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ORIGINAL ARTICLE

Descriptive Study of Snakebite Patients in Northern Taiwan: 2009 to 2016

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Background: Taiwan is located in a subtropical area where there are approximately 50 kinds of land snakes and six principal kinds of venous snakes. Snakebite envenomation is not an uncommon issue in Taiwan. We design a study to obtain an understanding of the characteristics of snakebites and snakebite patients in a medical center in northern Taiwan. **Materials and Methods:** This was a retrospective medical records study of an 8-year period. We used the key word "snake" to search the emergency department (ED) diagnosis of all patients and then used antivenom management codes to select patients for inclusion. The species of snake involved, time and site of the bite, geographic data of the patients and patient outcomes were recorded. **Results:** In total, there were 125 snakebite patients (male 70%, female 30%). The snakes involved were *Protobothrops mucrosquamatus* (50%), followed by *Trimeresurus stejnegeri* (7%). The feet and ankles were the most frequently bitten areas (42.4%). The peak months were July and October. The average ED stasis time was 2 hours and 45 minutes, and 65.6% of snakebite patients received antivenom. In patients bitten by *P. mucrosquamatus*, there was a high surgical rate, 23.8% higher than those reported in other studies. No mortalities or side effects of antivenom were reported in these patients. **Conclusion:** We propose a clinical flow chart for physicians who are treating patients bitten by *P. mucrosquamatus*. Snakebites, especially those inflicted by *P. mucrosquamatus*, induce severe soft tissue swelling, which can mimic compartment syndrome. Antivenom for *P. mucrosquamatus* is the first and only choice of treatment. The amount of antivenom needs to match the clinical symptoms. Patients bitten by *P. mucrosquamatus* may need longer observation times than patients bitten by other species of snakes, in addition to toxicologist consultations, sonographic examinations, and measurement of the objective compartment pressure before surgery.

Key words: Snake, compartment syndrome, *Protobothrops mucrosquamatus*, *Trimeresurus stejnegeri*

INTRODUCTION

Snakebite envenomation is not an uncommon issue in Taiwan. It is important for clinical physicians to understand the characteristics of snakebites. Taiwan is located in a subtropical area where there are approximately 50 kinds of land snakes and six principal kinds of venous snakes belonging to two families, the *Viperidae,* and the *Elapidae*.[1]

Dr. Hong indicated that snakebites on the whole island were most commonly attributed to *Protobothrops mucrosquamatus* and *Trimeresurus stejnegeri* between 1995 and 2000.[2] The epidemiological distribution of bites from other snakes varies, with *Deinagkistrodon acutus* and *Daboia russelli siamensis* in the southern and eastern parts of the island and *Naja atra* the most common in central Taiwan.[2] However, as time passes, the incidence of snakebites may be changing. The characteristics of and surgical interventions performed on snakebite patients in Northern Taiwan had not been evaluated. We designed a single-hospital retrospective chart review study from 2009 to 2016 to evaluate the most commonly encountered snake species,

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the most common time of year for snakebites, the most frequently bitten sites on the body, and the disposition and management of snakebite patients. *P. mucrosquamatus* was the most commonly encountered snake in Northern Taiwan, and about half of the patients bitten by this snake were discharged from the emergency department (ED) after longer observation times, having received, on average, 4 vials of antivenom. Higher surgical rates were also observed in the patients bitten by *P. mucrosquamatus*.

MATERIALS AND METHODS

Tri-Service General Hospital is a medical center located in Northern Taiwan, in the Neihu area, surrounded by mountains. Tri-Service General Hospital receives snakebite patients from the Jinshan, Wanli, and Ruifang District as well as from Keelung City. Approval was obtained from the Institutional Review Board of the Tri-Service General Hospital (1-106-05-103). For the 8-year period from 2009 to 2016, in this retrospective study, we used the keyword "snake" to search the medical records of patients treated in the ED. The inclusion criteria are the snake-bite patient, from medical record. The species of snake involved, the time of year of the bite, the site of the bite, the gender and age of the patients, and the outcomes of patients (admission days, surgical intervention, and ED stasis time) were reviewed manually. We also used the management code for antivenom (in the Details of Ambulatory Care Orders of the National Health Insurance research databases) to search for and confirm the patients who received antivenom. "Antivenin of *Bungarus multicinctus* and *N. atra*" is coded as J000006212 and "Antivenin of *P. mucrosquamatus* and *T. gramineus*" is coded as J000009212. We used the two methods to ensure that we included all snakebite patients. The chart review was performed by an ED physician and information identifying the patients was removed. The abstractor did not know the results before data collection and the collective data, such surgical decision, the kind and the amounts of antivenom, the ED observation time, the admission days were all recorded from medical records, no artificial error.[3]

RESULTS

Demographic data

During the 8-year period (2009–2016), there was a total of 125 snakebite patients (male 70%, female 30%), with an average of 15.6 snakebite patients per year. The peak months were July and October [Figure 1a]. The foot (including toes and ankle, 65 patients, 52%) was the most common site of the snakebites [Figure 1b].

