ORIGINAL ARTICLE

Use of Snake Antivenom and Clinical Outcomes in Snake Envenomation: A Retrospective Study in a Tertiary Hospital in Penang, Malaysia

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Abstract

Backgrounds: Snake antivenom (SAV) is the definitive treatment for snake envenomation. But SAVs are specific, expensive and limited in supply. SAVs also come with risk of adverse reactions. Hence, this study was conducted to assess the use of SAV, adverse reactions to SAV and its clinical outcomes in snakebite patients.
Methods: This was a retrospective study. Medical records of snakebite patients for the period from January 2014 to September 2017 were reviewed and study data was extracted. Clinical outcomes were measured by mortality rate in those receiving SAV.
Results: Among 165 subjects, only 9 patients (5%) were treated with SAV after presenting with envenomation symptoms in which five cases with identified snakes were given monovalent SAV namely pit viper (two cases), king cobra, sea snake and cobra with one case each. Meanwhile, three cases of unidentified snake received polyvalent SAV and one case received pit viper SAV. Most of the patients (8/9, 88.9%) received SAV within 24 hours after snakebite. The average time gap to first administration was 7.23 hours. In patients receiving SAV, six out of 9 cases required two to four vials of SAV. All the patients receiving SAV did not encounter any adverse effects except a child who had pyrogenic reaction. All patients survived without significant morbidity at discharge. The total cost of SAV for the 9 patients was US$ 24,082.68.
Conclusion: From this study, the incidence of snakebites requiring SAV was low. Low incidence of adverse effects and no mortality were observed in patients receiving SAV.

Keywords: Adverse Reactions; Antivenom; Snake Bites

How to cite this article: Chen HL, Chuah YQ, Eng KL, Michelle YYL, Roziana AB. Use of Snake Antivenom and Clinical Outcomes in Snake Envenomation: A Retrospective Study in a Tertiary Hospital in Penang, Malaysia. *Asia Pac J Med Toxicol* 2019;8:78-82.

INTRODUCTION

It is assessed that Malaysia experiences 400–650 snakebites among each 100,000 people annually and it conveys an annual death pace of 0.2 in each 100,000 people (1). For the years 2010 to 2014, a total of 15,698 snakebites cases and 16 deaths had been reported by the Malaysian Health Informatics Center. However, the information about number of cases that did not present to a health care facility is not available. In Malaysia, there are several families of venomous snakes, including all members of the family of Elapidae and Viperidae and a few in the family Natricidae. Elapidae family includes cobras, king cobra, kraits, coral snakes, sea snakes and their allies. Viperidae comprises two subfamilies, true viper or Old World vipers (Viperinae) and pit vipers (Crotalinae) (2).

Snake antivenom (SAV) is the definitive treatment for snake envenoming. It is the type of snake that determines which antidote to use. In case the snake species is recognized, the monovalent antivenin would be ideal. On the other hand, in case the identification of the snake species fails, the polyvalent antivenin is suggested (3). There are limited studies available on the use of antivenom and the outcome of the treatment. Jamaiah et al. (2006) illustrated that 25% (32 instances) of 126 cases had received polyvalent antivenin in a five-year time frame in a tertiary hospital based in Kuala Lumpur, Malaysia (4).

SAV should be used only in patients whom the benefits of treatment are considered to exceed the risks of anti-venom reactions. Indications of SAV include signs of systemic and/or severe local envenoming. The reasons for restricting of SAV usage are mostly due to the short supply and cost issue, and also side effects which consist of early anaphylactic response, pyrogenic reaction and delayed serum sickness (5). Hence, this study was conducted to assess the use of SAV, adverse reactions to SAV and clinical outcomes in the hospital. This is important because the findings would serve as a guide when determine the indication, type and dose of SAV in the future. The findings also help to promote the rational use of the drug.

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Received 06 June 2019; Accepted 18 August 2019

METHODS

This was a retrospective study. All snakebites patients admitted to Emergency Department from January 2014 to September 2017 were included in the study. Data of registered snakebites cases including the demographic data, types of snakebites, signs and symptoms experienced by the patients as well as the corresponding treatment given were obtained from the medical record. Data on time gap to first administration of SAV, type of SAV, number of SAV vials and adverse effect of SAV were also collected. Clinical outcomes were measured by mortality rate in those receiving SAV. All data were extracted into the designated data collection form.

