ORIGINAL ARTICLE

The Prevalence of Hypersensitivity Reactions to Snake Antivenoms Administered in Sultanah Nur Zahirah Hospital From 2013 To 2016

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ABSTRACT

Introduction: Snakebite is an important medical emergency. Antivenoms remain the only proven treatment for snake envenoming. However, the use of antivenom is associated with hypersensitivity reactions. The aims of this study were to determine the prevalence and types of hypersensitivity reactions and types and outcomes of pharmacological and non-pharmacological treatments for antivenom reactions among snakebite patients that received antivenoms.

Methods: This was a 4-year cross-sectional study of snakebite patients from January 2013 to December 2016 in Hospital Sultanah Nur Zahirah (HSNZ), Terengganu. Data was extracted from the Pharmacy Record on the usage of antivenom and patients of snakebites treated with antivenom were identified. Data of patients were then obtained from the electronic medical records.' Demographic details, clinical features and characteristics of antivenom reactions of patients were recorded in standardized data collection forms and analyzed using chi-square or Mann-Whitney U tests.

Results: Of the 44 patients who received antivenom, 24 (54.5%) developed hypersensitivity reaction. All patients developed reaction early. No patient developed delayed (serum-sickness) reaction. Of the 24 patients, 14 (58.3%) had moderate to severe hypersensitivity reaction and 9 (37.5%) patients had mild reactions. Only one (4.2%) patient presented with bradycardia.

Conclusion: The prevalence of early hypersensitivity reaction to snake antivenom in HSNZ was relatively high. Healthcare providers should be aware of the appropriate method of preparing and administering antivenom, and the management for acute hypersensitivity reactions. This will optimize the management of snakebite and ensure patient safety.

KEY WORDS:
Anaphylaxis, antivenom, emergency, snakebite

INTRODUCTION

Snakebite is among the common causes of hospital admission in Malaysia. The estimated number of snakebite cases in Malaysia is 400 - 650 per 100,000 population per year and the mortality rate for snakebites is 0.2 per 100,000 population per year.[1] There are four families of snakes that are of medical significance: (1) Elapidae (fixed front-fanged snakes equipped with venom that includes sea snakes, the cobras, the king cobra, kraits and coral snakes); (2) Viperidae (only the Crotalinae group of pit vipers with retractable front fangs equipped with venom); (3) Colubridae (several non-front-fanged snake species are venomous and potentially dangerous); and (4) Pythonidae (non-venomous, but all species of pythons in Malaysia are potentially dangerous to human).[2]

Antivenom remains the only proven and effective treatment for snake envenoming.[3] However, the use of antivenom is associated with risks of early or late hypersensitivity reactions, which includes anaphylactic shock, pyrogenic reaction and serum sickness.[4] Currently, snake antivenom is not produced in Malaysia, therefore antivenoms appropriate for use in Malaysia is imported from manufacturers in Thailand and Australia.[1] In general, there are two types of antivenom preparations, namely monospecific and polyspecific antivenoms.[4] The monospecific antivenoms are raised from the venom of individual snake species of high medical relevance within a specified geographical area. In Malaysia, monospecific antivenoms available include for bites of the common cobra, King Cobra, green Pit Viper, Malayan Pit Viper and sea snakes. They are used for significant envenoming from the same species or from closely related species. The polyspecific antivenoms are manufactured to contain antivenom from more than one species of snake. The polyspecific antivenoms are the Neuro Poly and Hemato Poly. The indication for polyspecific or monospecific antivenom is determined by several clinical parameters that indicates significant envenoming syndrome.

The World Health Organization (WHO) Snakebites Management Guideline reports that more than 10% of

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patients who received antivenom developed reactions to antivenom.[5] To date, there is no published report regarding the incidence or prevalence of antivenom reactions in Malaysia. In Thailand, randomised trials have shown that the efficacy and safety of antivenoms manufactured by the Thai Red Cross Society.[6] The trials concluded that antivenom in sufficient dose administered at the appropriate times are effective. However, the use of antivenom has been associated with risks such as anaphylactoid reactions and serum sickness.[6,7]

The objectives of this study were to identify the prevalence of antivenom reaction, the characteristics and types of hypersensitivity reactions, and the clinical outcomes of the pharmacological and non-pharmacological treatments used for the reported antivenom reactions in a tertiary referral center in Malaysia.