Seventy-five patients (60%) were bitten by venomous snakes, 3 patients (2%) were bitten by nonvenomous (NV) snakes, and 47 patients (38%) were bitten by snakes of unknown type that were possibly NV [Table 1]. Most patients were bitten by *P. mucrosquamatus* (63 patients, 50%), followed by *T. stejnegeri* (9 patients, 7%), and *N. atra* (2 patients, 2%); only one patient was bitten by *B. multicinctus* (1%) [Table 1]. There were no patients bitten by *D. russelli siamensis* or *D. acutus* in this area. The three kinds of NV snakes were recorded as *Python regius*, *Dinodon rufozonatum, and Elaphe porphyracea nigrofasciata*.

Antivenom: Doses, frequency, and side effects

Among all snakebite patients, 82 patients (65.6%) received antivenom [Table 2]. Among the 75 patients bitten by venomous snakes, 70 patients (93%) received antivenom in our hospital [Table 2]. The other five patients initially received antivenom in another hospital and were transferred to our ED for surgery. On the other hand, among the patients bitten by unknown species of snakes, there were 12 patients (25.5%) who received antivenom [Table 2]. In Taiwan, the horse-derived antivenom is manufactured by the Centers for Disease Control, Department of Health, Taiwan (Taiwan CDC).[4] The Taiwan's National Poison Control Center (PCC-Taiwan) uses antivenom to neutralize

Table 1: Disposition of snakebite patients: Persons (%)

Snake	Admission (%)			OPD (%)	AMA (%)	Total (%)
	Surgery	Wound monitor	Total			
PM	15 (22)	23 (37)	38 (59)	23 (38)	2 (3)	63 (50)
TS	1 (11)	0	1 (11)	8 (89)	0	9 (7)
NA	1 (1)	0	1 (1)	1 (1)	0	2 (2)
BM	0	0	0	1 (100)	0	1 (1)
UK	0	0	0	47 (100)	0	47 (38)
NV	0	0	0	3 (100)	0	3 (2)
Total	17 (14)	23 (18)	40 (31)	83 (67)	2 (2)	125 (100)

PM=*Protobothrops mucrosquamatus*; TS=*Trimeresurus stejnegeri*; NA=*Naja atra*; BM=*Bungarus multicinctus*; UK=Unknown kinds; NV=Nonvenous snake, OPD=Outpatient department, AMA=Against medical advice

Table 2: Condition of antivenom usage among various kinds of snakes

	Snake kinds						Total
	PM	TS	NA	BM	UK	NV	
Received antivenom (patients)	59	8	2	1	12	0	82
Average (vials)	4.5	2.8	4	5	2	0	4.1
Nonreceived (patients)	4	1	0	0	35	3	43
Total	63	9	2	1	47	3	125

PM: *Protobothrops mucrosquamatus*; TS: *Trimeresurus stejnegeri*; NA: *Naja atra*; BM: *Bungarus multicinctus*; UK: Unknown kinds; NV: Nonvenous snake