Patients who were discharged against medical advice and cases of unknown bites in the absence of fang marks or any other symptoms that suggest venomous snakebites were excluded from this study.

RESULTS

In this study, a total of 165 cases of snake bites were included. Only 9 patients (5%) were treated with SAV after presenting with envenomation symptoms. Table 1 shows the demographic characteristics of the total 165 patients and the 9 patients with SAV. There were eight adult patients aged ranging from 25 to 60 years old and a 9-year old child. All the patients who received SAV are males except one female patient. Seven patients were directly admitted to the hospital while another two were cases referred from other hospitals in Penang.

As seen in Table 2, types of snakebites reported include identified snakebite (viper, python, cobra, sea snake, king cobra and coral snake) and unidentified snakebite. Five cases with identified snakes were given monovalent SAV namely pit viper (two cases), king cobra, sea snake and cobra with one case each. Meanwhile, three cases of unidentified snake received polyvalent SAV (hemato and neuro polyvalent SAV) and one case received pit viper SAV. All the 9 patients presented symptoms of local envenoming, which include local swelling involving more than half of the bitten limb and rapid extension of swelling. Eight out of nine patients developed one or more of the systemic envenoming signs, which include bleeding disorder, neurotoxic signs, cardiovascular abnormalities, acute kidney injury (renal failure) and haemoglobin-/ myoglobin-uria. The signs and symptoms experienced by the patients are shown in Table 3.

Most of the patients (8/9, 88.9%) received SAV within 24 hours after snakebite. The average time gap to first

Table 1. Demographic and other baseline characteristics of all snakebite patients (n=165) and patients given antivenom (n=9)

Characteristics	Groups	All Snakebite Patients (n=165)	Patients Given Antivenom (n=9)
Age	< 18	25 (15.2%)	1 (11.1%)
	More than or equal to 18	140 (84.8%)	8 (88.9%)
Gender	Male	130 (78.8%)	8 (88.9%)
	Female	35 (21.2%)	1 (11.1%)
Ethnicity	Malay	54 (32.7%)	2 (22.2%)
	Chinese	60 (36.4%)	6 (66.7%)
	Indian	17 (10.3%)	None
	Foreigner	34 (20.6%)	1 (11.1%)
Type of admission	Direct admission	131 (79.4%)	7 (77.8%)
	Referral	34 (20.6%)	2 (22.2%)

Table 2. Types of snake bites

Types of snake bites	All Snakebite Patients (n=165)	Patients Given Antivenom (n=9)
Viper	27 (16.4%)	2 (22.2%)
Python	19 (11.5%)	None
Cobra	11 (6.7%)	1 (11.1%)
Sea snake	5 (3.0%)	1 (11.1%)
King cobra	3 (1.8%)	1 (11.1%)
Coral snake	1 (0.6%)	None
Unidentified	99 (60%)	4 (44.4%)

Table 3. Signs and symptoms experienced by the snakebite patients

Signs and Symptoms	Groups	All Snakebite Patients (n=165)	Patients Given Antivenom (n=9)
Local	Fang mark	122 (73.9%)	7 (77.8%)
	Pain	59 (35.8%)	4 (44.4%)
	Swelling	49 (29.7%)	9 (100%)
	Erythematous	25 (15.2%)	1 (11.1%)
	Bleeding	21 (12.7%)	2 (22.2%)
	Numbness	20 (12.1%)	2 (22.2%)
	Tenderness	20 (12.1%)	3 (33.3%)
	Cellulitis	4 (2.4%)	1 (11.1%)
	Blistering	4 (2.4%)	4 (44.4%)
	Itchiness	1 (0.6%)	None
	No symptoms experienced	15 (9.1%)	None
Systemic	Neurological disorder	5 (3.0%)	4 (44.4%)
	Bleeding disorder	4 (2.4%)	3 (33.3%)
	Cardiovascular disorder	2 (1.2%)	1 (11.1%)
	Renal disorder	2 (1.2%)	2 (22.2%)
	Haemoglobin/ myoglobin-uria	1 (0.6%)	1 (11.1%)
	None	147 (89.1%)	1 (11.1%)

Table 4. Number of SAV vials used for initial dose and total dose

Number of Vials	Initial Dose Number of patient (n=9)	Total Dose Number of patient (n=9)
1 - 5	8	6
6 -10	0	1 (10 vials)
11-15	1 (13 vials)	1 (12 vials)
More than 15	0	1 (33 vials)

administration was 7.23 hours. Table 4 shows the number of SAV vials used for initial dose and total dose. Eight out of nine patients (88.9%) were administered with a low initial dose of 1-5 vials. Six out of nine cases required SAV in the range of 2-4 vials in total. King cobra envenomation used the most SAV dosage (i.e. 33 vials per case). The average number of vials administered was 8.33 vials.

