred in four patients with negative skin tests, and one of them developed anaphylaxis. Serum sickness occurred in three patients who received four, six, and nine vials of antivenom, respectively, two of whom had a positive antivenom skin test.

Among the 12 cases with respiratory failure (Table 3), five had aspiration pneumonia and two of whom had delirium tremens secondary to alcohol withdrawal or intensive care unit related delirium. Five cases received antivenom doses at or higher than the currently recommended dose (i.e., 2–4 vials) before endotracheal intubation (two vials in three, five in one, and six in one). When no complications occurred during hospitalization, patients ($N = 7$) were successfully weaned from mechanical ventilator after 1.3–2.5 days. In cases with complications ($N = 5$), they had more prolonged ventilator-dependent days (4.3–15.4 days). Sixteen cases received at least an outpatient follow-up after discharge, 10 of whom attended the outpatient clinic within 2 weeks. Nine patients had persistent limb or body numbness, pain, soreness, or weakness. Two patients had persistent GI effects, including GI upset or constipation. No death was reported during the study period. The median follow-up time was 22 days (range: 3–883 days). The prolonged follow-up time in certain cases was due to their underlying medical diseases such as hypertension, degenerative joint disorders, or diabetes mellitus.

DISCUSSION

We carried out a preliminary analysis of the predictors of respiratory failure based on patients' clinical characteristics. General weakness, ptosis, dysarthria, and dilated pupils were significantly associated with the development of respiratory failure. However, after careful review of the medical records, we found that the abovementioned manifestations were usually recorded during or shortly after the onset of respiratory failure that occurred quite fast (< 6 –7 hours) post-bite. Therefore, their predictive role could not be accurately determined in such a retrospective study. As a result, all suspected cases of envenomation should be closely monitored during the first few hours, and sufficient doses of antivenom should be administered promptly if signs and symptoms of *B. multicinctus* envenomation appear.⁹

TABLE 1
Demographic and clinical characteristics of patients with and without respiratory failure after *Bungarus multicinctus* bite in Taiwan

	No respiratory failure	Respiratory failure	Overall	P value
Number of patients	32	12 (27.3%)	44	
Sex (male)	28	11	39 (88.6%)	1
Age in years, median (range)	40 (19–80)	44 (25–72)	41.5 (19–80)	0.16
Snake identification				0.295
Definite case	4	2	6	
Suspected	18	9	27	
Clinical cases	10	1	11	
Bite location				0.50
Upper limbs	20	9	29	
Lower limbs	12	3	15	
Bite place				
Home or yard (space surrounding a home)	5	2	7	
Farm	4	2	6	
Road	3	1	4	
Others*	20	7	27	
Signs and symptoms				
Asymptomatic	9	0	9	
Motor effect	21	12	33	0.02
General weakness	13	12	25	< 0.001
Ptosis	17	12	29	0.003
Diplopia	12	8	20	0.08
Difficult in opening mouth, chewing, or swallowing	9	6	15	0.28
Dysarthria	1	5	6	0.004
Sensory effect	27	11	38	1
Local numbness	10	3	13	1
General numbness	10	6	16	0.30
Pain	22	5	27	0.16
Limb soreness	5	2	7	1
Eyes pain	8	0	8	0.08
Throat pain	7	3	10	1
Head, facial, or neck pain	8	2	10	0.70
Abdominal pain	7	4	11	0.46
Back pain	1	0	1	1
General pain	11	1	12	0.13
Miscellaneous effect	24	11	35	0.41
Dilated pupils (≥ 5 mm)	4	9	13	< 0.001
Abnormal taste	2	0	2	1
Nausea or vomiting	5	2	7	1
Urinary retention	6	1	7	0.65
Sweating	2	3	5	0.12
Hypertension ($> 140/90$ mm of Hg)	21	7	28	0.73
Tachycardia (> 100 beats/minute)	7	5	12	0.26
Bradycardia (< 60 beats/minute)	1	1	2	0.48
Laboratory finding				
Hyponatremia (≤ 135 mEq/L)†	2	1	3	1
Hyperglycemia (≥ 200 mg/dL)	3	4	7	0.08
Rhabdomyolysis (CK ≥ 1000 U/L)	1	0	1	1

CK = creatine kinase.