MATERIALS AND METHODS

This is a cross-sectional, retrospective review of snakebite patients presented to Hospital Sultanah Nur Zahirah (HSNZ) Kuala Terengganu, Terengganu from 2013 to 2016. All patients admitted for snakebites and received antivenoms were included. Data of patients were retrieved from the hospital computerized system. This study was approved by the Ethics Committee of the Universiti Teknologi MARA (REC/369/17) and the Medical Research and Ethics Committee of the Ministry of Health Malaysia (KKM.NIHSEC/P17-1820(6)). Specific data was recorded in standardised data collection form, which comprised of two sections. The first section recorded information on patients that included the demographics, types of cases (referral or primary), time and date of the arrival of the patient at the facility, geographical location where the snakebite occurred, anatomical site of snakebite, documented diagnosis, and the species of snake identified.

Section two recorded the type and total amount of antivenom used, indication for administering antivenom, time and date of antivenom administration. For patients who developed antivenom reaction, the clinical features of the reaction and time of onset was recorded. The outcomes of the antivenom reaction in terms of length of hospitalisation or mortality was documented. The pharmacological and non-pharmacological treatments given and the adverse drug reaction associated with the treatments were also recorded.

Data was analyzed using the Statistical Packages for Social Science Version 23. The chi-square and Mann-Whitney U tests were used with a p-value of < 0.05 was considered significant.

RESULTS

Based on the Pharmacy Record Databases on Antivenom Usage, there were 48 patients with snakebites treated with antivenoms. Four out of the 48 patients were excluded from the study due to incomplete data and missing records. Therefore, only 44 patients were included for data analysis.
Most snakebite patients who received antivenoms were between the age of 20 - 59 years old. The youngest patient was 1 year old and the oldest was 77 years old. The mean age was 34 with a standard deviation (SD) of 21 (Table I). Approximately one third of patients (31.8%, 14/44) were bitten at their work places with 15.9% (7/44) were working in plantations, 11.4% (5/44) were Civil Defense Force officers rescuing snakes, and 4.5% were labourers. The rest of the patients were bitten in residential areas. The annual number of snakebites appeared to reduced, however the use of antivenom has increased in frequency (Figure 1).

The most common type of antivenom used was the Cobra Monovalent Antivenom (31.8%, 14/44) followed by the Neuro Poly Antivenom (25%, 11/44) and Hemato Poly Antivenom (11.4%, 5/44) (Table II). The King Cobra Antivenom and Malayan Pit Vipers Antivenom were administered to three patients, respectively. There were eight (18.2%) patients who received the inappropriate Polyvalent antivenom manufactured by ViNS Bioproduct, India. Of the 44 patients who received antivenom, 24 patients experienced hypersensitivity reactions (54.5%, 24/44) and they all showed an early type reaction (Table III). None of the patients presented with a late type reaction (serum sickness). There was no significant association between the occurrences of antivenom reaction with patients' characteristics (Table IV).

The most common type of reactions reported were generalised rashes or urticaria (58.3%, 14/24) followed by difficulty in breathing or shortness of breath 41.7% (10/24), hypotension 33.3% (8/24) and itchiness (25%, 6/24) (Figure 2). Fourteen (58.3%) patients had an early hypersensitivity reaction with 37.5% (9/24) of them had mild reaction (Table V). Only one patient (4.2%, 1/24) presented with bradycardia. In this study, patients who developed antivenom reactions in the emergency department (ED) were managed with supportive treatment (e.g., intravenous fluids), medications (e.g., adrenaline, steroids, or antihistamines) and by withholding antivenom administration until all symptoms and signs of hypersensitivity reaction subsided.