All the patients receiving SAV did not encounter any adverse effects except a child who had pyrogenic reaction. The 9-year old patient had spikes of temperature (38.3°C being the highest temperature recorded 2 days after SAV administration), the fever soon subsided to 37.2- 37.5°C after day four to day seven post SAV administration with the IV Cloxacillin and Syrup Paracetamol. The rest of the patients recovered without any complications or delayed adverse response with average hospitalization stay of 6.11 days. The total cost of SAV for the 9 patients was US$ 24,082.68. The SAV cost was ranged from US$ 216.56 (2 vials of pit viper SAV) to US$ 16,658.76 (4 vials of sea snake SAV).

DISCUSSION

A total of 60% of the snakebite cases reported with unidentified snake species.. Similar result also found in two other studies done by Jamaiah et al, 2006 (60%) and Chew et al, 2010 (52.9%) (4, 6). This can be due to patient's condition that were frequently anxious and frightened which can cloud their ability to identify snake species during the snakebite incident (6). According to Ministry of Health (MOH) Malaysia Guideline on Management of Snakebite 2017, symptoms and signs vary according to the species responsible for the bite, size and the amount of venom injected to the victims (2). If the biting species is unidentified, close observation of the patient for at least 24 hours allows recognition of the emerging pattern of symptoms, signs and results of laboratory tests, such as coagulation profile, full blood count, renal profile and liver function test. Together with the history reported by patient, this may assist in identifying the snake species. In this study, the most common identified snakebite species is viper. Study done by Chew et al. (2011) in a tertiary university hospital in Kelantan showed that cobra bites are the most common (6).

In this study, antivenom treatment was only given to 9 patients that develop systemic and/or local envenoming, as recommended by both WHO & MOH guideline (2, 5). Of

these 9 cases, all the identified snakebite species was treated with monovalent antivenom, otherwise polyvalent antivenom was selected as choice of treatment based on the clinical symptoms presented by patient. Hemato polyvalent antivenom was given based on the signs of deranged coagulation profile (INR increasing trend and low platelet count). On the other hand, neuro polyvalent antivenom was given to patients who experienced neurological symptoms such as ptosis and difficulty opening eyes.

Many SAV guidelines stated that SAV treatment should be given as soon as it is indicated. Ahmed et al. (2008) indicated SAV should be administered within 4 hours of the bite, while Warrell et al. (1976) postulated the possibility of effectiveness of SAV in preventing local necrosis if the SAV is given within the first few hours after the bite (7, 8). However, SAV still effective if given within 24 hours (7). The time gap between the snake bite until the SAV administration in our study is comparable to those studies in which 88.9% of patients receive SAV within 24 hours. WHO (2016) also stated that antivenom treatment can reverse systemic envenoming even if it has persisted for weeks and for two or more weeks in the case of haemostatic abnormalities (5).

Up to date, there are no clinical trials to determine the ideal dose, optimum dose, frequency of administration, and duration of therapy (9). However, there is accord that equivalent measure of SAV ought to be administered to the youngsters and grown-ups to counteract a specific infused measure of venom as snakes infuse a similar portion of venom into kids and grown-ups (5). By and by, the decision of the first portion of antivenin depends on the seriousness of clinical introduction. It is an impression of the measure of venom infused by the snake. In any case, the initial dosage and the wellbeing levels of antivenin are to a great extent dependent on the producer's suggestion. In this study, four out of nine patients were administered with initial dose of SAV according to the manufacturer's recommendation. Only one patient received higher initial dose (13 vials) of king cobra antivenom, due to the severe clinical presentation with neurotoxicity impeding compartment syndrome, neuropathy, acute kidney injury and rapid extension of swelling on the hand.