*Workplaces, riverside, bush, forest, or an unrecorded place.

†125, 128, and 134 mEq/L, respectively.

Notably, seven of our patients who developed respiratory failure received no antivenom or only a small fraction (0–10 vial) of the eventual total dose prior to intubation. Unfamiliarity with managing rare snakebites and limited timely access to antivenom may delay or impede timely antivenom administration.

In Taiwan, only envenomation by *B. multicinctus*, *N. atra*, and *D. siamensis* is known to cause neurologic effects. With *D. siamensis*, the principal clinical effects are hematologic disturbances and renal failure in addition to wound swelling and pain.¹⁰ Although presynaptic neurotoxic phospholipase A₂ (PLA₂) is present in the venom of *D. siamensis*, in human cases only transient drowsiness, dizziness, and faintness, but not neuromuscular block were infrequently observed.^{10,11} In *N. atra* snake envenomation, the principal effect is wound necrosis or infection, with a few cases manifesting transient

and mild weakness or ptosis in the presence of wound swelling and pain.^{2,12,13} On the other hand, *B. multicinctus* causes negligible wound reaction despite the presence of overt neuromuscular blockade and descending paralysis.^{7,9} Although assay of *B. multicinctus* venom was not performed in this study because of its unavailability in all health-care facilities in Taiwan, physicians could easily differentiate *B. multicinctus* envenomation from other venomous snakebites based on clinical examination. In addition, the venom yield of *B. multicinctus* is only one-fifth to that of *Bungarus caeruleus* (4.4 mg versus 22.7 mg), which may make its venom detection in serum samples more difficult.^{2,9,14} In this study, all cases were carefully examined by physical examination, serial wound inspection, and a relevant history; in addition, the signs and symptoms were similar between definite, suspected, and clinical case groups (data not

TABLE 2
Treatment and outcome of 35 *Bungarus multicinctus* envenomed cases

	No respiratory failure	Respiratory failure	Overall
Number of patients	23	12	35
Positive antivenom skin test	4	0	4
Skin allergy to antivenom*	1	3	4
Anaphylaxis to antivenom	0	1	1
Serum sickness	1	2	3
Time elapsed between snakebite and antivenom administration			
< 4 hours	19	11	30
4–8 hours	3	1	4
> 8 hours	1	0	1
Total dose, vial (median, range)	6 (1–13)	8 (2–11)	7 (1–13)
Complication during hospitalization			
Delirium†	0	2	2
Pneumonia‡	0	5	5
Hospital stay, day (median, range)	2 (1–6)	7.5 (4–29)	3 (1–29)
Any numbness, soreness, or weakness 2 weeks after discharge	3/4	6/6	9/10
Any GI symptoms 2 weeks after discharge	2/4	0/6	2/10

GI = gastrointestinal.

*Rash, urticaria, or angioedema.

†Alcohol-withdrawal delirium tremens in one and intensive care unit related delirium in the other.

‡Aspiration pneumonia.

shown). Given that only single krait species (*Bungarus* sp.) was distributed to Taiwan, clinical diagnosis of *B. multicinctus* envenomation is very likely to be convincing.

Other differential diagnosis of respiratory paralysis with/ or resembling descending paralysis may include botulism, myasthenia gravis, and Miller–Fisher syndrome.^{15,16} All 12 patients with respiratory paralysis in this study were carefully assessed for the abovementioned disorders. All of them were bitten when they caught the snake and were free from neuromuscular symptom before the snakebite. Only one case consumed alcohol every day and the blood alcohol level before performing endotracheal intubation was 171 mg/dL. There was also no cluster occurrence of paralysis among the study subjects, which made food-borne botulism less likely.¹⁶ Moreover, all patients recovered rapidly after the administration of specific bivalent antivenom for *B. multicinctus* and *N. atra*, a finding that should have excluded the diagnosis of botulism.