The mean time of onset of antivenom reaction was 48 minutes. The mean days of admission for snakebite patients who received antivenoms with hypersensitivity reactions was 7 days (SD = 5.3). The mean days of admission for snakebite patients who received antivenoms without hypersensitivity reaction was 5 days. Result from the Mann-Whitney test showed that there was no significant difference in the length of hospitalisation among patients with hypersensitivity reaction and those without hypersensitivity reaction ($U = 152.5$, $z = 0.049$, $p = 0.961$). There was no death reported due to hypersensitivity reactions to antivenom.

DISCUSSION

This study showed that 54.5% (24/44) of patients who received antivenom developed antivenom reactions. This figure is significantly higher compared to that reported in various related studies involving the same antivenoms.[8] There are some factors that can contribute to antivenom reactions. Patients who have been exposed and sensitized to horse proteins may have higher risk for developing anaphylactic reactions. Studies have also shown that horse

Table I: Patients' Demographic Characteristics (N=44)

Age (in year)	No. of patients based on gender		n (%)
	Male (%)	Female (%)	
<10	4	1	5 (11.4)
10-19 (adolescent)	2	5	7 (15.9)
20-59 (adult)	21	3	24 (54.5)
>60 (elderly)	4	4	8 (18.2)
Total	31 (70.5)	13 (29.5)	44 (100)

Table II: Type of antivenom used and species of snake implicated

Type of Snake Bite / Snake species	Frequency of Antivenom Use					
	King Cobra	Cobra Viper	Malayan Pit Polyvalent	Neuro Polyvalent	Hemato (Indian)	Polyvalent
Identified species						
King Cobra	2	-	-	1	-	-
Naja Kouthia	-	6	-	-	-	-
Malayan Pit	-	-	-	-	-	-
Viper	-	-	-	-	1	-
Green Pit Viper						
Unidentified species	1	8	3	10	4	8
Total	3	14	3	11	5	8

* All antivenoms are manufactured by Queen Saovabha Memorial Institute (Thai Red Cross Society) except Indian Polyvalent Antivenom

Table III: Types of antivenom used and associated frequency of early and late reactions

Antivenom	[a]Frequency of use	[b]Frequency of early reaction	Frequency of late reaction
King Cobra Antivenin	3	1 (33.3%)	-
Cobra Antivenin	14	7 (50%)	-
Malayan Pit Viper Antivenin	3	3 (100%)	-
Neuro Polyvalent Snake Antivenom	11	6 (54.5%)	-
Hemato Polyvalent Snake Antivenom	5	5 (100%)	-
Indian Polyvalent Antivenom	8	2 (25%)	-

[a] Only one patient was given two types of antivenoms (King Cobra and Neuro Polyvalent antivenom)
[b] All 24 patients who developed early reaction only received one type of antivenom.

Table IV: Tabulation of Patients' Characteristics with the Occurrence of Hypersensitivity Reaction from Antivenom Use

Variables	Hypersensitivity Reaction		p value
	Yes	No	
Gender			
Male	19 (43.2%)	12 (27.3%)	*0.462
Female	5 (11.4%)	8 (18.2%)	
Age group			
≤ 30 years	13 (29.5%)	11 (25.0%)	*0.577
>30 years	11 (25.0%)	9 (20.5%)	
Types of Antivenom			
Mono specific	11 (30.6%)	9 (25%)	*0.40
Poly specific	13 (30.6%)	11 (13.9%)	

Table V: The Pharmacological And Non-Pharmacological Treatment Given To Patient With Hypersensitivity Reactions

Types of Hyper-sensitivity Reactions	Frequency of Reaction (n)	Pharmacological Treatment Given				Non-pharmacological Treatment Given
		Adrena-line (n)	Hydro-cortisone (n)	Chlorpheni- ramine (n)	Rani-tidine (n)	
Anaphylaxis	14	12	10	8	5	Withhold antivenom and restart with slow infusion rate
Mild reaction	9	-	9	8	5	Slow the infusion rate of antivenom
Other (Bradycardia only)	1	-	-	-	-	Withhold antivenom, close monitoring, start infusion once stable, pre-medication prior to the next dose