In our study, majority of the patients (88.9%) were administered with a low initial dose of 1-5 vials, which is contrary to the high initial dose suggested by many studies and guidelines. Theakson et al. (1991) and Isbister et al. (2015) recommend a high loading dose of 10 vials (100 ml) administered as an IV push to effectively neutralize neurotoxins before they become irreversibly bound to tissue receptors (10, 11). Similarly, WHO guidelines also suggested an initial 10 vials of SAV should be given after bites by South Asian cobras and kraits. All the 8 patients were fully recovered, suggested that low initial dose SAV work as effectively as high dose SAV. Similar conclusion can be observed in several randomized controlled trials from India that claimed to demonstrate that lower doses were equally effective in victims of predominantly hemotoxic snakebites in South India (12, 13), although their results are uninterpretable due to limitations in patient selection and snake species identification. The study of Alirol et al. (2017) also found no significant different in the higher dose group in composite primary end points which included in-hospital death, the need for assisted ventilation and worsening or recurrence of neurotoxicity as compared to the low initial group in Nepali patient. Moreover, the rate of progression was slower and the occurrence of adverse effects slightly higher in the high dose (14).

Subsequent doses are given according to the clinical symptoms. In this study, four out of nine patients were given more antivenom after administering the initial dose. One of the patients showed persistence of blood incoagulability and bleeding after initial dose. The patient was given subsequent dose of 8 vials hemato polyvalent antivenom, with 4 vials each time. The other three patients show deteriorating neurotoxic sign after 1 hour, which indicate for repeating the initial dose of antivenom as stated in the WHO guideline (2016).

The practice of the administration of SAV in this study has shown to be safe as the incidence of SAV adverse effects is 11.1%. Only one patient is believed to experience pyrogenic reaction that may be caused by bacterial lipopolysaccharides that present in SAV when there is contamination during manufacturing process. This reaction can occur within first hour of antivenom of infusion. However, there are no determinants or study done to predict this reaction.

In other studies done in Sri Lanka and Bangladesh, the incidence of adverse effects was much higher than in our studies. A study conducted in Bangladesh by Amin et al. (2008), 64.5% of the snake bites patients experienced early anaphylactic reaction with average onset of 28 minutes. Average dose of SAV given in the study was 55 ml (15). In Sri Lanka, 50% of them have anaphylactic reaction while 63% had pyrogenic response when they used diluent not given by manufacturer. These two reactions occurred more common when given polyvalent SAV (16). In Thailand, among 254 patients receiving Thai Red Cross (TRC) antivenoms during 1997–2006, early reactions occurred in 9 (3.5%) (5).

Unlike pyrogenic reaction, serum sickness reaction which can cause fever, arthralgia and cutaneous eruptions that might develop in eight to twelve days after administration of SAV. This is a delayed reaction as immune system takes several days to recognize heterologous horse antibodies as foreign bodies before an Ig G mediated antibody response kicks in. A study by LoVecchioet al. (2003) that use symptoms of fever, arthralgia and pruritus as determinants of serum sickness has reported incidence of 56% of patients developing late serum sickness after receiving Antivenin (Crotalidae) Polyvalent (ACP) (17).

LIMITATIONS

There are some limitations in our study. All the data collected could only base on what was documented at that time due to the limited information in the case notes. Besides, the species of snakes taken from the hospital case notes were based mostly on the description given by the patients and other witnesses as well as signs and symptoms

experienced. Furthermore, this study was conducted only in one center, thus the study findings may not truly reflect the epidemiological trend in Malaysia as a whole.

CONCLUSION

From this study, the incidence of snakebites requiring SAV was low. Low incidences of adverse effects and no mortality were observed in patients receiving SAV. Prospective study involving multicenter should be conducted in future to validate these findings.

Conflict of Interest: None to be declared.

Funding and Support: This was an investigator initiated research. This research has been approved by Medical Research and Ethics Committee Ministry of Health, Malaysia with ID number of NMRR-17-2497-38221 (IIR).

ACKNOWLEDGMENTS

We thank the Director-General of Health Malaysia for the permission to present these findings. We also thank Dr Yoon Chee Kin, Head of Clinical Research Centre, Hospital Pulau Pinang who provided insight that greatly assisted the research. We would like to show our gratitude to Sherene Tan Su Ann, Clinical Pharmacist, Hospital Pulau Pinang for her guidance throughout the research.

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