Bungarus multicinctus venom contains several neurotoxins and enzymes, including muscle or neuronal nicotinic acetylcholine receptor (AChR) and muscarinic receptor antagonists. α -Bungarotoxin, first isolated from *B. multicinctus* in Taiwan, binds to the mammalian muscle nicotinic AChR with high affinity, causing a rapid curare-like neuromuscular block, whereas β -bungarotoxin with PLA₂ activity acts pre-

synaptically in the neuromuscular junction, causing damage to nerve endings and further inhibiting impulse conduction.^{17,18} κ -Bungarotoxin blocks postsynaptic nicotinic AChRs in autonomic ganglia,¹⁹ whereas the novel γ -bungarotoxin, which has less characterized clinical effects, inhibits muscarinic and nicotinic AChRs and platelet aggregation.²⁰ The weight percentages of α -, β -, and κ -bungarotoxin in *B. multicinctus* venom are 13–61%,^{21,22} 22–26.4% (sum of β 1–5),^{22,23} and 0.1%,¹⁹ respectively. The median lethal doses (LD₅₀) of the crude venom and α -, β -, and γ -bungarotoxin in mice were 0.16, 0.3, 0.089 (s.c.),²² and 0.15 (i.v.) mg/kg,²⁴ respectively. These are rough estimates because venom from individual snakes may not include all the toxin isoforms. Other enzymes or peptides of unevaluated clinical significance are present in the venom as well.²⁵

The hallmark of *B. multicinctus* envenomation is neuromuscular blockade caused by bungarotoxins.^{9,22} Twenty-seven percent of our patients developed respiratory failure within 1.5–6.5 hours post-bite. It is generally accepted that presynaptic neurotoxin (e.g., β -bungarotoxin) is the primary cause of muscular paralysis.^{9,26} Rapid fixation and irreversible damage to the nerve terminals by β -bungarotoxin may account for the resistance to antivenom therapy when administration is delayed.^{22,26} Clinical experience suggested

TABLE 3
Characteristics of 12 patients with respiratory failure after *Bungarus multicinctus* bite in Taiwan

Patients number	Gender	Age (years)	Time elapsed from snakebite to respiratory failure (hours)	Ventilator dependence (days)	Dose of antivenom received before endotracheal intubation (vials)	Complications during hospitalization*
1	Male	36	6.5	1.3	2	No
2	Male	43	2.0	1.8	6	No
3	Female	40	5.0	2.1	5	No
4	Male	37	4.7	2.2	1	No
5	Male	72	2.4	2.4	1	No
6	Male	25	1.5	2.5	2	No
7	Male	47	2.0	2.5	1	No
8	Male	47	2.0	4.3	0	Yes
9	Male	42	1.8	6.3	1	Yes
10	Male	52	3.5	8.7	0	Yes
11	Male	45	5.0	12.2	1	Yes
12	Male	51	2.5	15.4	2	Yes

*Complications listed in Table 2.

that unless antivenom is administered within 4 hours after a snakebite causing presynaptic neurotoxicity, most patients continued to deteriorate and required endotracheal intubation with mechanical ventilation.²⁷ In our study, patients developed respiratory failure in spite of antivenom administration within 4 hours post-bite, and in a few patients, the preintubation doses were significantly higher than the currently recommended dose of 2–4 vials.² Our observation suggests that the recommended doses of *B. multicinctus* and *N. atra* antivenom are not sufficient to prevent respiratory failure, perhaps because of its intrinsic pharmacokinetic properties compared with the far more rapid distribution of toxins.^{28,29} On the other hand, our study is consistent with previous reports that early antivenom administration was associated with accelerated recovery which might have been related to various proportions of β -bungarotoxin in the individual snakes.^{23,30,31} Nevertheless, the contribution of α -bungarotoxin in neuromuscular paralysis is unassessed.