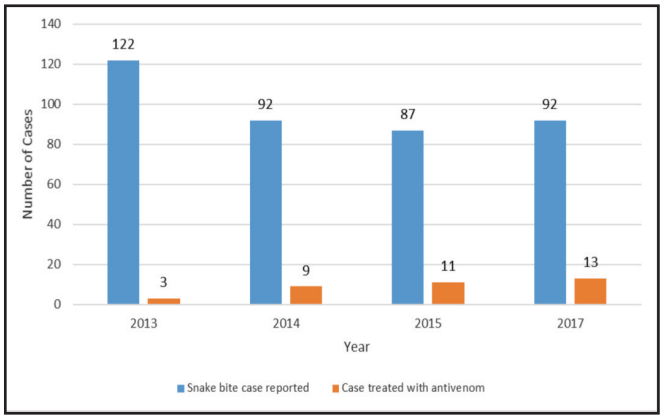

Fig. 1: Number of snake bite cases and frequency of antivenom use in Hospital Sultanah Nur Zahirah from 2013 to 2016.

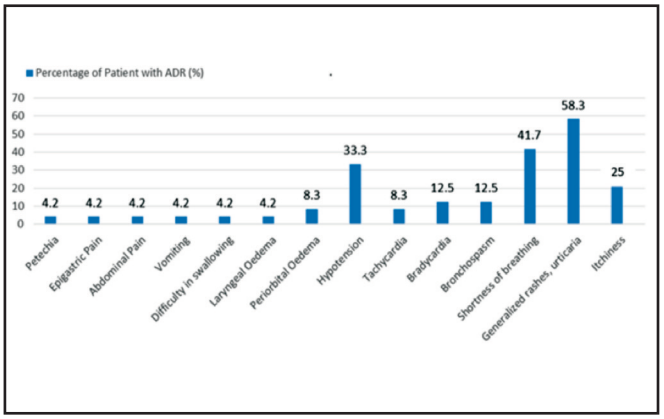

Fig. 2: Characteristics and Frequency of Antivenom Reactions.

IgG(T) is highly glycosylated. This type of immunoglobulin is more immunogenic compared to other antibody isotypes such as those from sheep or camels.[9,10] The other contributing factor that can lead to antivenom reactions is the presence of protein aggregates that can provoke complement system activation. The presence of such protein aggregates in antivenoms can be influenced by storage duration and temperature.[11]

Antivenoms stored for several years, may have reduced efficacy due to antibody denaturation. Additionally, this denaturation of antibody will result in an increase in the level of protein aggregates that may trigger antivenom reactions. The storage temperature of antivenoms (especially liquid form) is another important factor that may influence antibody denaturation and the formation of protein aggregates in antivenoms. A study has shown that antivenom that is stored at 20°C or more for a year had higher level of protein aggregates as compared to that stored in an environment with temperature of 4°C.[10]

The reconstitution technique during antivenom preparation is also important to avoid denaturation of antibody in antivenoms. Antivenoms if shaken vigorously during preparation can result in the formation of foaming. This foaming may result in the denaturation of antibody thus could diminish the activity of antivenoms and increase protein aggregate levels. It is therefore recommended that the vial to be swirled during product reconstitution.[10]

The antivenoms in HSNZ are stored in an environment with a temperature below 20°C. The issuance of antivenoms followed first expired first out (FEFO) basis. However, it was uncertain if the management of the snakebite patient and antivenom administration had followed guideline for the healthcare practitioners such as the WHO Snake Bite Management Guideline and Malaysian Snakebite Management Guideline. It is also unclear if all snakebite cases in HSNZ were consulted early with Remote Envenomation Consultancy Services (RECS) for optimal management including the indication and administration of antivenom.