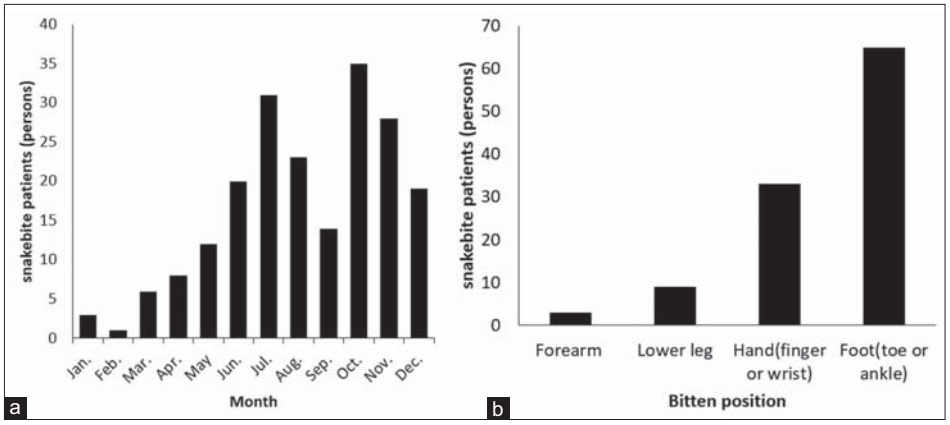

Figure 1: Timing and anatomic sites of snakebite during 2009–2016, total 125 snakebite patients (a) the peak incidence was noted in October (35 patients) and July (31 patients). (b) The most bitten area was foot area (including toe or ankle) (65 patients, 52%)

lethal doses of crude snake venom, and the recommended antivenom doses are 1–2 vials for *T. stejnegeri*, 2–4 vials for *P. mucrosquamatus*, 2–4 vials for *D. acutus*, 2–4 vials for *D. russelli siamensis*, 6–10 vials for *N. atra*, and 2–4 vials for *B. multicinctus*.[5] In our study, the average doses of antivenom were 4.5 vials for *P. mucrosquamatus*, 2.8 vials for *T. stejnegeri*, 4 vials for *N. atra*, 5 vials for *B. multicinctus*, and 2 vials for unknown species [Table 2]. These doses of antivenom were close to the doses recommended by the PCC-Taiwan, except that used to treat bites by *N. atra*.[5] There were only two cases of *N. atra* bites during this 8-year period. One patient was admitted for debridement and received 6 vials, and the other was discharged from ED after initially receiving 2 vials. There was only one patient bitten by *B. multicinctus*; that patient did not present respiratory failure, received 5 vials of antivenom and then was discharged from the ED after a stasis time of 5 days. Dr. Mao indicated that of the patients bitten by *B. multicinctus*, 20.5% had no significant symptoms, 27.3% had respiratory failure and 27.3% had severe general pain.[6]

Dispositions of snakebite patients: Emergency department stasis, admission, antibiotics, and surgery

Of the 125 snakebite patients, 84 patients (67%) could be discharged after appropriate treatment in the ED and then followed in the outpatient department [Table 1], and the average ED stasis time was 2 h and 45 min [Table 3]. Of the snakebite patients, 39 (31%) were admitted, and the average number of days spent in the hospital was 8 [Tables 1 and 3]. In our hospital practice, emergent physicians care the snakebite patients initially and consulted with the plastic surgeon if the wound got severe swelling and tense. Then, the plastic surgeon decided to admit or not. Of the admitted patients, 16 (41%) received surgery, and the other 23 (59%) were admitted for wound observation [Table 3]. Patients had significant longer hospital stays for surgery than for wound monitoring (11.8 vs. 5 days) and received, on average, 3.8 vials and 5.4 vials of antivenom, respectively [Table 3].

Table 3: Disposition of patients

Disposition	Patients (%)	Admission/ED observation	Antivenom (vials)
Admission	39 (31)	8 days	4.7
Fasciotomy	16 (41)	11.8 days	3.8
Conservative[#]	23 (59)	5 days	5.4
ED discharge (excluded AMA)	84 (67)	2.8 hours	1.8

[#]Conservative treatment: Patients admitted for antibiotics treatment.
ED: Emergency department, AMA: Against medical advice

Table 4: Antibiotics versus disposition and kinds of snake

Kinds of antibiotics	Total patients	Kinds of snake					
		PM	TS	BM	NA	UK	NV
Nonuse	48	25	3	0	2	17	1
Cephalosporin	41	14	2	1	0	24	0
Penicillin derivatives	34	23	3	0	0	6	2
Clindamycin	1	0	1	0	0	0	0
Fluroquinolone	1	1	0	0	0	0	0
Total	125	63	9	1	2	47	3

PM: *Protobothrops mucrosquamatus*; TS: *Trimeresurus stejnegeri*; NA: *Naja atra*; BM: *Bungarus multicinctus*; UK: Unknown kinds; NV: Nonvenous snake

Of the 16 snakebite patients who received surgery, *P. mucrosquamatus* bites were the most common cause (14 patients, 87.5%) [Table 1]. One patient was bitten by *T. stejnegeri* and another by *N. atra* [Table 1].