The second most frequent distinct symptom of *Bungarus* snakebite is pain remote from the bite site of undetermined mechanism, which has been described in cases of *Bungarus* spp. envenomations including abdominal pain due to bites from *Bungarus* cf. *sindanus*,³² *B. caeruleus*,³³ and *Bungarus lividus*³⁴; generalized burning sensation due to bites from *B. lividus*³⁴; or muscle pain due to bites from *B. caeruleus*,³⁵ *Bungarus candidus*,³⁶ *Bungarus niger*,³⁷ and *B. multicinctus*.⁷ A significant proportion of our patients developed severe general pain. Patients described the pain as similar to myalgia after heavy exercise but much more intense, especially in the head and neck and trunk in addition to the limbs. It is known that curare-like muscle relaxation (e.g., α -bungarotoxin or nondepolarizing muscle relaxants) is not associated with muscle pain, whereas depolarizing relaxation induced by succinylcholine can lead to muscle pain in the throat, shoulder, and abdomen.^{38–40} The biochemical mechanisms that have been associated with succinylcholine-induced myalgia included increased myoplasmic calcium, activation of cellular PLA_2 and resultant myocyte phospholipid degradation, and release of free fatty acids.⁴¹ β -Bungarotoxin, which has PLA_2 activity, might degrade the postsynaptic muscle membrane as well as the presynaptic nerve terminals.⁴² In fact, the CK level was slightly, but significantly higher in patients with general pain, a phenomenon that is also observed in succinylcholine-induced myalgia.⁴¹ Moreover, the painful area occurred in anatomic regions did not correspond to the distribution of peripheral nerves. It is possible that general pain developed after *B. multicinctus* envenomation is related to the enzymatic effect of β -bungarotoxin on muscles. In our observation, patients usually did not experience pain relief after nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ketoprofen or ketorolac) administration. Instead, the pain was ameliorated by tramadol treatment. Further prospective evaluation is warranted to quantify the nature of pain and see whether better pain management can be achieved with antivenom, NSAIDs, or tramadol/other opioids.^{39,40}

Autonomic effects have been described after *B. multicinctus*^{4,6,7} and other *Bungarus* spp. envenomations,^{34,43} including dilated pupils, nausea or vomiting, urine retention, changes in blood pressure or heart rate, sweating, and hyperglycemia. Prolonged decreases in parasympathetic functions (i.e., mydriasis, tachycardia, hypertension, consti-

pation, or difficulty in urinating) lasting for months to years, have been reported in patients with *B. candidus* envenomation who were not given antivenom.⁴⁴ Two patients in our study had prolonged constipation or GI upset, and two others experienced abnormal taste sensations. β -Bungarotoxin may also have an inhibitory effect on the parasympathetic nerve terminals at the neuroeffector junction in mammals.⁴⁵ By contrast, α -bungarotoxin did not affect ganglionic nicotinic neurotransmission in mammals.⁴⁶ Although in *in vitro* studies, the minor component κ -bungarotoxin (0.1%) potently blocked postsynaptic nicotinic AChRs of various species, including avian ciliary ganglia (parasympathetic system), avian and rat sympathetic ganglia, cultured bovine chromaffin cells, and even invertebrate central nervous system cells,^{46,47} given the difference in weight percentages of β - and κ -bungarotoxin in the venom, these effects are more likely to be induced by β -bungarotoxin.¹⁹ The mechanism of abnormal taste remains unknown but might also involve the acetylcholine transmission pathway.⁴⁸ As the effect on autonomic and taste functions was not vigorously evaluated in this study, the clinical significance of these effects may have been overlooked.

Recently, a new syndrome of life-threatening hyponatremia was identified in cases of *B. multicinctus* and *B. candidus* envenomation in Vietnam.^{49,50} Approximately 42–50% of patients who did not receive antivenom developed significant hyponatremia (< 130 mEq/L) 2–3 days post-bite.^{7,30,49} In Taiwan, life-threatening hyponatremia was not observed after *B. multicinctus* envenomation, which might be due to geographical variation in the venom of *B. multicinctus*. Nevertheless, early administration of specific antivenom might have prevented serious hyponatremia, as only three cases in this study had developed hyponatremia and all spontaneously recovered.

Four types of antivenom, ammonium sulfate-precipitated and lyophilized formulations containing F(ab')_2 , are available in Taiwan. They are bivalent *B. multicinctus* and *N. atra* antivenom, bivalent *T. stejnegeri* and *P. mucrosquamatus* antivenom, and monovalent *D. acutus* and *D. siamensis* antivenom.² One vial of bivalent specific antivenom for *B. multicinctus* and *N. atra* roughly neutralizes 2 mg venom of *B. multicinctus*.² Because the mean quantity of *B. multicinctus* venom extracted by milking is 4.4 mg, the Taiwan Poison Control Center has thus recommended 2–4 vials of antivenom to be administered in an envenomed case.² The abovementioned recommendation, however, was not validated in any prior study. Because F(ab')_2 fragment has much slower distribution kinetics than venom, a higher dose may have been required to achieve effective tissue accumulation after envenomation.²⁹