All patients with hypersensitivity reactions demonstrated an early type reaction that developed as early as 10 minutes of initiating the antivenom infusion. Common reported clinical presentations of the antivenom reactions included itchiness of the scalp, urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. No patient showed any form of late antivenom reactions. According to earlier study, late (serum sickness) reactions appear to be uncommon and if occurred, were normally mild.[12]

There were eight (18.2%) patients who received the inappropriate Polyvalent antivenom produced in India which is not suitable to be used in Southeast Asia. The main concern is regarding the venoms from the snake species which are not similar to the Malaysian snake species in terms of geographically and antigenically.[1] Thus, it should not be used in Malaysia. The factors that contributed to it being used was a misunderstanding and belief of healthcare practitioners and pharmacist regarding the term of polyvalent and unavailability of other types of polyvalent at that time. After 2014, Indian Polyvalent antivenom was no longer being used in this hospital.

In this study, 70.8% (17/24) patients with hypersensitivity reactions to antivenoms were transferred to the ICU. Among those, two patients were intubated due to systemic neurotoxic envenomation. Almost half of the patients (50%, 6/14) who developed anaphylaxis reactions were transferred to the ICU for close medical observation. Whereas, seven out of nine patients who had a mild reaction were also transferred to the ICU. The condition of these patients did not deteriorate further. Additionally, one person discontinued antivenom therapy and was not re-started. Fourteen out of 20 (70%) patients who did not develop hypersensitivity reactions were transferred to the ICU for close observation for compartment syndrome and pregnancy.

As outlined by the WHO Snakebite Management Guideline, adrenaline is the first line treatment for anaphylaxis. The drug reduces bronchospasm and capillary permeability.[5] Intramuscular Adrenaline should be appropriately diluted and drawn up prior to administering antivenom, and initiated when indicated.[5] Intravenous hydrocortisone and

chlorpheniramine has also been used as pharmacological treatments. As demonstrated in a 2004 study, intravenous hydrocortisone given together with antihistamine such as chlorpheniramine may be more effective in reducing acute adverse reaction compared to using intravenous hydrocortisone alone.[13,14]

Non-pharmacological management of early antivenom reactions involved the temporary discontinuation of antivenom administration. Antivenom administration is withheld until reactions are treated and resolved. Subsequently, antivenom is re-started by infusing it at a slower rate. This slow infusion should be complemented with close observation for possible recurrence of reaction.[1] For patients with mild adverse reaction that only include rashes, without developing hypotension or bronchospasm, a slower infusion rate and medical treatment is recommended. In practice, pre-medication to prevent antivenom reactions is not routinely performed except for patients with known hypersensitivity to antivenoms. Several studies have reported the use of prophylaxis to prevent antivenom reactions. It has been shown that the administration adrenaline at low doses is effective to prevents anaphylactic reactions.[14] On the contrary, clinical studies have shown that the use of anti-histamines or steroids is not effective in preventing the reactions. Nevertheless, the use of adrenaline as prophylaxis of antivenom reactions remains controversial especially in specific populations such as pregnant women and older people due to the limited evidence on safety and efficacy in these populations. Additionally, adrenaline may cause hypertension depending on the dose and route of administration. Therefore, adrenaline should be used with caution in snakebite patients with hemorrhage and coagulopathy due to higher risk of intracranial hemorrhage.[15] Patients without severe complications and do not require ICU care can be safely managed in general medical wards. However, it is important to ensure that trained healthcare professionals, and equipment for monitoring and resuscitation of patients are available in these facilities.[12]

LIMITATION

As the study was cross-sectional in design and information was extracted retrospectively from medical records, the data collected dependent on the documentations by the treating clinicians and may not reflect the true nature and accuracy of the diagnosis, and disease management. This study was limited to a small number of patients from one hospital. A better controlled study with progressive incident reporting of antivenom use, reaction and practice is recommend to minimize bias, documentation errors and data loss.

CONCLUSION

The prevalence of early hypersensitivity reactions to snake antivenom in HSNZ was very high and the reason for this was not identified. Until such a time when we can identify the actual cause for this high rate of antivenom reaction, healthcare providers should be vigilant for the signs and symptoms of such reactions and also be aware of the management options. Continuous medical education programs on this topic should be encouraged in order to ensure the optimal management for snakebite envenoming patients.

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