Seventy-seven snakebite patients (62%) received antibiotics; the most commonly used antibiotics were

cephalosporin (41 patients, 53%), followed by penicillin derivatives (34 patients, 44%) [Table 4].

Further analysis of patients bitten by *Protobothrops mucrosquamatus*

Among the sixty-three patients bitten by *P. mucrosquamatus*, thirty-eight patients (60%) were admitted for either fasciotomy (15 patients, 39%) or wound condition monitoring (23 patients, 61%). Patients admitted to receiving surgery were administered less antivenom than those admitted for wound observation (3.8 vials vs. 5.4 vials) but had longer hospital stays (11.8 days vs. 5 days). Twenty-three patients (38%) (excluding two patients who were discharged against medical advice) bitten by *P. mucrosquamatus* were discharged from the ED after receiving an average of 3.9 vials of antivenom and having been observed for 19.9 h, which was longer than the average ED stasis time of 2.8 h of all snakebite patients [Table 1].

DISCUSSION

We reported the characteristics of snakebites in North Taiwan to understand the incidence and management of snakebite patients from 2009 to 2016. A high surgical rate for the patients who were bitten by *P. mucrosquamatus* was noted in our hospital. The progressive swelling of the wound and presentation as compartment-like syndrome is the major surgical concern. In addition, the incidence of snakebite in Northern Taiwan has changed. In our study, from 2009 to 2016, *P. mucrosquamatus* became the most commonly encountered snake in North Taiwan.

The surgical rate for patients bitten by *P. mucrosquamatus* in our study, 23.8%, was higher than in other studies, such as the 9.2% reported in Shin's study (1999–2004, 54 patients).[7] Compartment-like syndrome is the main cause of surgery. Compartment syndrome is a clinical diagnosis according to the clinical syndromes, such as pain, paresthesia, pallor, paralysis, pulselessness, and poikilothermia. Of our surgical patients, none had definite compartment pressure detected before surgery by any objective measurement of pressure.[8,9] Among the patients bitten by *P. mucrosquamatus*, even with antivenom therapy, extensive swelling, and ecchymosis at the bite site were very common and easy to recognize as compartment syndrome.[10] Phospholipase A2 breaks down the integrity of the plasma membrane of muscle fibers and snake venom metalloproteinase hydrolyzes the type IV collagen of the basement membrane of capillaries.[11,12] The snake venom itself can directly destroy the tissue, not just indirectly by the pressure to lead to vessel or nerve injury.[13,14] In addition to the effects of the toxin, the host defense response, such as the neutrophil extracellular traps may contribute to the local tissue damage.[15] In snake envenoming, the swelling and inflammation are located in the subcutaneous space, unlike in compartment syndrome, when the swelling is located in the subfascial spaces.[16] In animal models, only antivenom improved the myotoxicity, and fasciotomy worsened the muscle function.[14,17,18] For snakebite patients, fasciotomy increased the percentage of myonecrosis and decreased the tension force of the muscle.[18,19] In our study, the patients who received surgery had significantly longer hospital stays than those who were admitted for wound monitoring (11.8 vs. 5 days) [Table 3]. In our study, the surgeon use the "clinical symptoms," not objective compartment pressure level, as the guiding for the indication of fasciotomy. However, as mentioned above, the clinical diagnosis may be adequate for the crushing injury related compartment syndrome, not for the snake-bite wound. Based on this study results and our accumulated experiences, we propose a clinical flowchart for physician to deal with the patients bitten by *P. mucrosquamatus* [Figure 2]. Initially, the physician identified the snake from the snake body or the event location. *P. mucrosquamatus* has brown over whole body and curved back plaques staggered left and right over the midline of back [Figure 3a and b]. If there was no snake or picture with the patients, the event location and wound are the important clues. In the Northern Taiwan, the snakebite wound which presented as cyanosis, swelling and ecchymosis are highly possible bitten by *P. mucrosquamatus* [Figure 3c]. The antivenom of *P. mucrosquamatus* should be used as soon as possible and doses need to match with clinical symptoms. Epinephrine should be prepared for the anaphylactic reaction.[12] Monitor is also important, including white blood cell count, Hb level and platelets count, prothrombin time/partial thromboplastin time, creatine kinase, troponin-I, D-dimer. Sonography is suitable to differentiate the location of interstitial fluid and to detect whether if the blood vessel compressed by compartment pressure [Figure 3d-g].[20,21] A long treatment and observation time, about 24–48 h, is anticipated and needed to inform the patient initially. If the wound swelling still progressed, objective compartment pressure detected is suggested and the amount of antivenin may increase. If compartment syndrome is still suspected, intercompartmental pressure should be objectively measured.[16] If the intercompartment pressure is lower 20 mmHg than diastolic pressure, the snakebite related compartment syndrome may be considered and plastic surgeon and toxicologists are needed consulted.[22] In summary, antivenom is still the first choice for snake venom-induced myotoxicity, and sonography plays an important role to diagnose whether there is compartment syndrome. The compartment pressure needs to be measured if compartment syndrome is still suspected in the snake-bite patients.[16]