In this study, not all treatments adhered to the protocol recommended by the Taiwan Poison Control Center.² Therefore, it is difficult to evaluate the effectiveness of different dosing regimens of antivenom. However, it appears that the dosage administered in respiratory failure cases is higher than that in patients without respiratory failure. Hung and others recommended that first and second doses totaling 5–10 vials of antivenom given 6–8 hours apart be used to treat a *B. multicinctus* bite.³⁰ Silva and others reported using 20 vials of antivenom once to treat a patient bitten by *B. caeruleus*.^{9,14,51} Based on the limited evidence, we suggest that an initial dose of four vials of antivenom be administered

in all envenomation cases, and a subsequent four vials be considered if the patient's condition is deteriorating.⁵² Further evaluation is needed to determine the optimal dosing regimen for management of *B. multicinctus* bites.

An antivenom skin test is recommended by the manufacturer before administration of the antivenom.² In our study, four patients had a positive skin test, and skin rashes occurred in another four patients (11.4%) who had a negative skin test. The reported incidence of early adverse reactions after the administration of ammonium sulfate-precipitated IgG or F(ab')₂ antivenom ranges from 10–87%.⁵³ It has been proposed that routine premedication with low-dose epinephrine would decrease severe allergic reaction, in which the incidence of such reaction was high.⁵⁴ In Taiwan, only 0.7–3% of patients receiving bivalent *T. stejnegeri* and *P. mucrosquamatus* antivenom were reported to have a skin allergy.^{55,56} Moreover, anaphylaxis was only reported in this study despite the fact that nearly 1,000 cases received antivenom in Taiwan each year.¹ Because of the overall low incidence of allergic reactions after antivenom administration, routine premedication with epinephrine or antihistamines and corticosteroids is not recommended in Taiwan.⁵⁷ Moreover, all patients received antivenom regardless of the result of antivenom skin test in this study. Given that the administration of a small test dose of antivenom to identify patients who may develop acute adverse reactions to the antivenom is both insensitive and nonspecific,⁵⁴ the antivenom skin test should better be omitted.⁵²

Limitations. This study has several limitations. First, because laboratory venom test is not available in Taiwan, a diagnosis via venom assay remains problematic. However, among the six major species of venomous snakes, *B. multicinctus* causes unique clinical signs and symptoms. Clinicians therefore could easily differentiate *B. multicinctus* envenomation from the other possibilities. Second, the number of patients was small, which may limit the analysis of some potential, clinically significant predictors of respiratory failure. Finally, this is a retrospective observational study and the occurrence of various symptoms partly depends on the intensity of monitoring. Therefore, our findings should be cautiously interpreted.

CONCLUSIONS

Of 44 cases of *B. multicinctus* snakebite, nine (20.5%) were asymptomatic, 12 patients (27.3%) experienced respiratory failure, and 12 (27.3%) had transient but debilitating severe general pain. The toxic effects of venom began between 0.5–6 hours post-bite and respiratory failure occurred within 1.5–6.5 hours post-bite. The neuromuscular, pain, or autonomic effects may have been caused, at least partly, by β -bungarotoxin. Because patients envenomed by *B. multicinctus* may develop respiratory failure within a short time, all suspicious envenomed cases should be closely monitored in the first few hours. We suggest that four vials of antivenom be administered in all envenomed cases and a subsequent four vials be considered if the patient's condition is deteriorating. Further prospective study is warranted to characterize the nature of pain and to identify the optimal antivenom dosing regimen in the management of *B. multicinctus* envenomation.

Received January 3, 2017. Accepted for publication February 14, 2017.

Published online March 27, 2017.

Disclaimer: The authors alone are responsible for the content and writing of this paper.

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REFERENCES

1. Mao YC, Hung DZ, 2015. Epidemiology of snake envenomation in Taiwan. *Clinical Toxinology in Asia Pacific and Africa*. Singapore: Springer, 3–22.
2. Mao YC, Hung DZ, 2015. Management of snake envenomation in Taiwan. *Clinical Toxinology in Asia Pacific and Africa*. Singapore: Springer, 23–52.
3. Uetz P, Freed P, Hošek J, (eds), 2016. *The Reptile Database*. Available at: <http://www.reptile-database.org>. Accessed February 1, 2017.
4. Pe T, Myint T, Htut A, Htut T, Myint AA, Aung NN, 1997. Envenoming by Chinese krait (*Bungarus multicinctus*) and banded krait (*B. fasciatus*) in Myanmar. *Trans R Soc Trop Med Hyg* 91: 686–688.
5. Sawai Y, Kawamura Y, Toriba M, Kobayashi T, Wang NP, Li CB, Li ZY, Li HP, Tang SX, 1992. An epidemiological study on the snakebites in Guangxi Zhuang autonomous region, China in 1990. *The Snake* 24: 1–15.
6. Kuo TP, Wu CS, 1972. Clinico-pathological studies on snakebites in Taiwan. *J Formos Med Assoc* 71: 447–466.
7. Hung HT, Hojer J, Du NT, 2009. Clinical features of 60 consecutive ICU-treated patients envenomed by *Bungarus multicinctus*. *Southeast Asian J Trop Med Public Health* 40: 518–524.
8. Hung DZ, Wu TC, Deng JF, 1997. The painful experience of inappropriate therapy of snake bites: a report of two cases. *Zhonghua Yi Xue Za Zhi (Taipei)* 60: 326–330.
9. Silva A, Maduwage K, Sedgwick M, Pilapitiya S, Weerawansa P, Dahanayaka NJ, Buckley NA, Johnston C, Siribaddana S, Isbister GK, 2016. Neuromuscular effects of common krait (*Bungarus caeruleus*) envenoming in Sri Lanka. *PLoS Negl Trop Dis* 10: e0004368.
10. Hung DZ, Wu ML, Deng JF, Lin-Shiau SY, 2002. Russell's viper snakebite in Taiwan: differences from other Asian countries. *Toxicon* 40: 1291–1298.
11. Myint L, Warrell DA, Phillips RE, Tin Nu S, Tun P, Maung Maung L, 1985. Bites by Russell's viper (*Vipera russelli siamensis*) in Burma: haemostatic, vascular, and renal disturbances and response to treatment. *Lancet* 2: 1259–1264.