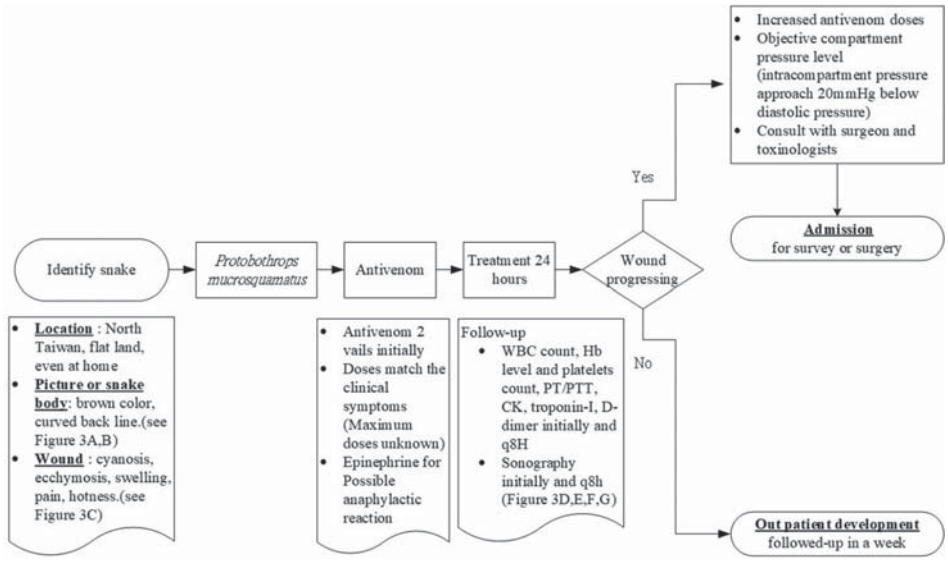

Figure 2: Proposed flowchart for management of *Protobothrops* mucrosquamatus

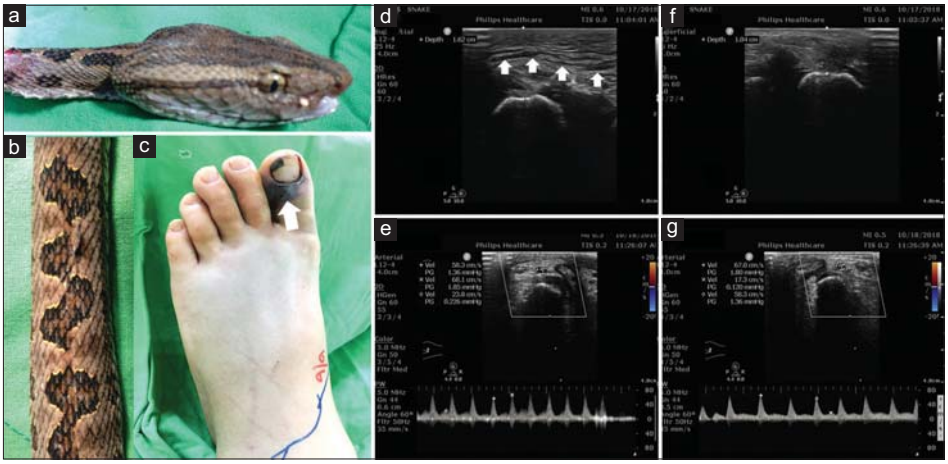

Figure 3: *Protobothrops mucrosquamatus* identification and sonography assisted. (a) There is a horizontal brown band of diffuse pigment across middle of eye. (b)The upper body is light brown with mid-dorsal of series chocolate shades. (c) A 30-year-old male, he was bitten over the left big toe (arrow). Ecchymosis presented over the big toe and cyanosis, swelling distended over the dorsal foot. (d-g) The 8-year-old patient was bitten over left medial malleolus with two fang markers (picture not shown). Sonography showed cobblestone sign (arrow) over the subcutaneous area, not in the fascia, with increased depth 1.62 cm (d) compare with the healthy side, 1.04 cm (f). Pulsed Doppler over the dorsalis pedis artery revealed equal blood flow velocity between the lesion site (e) and healthy site (g)

Toxicologist and plastic surgeon needs to be consulted before surgery, owing to different mechanism of wound swelling between trauma and snakebite related.