12. Wang W, Chen QF, Yin RX, Zhu JJ, Li QB, Chang HH, Wu YB, Michelson E, 2014. Clinical features and treatment experience: a review of 292 Chinese cobra snakebites. *Environ Toxicol Pharmacol* 37: 648–655.
13. Mao YC, Liu PY, Hung DZ, Lai WC, Huang ST, Hung YM, Yang CC, 2016. Bacteriology of *Naja atra* snakebite wound and its implications for antibiotic therapy. *Am J Trop Med Hyg* 94: 1129–1135.
14. Whitaker R, Whitaker S, 2012. Venom, antivenom production and the medically important snakes of India. *Curr Sci* 103: 635–643.
15. Nelson L, Shawn L, 2012. Case studies in toxicology: descending paralysis ascending the path to diagnosis. *Emergency Medicine-Chatham* 44: 4.
16. Sobel J, 2005. Botulism. *Clin Infect Dis* 41: 1167–1173.
17. Nirthanam S, Gwee MC, 2004. Three-finger alpha-neurotoxins and the nicotinic acetylcholine receptor, forty years on. *J Pharmacol Sci* 94: 1–17.
18. Rowan EG, 2001. What does β -bungarotoxin do at the neuromuscular junction. *Toxicon* 39: 107–118.
19. Chiappinelli VA, 1983. Kappa-bungarotoxin: a probe for the neuronal nicotinic receptor in the avian ciliary ganglion. *Brain Res* 277: 9–22.
20. Chang LS, Chung C, Wu BN, Yang CC, 2002. Characterization and gene organization of Taiwan banded krait (*Bungarus multicinctus*) gamma-bungarotoxin. *J Protein Chem* 21: 223–229.
21. Chiappinelli V, 1991. κ -Neurotoxins and α -neurotoxins: effects on neuronal nicotinic acetylcholine receptors. *Snake toxins*. New York, NY: Pergamon Press, 223–258.
22. Chang CC, Lee CY, 1963. Isolation of neurotoxins from the venom of *Bungarus multicinctus* and their modes of neuromuscular blocking action. *Arch Int Pharmacodyn Ther* 144: 241–257.
23. Kondo K, Toda H, Narita K, Lee CY, 1982. Amino acid sequences of three beta-bungarotoxins (beta 3-, beta 4-, and beta 5- bungarotoxins) from *Bungarus multicinctus* venom. Amino acid substitutions in the A chains. *J Biochem* 91: 1531–1548.
24. Aird SD, Womble GC, Yates JR 3rd, Griffin PR, 1999. Primary structure of gamma-bungarotoxin, a new postsynaptic neurotoxin from venom of *Bungarus multicinctus*. *Toxicon* 37: 609–625.
25. Lee CY, Chang SL, Kau ST, Luh SH, 1972. Chromatographic separation of the venom of *Bungarus multicinctus* and characterization of its components. *J Chromatogr A* 72: 71–82.
26. Prasampun S, Walsh J, Awad SS, Harris JB, 2005. Envenoming bites by kraits: the biological basis of treatment-resistant neuromuscular paralysis. *Brain* 128: 2987–2996.
27. Harris JB, Scott-Davey T, 2013. Secreted phospholipases A2 of snake venoms: effects on the peripheral neuromuscular system with comments on the role of phospholipases A2 in disorders of the CNS and their uses in industry. *Toxins (Basel)* 5: 2533–2571.
28. Lee CY, Tseng LF, 1966. Distribution of *Bungarus multicinctus* venom following envenomation. *Toxicon* 3: 281–290.
29. Gutierrez JM, Leon G, Lomonte B, 2003. Pharmacokinetic-pharmacodynamic relationships of immunoglobulin therapy for envenomation. *Clin Pharmacokinet* 42: 721–741.
30. Hung HT, Höjer J, Kiem TX, Du NT, 2010. A controlled clinical trial of a novel antivenom in patients envenomed by *Bungarus multicinctus*. *J Med Toxicol* 6: 393–397.
31. Chiappinelli VA, Wolf KM, 1989. Kappa-neurotoxins: heterodimer formation between different neuronal nicotinic receptor antagonists. *Biochemistry* 28: 8543–8547.
32. Pillai LV, Ambike D, Husainy S, Khaire A, Captain A, Kuch U, 2012. Severe neurotoxic envenoming and cardiac complications after the bite of a 'Sind Krait' (*Bungarus cf. sindanus*) in Maharashtra, India. *Trop Med Health* 40: 103–108.
33. Ariaratnam CA, Sheriff MH, Theakston RD, Warrell DA, 2008. Distinctive epidemiologic and clinical features of common krait (*Bungarus caeruleus*) bites in Sri Lanka. *Am J Trop Med Hyg* 79: 458–462.
34. Kuch U, Sharma SK, Alirol E, Chappuis F, 2011. Fatal neurotoxic envenomation from the bite of a lesser black krait (*Bungarus lividus*) in Nepal. *Southeast Asian J Trop Med Public Health* 42: 960–964.
35. Theakston RD, Phillips RE, Warrell DA, Galagedera Y, Abeysekera DT, Dissanayaka P, de Silva A, Aloysius DJ, 1990. Envenoming by the common krait (*Bungarus caeruleus*) and Sri Lankan cobra (*Naja naja naja*): efficacy and complications of therapy with Haffkine antivenom. *Trans R Soc Trop Med Hyg* 84: 301–308.
36. Warrell DA, Looareesuwan S, White NJ, Theakston RD, Warrell MJ, Kosakarn W, Reid HA, 1983. Severe neurotoxic envenoming by the Malayan krait *Bungarus candidus* (Linnaeus): response to antivenom and anticholinesterase. *Br Med J (Clin Res Ed)* 286: 678–680.
37. Faiz A, Ghose A, Ahsan F, Rahman R, Amin R, Hassan MU, Chowdhury AW, Kuch U, Rocha T, Harris JB, Theakston RD, Warrell DA, 2010. The greater black krait (*Bungarus niger*), a newly recognized cause of neuro-myotoxic snake bite envenoming in Bangladesh. *Brain* 133: 3181–3193.
38. Appiah-Ankam J, Hunter JM, 2004. Pharmacology of neuromuscular blocking drugs. *Contin Educ Anaesth Crit Care Pain* 4: 2–7.
39. Nasser K, Arvien S, 2016. Effects of low-dose ketamine on succinylcholine-induced postoperative myalgia in outpatient surgeries: a randomized, double-blind study. *J Pain Res* 9: 503–508.
40. White DC, 1962. Observations on the prevention of muscle pains after suxamethonium. *Br J Anaesth* 34: 332–335.
41. McLoughlin C, Elliott P, McCarthy G, Mirakhur R, 1992. Muscle pains and biochemical changes following suxamethonium administration after six pretreatment regimens. *Anaesthesia* 47: 202–206.
42. Storella RJ, Schouchoff AL, Fujii M, Hill J, Fletcher JE, Jiang MS, Smith LA, 1992. Preliminary evidence for a postsynaptic action of beta-bungarotoxin in mammalian skeletal muscle. *Toxicon* 30: 349–354.
43. Bawaskar HS, Bawaskar PH, Bawaskar PH, 2014. Premonitory signs and symptoms of envenoming by common krait (*Bungarus caeruleus*). *Trop Doct* 44: 82–85.
44. Laothong C, Sitprija V, 2001. Decreased parasympathetic activities in Malayan krait (*Bungarus candidus*) envenoming. *Toxicon* 39: 1353–1357.
45. Muramatsu I, Fujiwara M, Miura A, Hayashi K, Lee C-Y, 1980. Beta-bungarotoxin and parasympathetic nerve blocking action. *J Pharmacol Exp Ther* 213: 156–160.
46. Chiappinelli VA, 1985. Actions of snake venom toxins on neuronal nicotinic receptors and other neuronal receptors. *Pharmacol Ther* 31: 1–32.
47. Pinnock R, Lummis S, Chiappinelli V, Sattelle D, 1988. κ -bungarotoxin blocks an α -bungarotoxin-sensitive nicotinic receptor in the insect central nervous system. *Brain Res* 458: 45–52.
48. Dando R, Roper SD, 2012. Acetylcholine is released from taste cells, enhancing taste signalling. *J Physiol* 590: 3009–3017.
49. Hojer J, Tran Hung H, Warrell D, 2010. Life-threatening hyponatremia after krait bite envenoming: a new syndrome. *Clin Toxicol (Phila)* 48: 956–957.
50. Trinh KX, Khac QL, Trinh LX, Warrell DA, 2010. Hyponatraemia, rhabdomyolysis, alterations in blood pressure and persistent mydriasis in patients envenomed by Malayan kraits (*Bungarus candidus*) in southern Viet Nam. *Toxicon* 56: 1070–1075.
51. Simpson ID, Norris RL, 2007. Snake antivenom product guidelines in India: "The devil is in the details." *Wilderness Environ Med* 18: 163–168.
52. World Health Organization Regional Office for South-East Asia, 2016. *Guidelines for the Management of Snake-bites*. New Delhi, India: World Health Organization Regional Office for South-East Asia.
53. Otero R, Gutierrez JM, Rojas G, Nunez V, Diaz A, Miranda E, Uribe AF, Silva JF, Ospina JG, Medina Y, Toro MF, Garcia

- ME, Leon G, Garcia M, Lizano S, De La Torre J, Marquez J, Mena Y, Gonzalez N, Arenas LC, Puzon A, Blanco N, Sierra A, Espinal ME, Lozano R, 1999. A randomized blinded clinical trial of two antivenoms, prepared by caprylic acid or ammonium sulphate fractionation of IgG, in *Bothrops* and *Porthidium* snake bites in Colombia: correlation between safety and biochemical characteristics of antivenoms. *Toxicon* 37: 895–908.
54. de Silva HA, Ryan NM, de Silva HJ, 2016. Adverse reactions to snake antivenom, and their prevention and treatment. *Br J Clin Pharmacol* 81: 446–452.
55. Chen YC, Chen MH, Wang LM, Wu JJ, Huang CI, Lee CH, Yen DH, Yang CC, 2007. Antivenom therapy for crotaline snakebites: has the poison control center provided effective guidelines? *J Formos Med Assoc* 106: 1057–1062.
56. Chen JC, Bullard MJ, Chiu TF, Ng CJ, Liaw SJ, 2000. Risk of immediate effects from F(ab)2 bivalent antivenin in Taiwan. *Wilderness Environ Med* 11: 163–167.
57. Lin CC, Chaou CH, Tseng CY, 2015. An investigation of snakebite antivenom usage in Taiwan. *J Formos Med Assoc* 115: 672–677.