Between 1904 and 1938, *T. stejnegeri* (47.3%) was the most commonly encountered snake, followed by *P. mucrosquamatus* (26.0%), *B. multicinctus* (7.1%), *N. atra* (4.7%), *D. acutus* (1.9%), and *D. russelli siamensis* (0.3%) over the whole island of Taiwan.[1] Between 1986 and 1989, the 444 snakebite cases registered by the PCC-Taiwan showed relatively equal incidences of encounters with *T. stejnegeri* and *P. mucrosquamatus* (22.3% vs. 22.1%).[1] In our study, *P. mucrosquamatus* (50%) was the most common source of snakebites, exceeding the incidence of snakebites by *T. stejnegeri* (7%). *T. stejnegeri* is an arboreal snake, and maybe the urbanization in these years affected the habitat, resulting in fewer encounters with *T. stejnegeri*.[1] However, the phenomenon still needs more studies to confirm this inference. From our studies, we can claim that *P. mucrosquamatus* was the most commonly encountered venomous snake in Northern Taiwan during these years.

In our study, 62% of snakebite patients received antibiotics, including cephalosporins and penicillin derivatives. It could

be difficult to differentiate between snakebite wound infection and envenoming reaction (redness, tenderness, swelling), especially in the initial stage. In Chen's study, cellulitis was noted in only 26% of patients (out of 149 patients) bitten by *P. mucrosquamatus* and 6% of patients bitten (out of 149 patients) by *T. stejnegeri.*[10] The bacteriology of snakebite wounds are well documented for *N. atra*, and the most three common pathogens are *Morganella morganii*, *Aeromonas hydrophila*, and *Enterococcus* species.[23] However, the bite wounds inflicted by *P. mucrosquamatus* and *T. stejnegeri*, both belonging to subfamilies of *Crotalinae*, are seldom complicated with cellulitis. Antibiotics might be withheld in patients bitten by *Crotalinae*.[5] In our studies, there was no cellulitis or severe wound infection noted in the 72 patients bitten by *P. mucrosquamatus* and *T. stejnegeri*. In summary, antibiotics are seldom needed for snakebite wounds, except in patients bitten by *Naja* species.

This was a retrospective chart review study, and it revealed that snakebites were managed differently by different treating physicians based on their clinical judgment. The rate of correctly identified snake species is based on the medical chart record, which depended on the physician at the time. The amount and frequency of antivenom used could not be controlled in this retrospective study. This is a descriptive study. We can just describe what happened and presented truly in this article. In future, when we had accumulated sufficient case numbers and we will have better statistic data. Although this was a medical center in Northern Taiwan and the patients came from Taipei and Keelung, it may not be representative of all of Northern Taiwan. However, from this single-hospital retrospective chart review, we can report more detailed information than in national population-based studies. We will establish a clinical protocol to use adequate numbers of vials of antivenom and conduct adequate sonographic monitoring of wound edema or vessels compressed rather than performing fasciotomy for the patients bitten by *P. mucrosquamatus* because the advantages of antivenom appear to be superior to those of fasciotomy.[16] Compartmental pressure should be objectively measured when compartment syndrome is highly suspected.[8,24]

CONCLUSION

Snakebites most occurred in July and October in each year. Feet (including ankles and toes) were the most common bite site. *P. mucrosquamatus* as the most commonly encountered species in this region of Northern Taiwan. No patients had wound infections or side effects from the antivenom, including acute reactions and serum sickness. The surgical rate for patients bitten by *P. mucrosquamatus* was higher than that in previous reports. Snakebite, especially *P. mucrosquamatus* bite, indeed induced severe soft-tissue swelling and mimic as compartment syndrome. Antivenoum for *P. mucrosquamatus* is the first and only choice of treatment. The amount of antivenoum needs to match with clinical symptoms. The patients bitten by *P. mucrosquamatus* may be needed longer observation time and toxicologist consultation, sonography, even objective compartment pressure detect before surgery.

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Conflicts of interest

There are no conflicts of interest.

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