Adverse Drug Reactions of Antivenom in Children: Frequency, Types, Severity and the Effectiveness of Pre-medications

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Abstract

Introduction: Antivenom is the only definitive lifesaving treatment for snakebite envenomation. However, the use of antivenom made from animal serum carries the risk of reactogenicity.

Objective: This study aimed to determine the frequency, types and severity of adverse reactions to antivenom following snakebites, and the association between the administration of pre-medications and the occurrence of antivenom-related adverse reactions in children.

Methods: All records of children receiving antivenom in paediatric ward in Hospital Sultan Abdul Halim from June 2011 to May 2016 were retrieved retrospectively from the Electronic Hospital Information System and Records Department. Demographic data, the documentation of snakebite and antivenom given, descriptions of adverse reactions to antivenom and pre-medications prescribed and the outcome of patient following antivenom treatment were recorded. The severity of antivenom reactions were classified as mild, moderate and severe.

Results: Thirty snakebite victims were included in this study. The median age was 8.5 years old and majority (63.3%) of the patients were among between seven to 12 years old. Seventeen subjects developed adverse reactions following antivenom infusion in which 58.8% of the adverse reactions were mild, 23.6% were moderate and 17.6% were severe. The most common adverse reactions were rash (88.2%) followed by itchiness (29.4%) and chest tightness (29.4%). Eleven (36.7%) patients in this study were given pre-medications before the administration of antivenom. The most prescribed pre-medications were the combination of hydrocortisone injection and chlorpheniramine (54.5%), followed by hydrocortisone injection alone (27.3%). The proportion of patient developing reactions (54.5%) after pre-medications was comparable to those without pre-medications (57.9%), and no statistically significant association was observed (p=1.00).

Conclusions: The adverse reactions to antivenom were high among the children regardless of the use of pre-medications. Further studies regarding the administration of pre-medications in children and the development of better quality and safer antivenom are warranted.

Keywords: snakebite, envenomation, antivenom reactions, pre-medications

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Introduction

The World Health Organization (WHO) estimated that about 5 million of snakebites occur each year. WHO has recognized snakebite envenomation into Category A of the Neglected Tropical Diseases (NTD-A) on 6th June 2013 (1). Similarly, snakebite injuries are common in tropical developing countries like Malaysia. Among the approximately 40 venomous snake species in Malaysia, Cobra and Malayan pit vipers contribute to most of the cases (2). The incidence of snakebite is highest among the children and young adults and the rate of fatality peaks in vulnerable paediatric and geriatric age groups (3, 4).

Antivenom is the only definitive lifesaving treatment for snakebite envenomation. However, the use of antivenom made from animal serum carries the risk of reactogenicity (5-8). Reported adverse reactions of antivenom include early fatal anaphylaxis, pyrogenic reaction and late allergic reaction (6,9,10-15). The reactions were estimated to occur in 20% of cases and hence, increasing the safety of snake antivenom use is crucial (2,3).

Antivenoms are immunoglobulins derived from the plasma of a horse, mule or donkey (equine) or sheep (ovine) that has been immunised with the venoms of one (monovalent) or more species (polyvalent) of snakes. The Fc fragment of immunoglobulin molecule is responsible for antivenom reactions and its removal produces F(ab')2 or Fab were believed to potentially reduce the frequency of the reactions (16). The antivenom neutralises snake venom by blocking the venom toxin from interacting with the target tissues (17). It should be given as soon as it is indicated because it can reverse systemic envenoming even if it has persisted for weeks (3, 18). The dosage of antivenom for children is similar to adults (2) as snakes inject the same dose of venom into children and adults (3).

Currently, there is no clear scientific evidence or policy for the use of pre-medications to prevent the adverse reactions of antivenom. The practice of pre-medications with hydrocortisone or antihistamine is not supported by strong evidence. Moreover, there is still controversy on the use of subcutaneous adrenaline as pre-medication for children although a few studies have shown its effectiveness as compared to placebo or other type of pre-medications such as antihistamines and hydrocortisone, or in combinations (9,12,19). As a result, there are variations in the management of snakebite and treatment of antivenom reactions among different settings. Therefore, this study aimed to determine the frequency, types and severity of adverse reactions to antivenom following snakebites, and the association between the administration of pre-medications and the occurrence of antivenom-related adverse reactions in children.

Method

A single-centred retrospective cross-sectional study was conducted in the paediatric ward of Sultan Abdul Halim Hospital in Sungai Petani, Kedah. All children aged 12 years old and below admitted due to snakebite and received antivenom from 1st June 2011 to 31st May 2016 were enrolled except patients whose antivenom were given in the emergency unit or other wards. We also excluded antivenom use without proper documentation or without sufficient detail.

The medical records of paediatric patients admitted due to snakebite were retrieved retrospectively from the Electronic Hospital Information System (e-HIS) and Medical Records Department. All retrieved records were screened for proper documentation. Demographic data, the documentation of snakebite and antivenom given, dilution and method of antivenom administration, descriptions of adverse reactions to antivenom and pre-medications prescribed as well as the outcome of patient following antivenom treatment were recorded into a data collection form.

A grading system developed by Brown (2004) (20) was used to classify the severity of antivenom reactions of the patients. The severity of antivenom reactions were classified as mild, moderate and severe as below:

- Mild – skin and subcutaneous tissues changes such as generalised erythema, urticaria, periorbital oedema, or angioedema;
- Moderate – features suggesting respiratory, cardiovascular, or gastrointestinal involvement, including dyspnoea, stridor, wheezing, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain; or
- Severe – hypoxia, hypotension, or neurological compromise including cyanosis, oxygen saturation 92% and below, hypotension with systolic blood pressure (SBP) less than 90 mmHg, confusion, collapse, or loss of consciousness.

This study was registered with the National Medical Research Register (NMRR) with the registration number NMRR-16-2737-33694 and ethics approval was obtained from the Ministry of Health (MOH) Medical Research and Ethics Committee (MREC).

The Statistical Package for Social Sciences (SPSS) version 19 was used to perform data analysis in this study. The comparisons of categorical data were carried out by using Fisher's exact test. A P-value of less than 0.05 was considered statistically significant.

Results

Throughout the studied period, 30 children were admitted due to snakebites in Sultan Abdul Halim Hospital. After screening the medical records, all 30 patients were included in the study. The basic characteristics of the study population were shown in Table 1. The median age of the included patients was 8.5 years old and snakebites were most common in the age group of seven to twelve years (n=19; 63.3%). Majority of the study population were male (n=21; 70.0%) and Malay (n=28; 93.3%). The most common bitten areas were finger (n=7; 23.3%) and lower limb (n=6; 20.0%) (Figure 1).

Most of the subjects (86.7%, n=26) were given pit viper antivenom while the remaining received cobra antivenom. As high as 56.7% of our study population (n=17) had developed adverse reactions following the administration of antivenom. With regards to the severity of antivenom reactions, most of the patients (58.8%) developed mild adverse reactions while severe reactions occurred in only three patients (17.6%). Rash was found to be the most frequent adverse reaction and it was reported in 88.2% of those who developed adverse reactions. This was followed by itchiness and chest tightness or bronchospasm in 29.4% of the patients respectively (Figure 2).

Of all 30 patients, 11 patients (36.7%) were given pre-medications before the administration of antivenom. The most prescribed pre-medications in our study were the combination of hydrocortisone injection and chlorpheniramine (54.5%), followed by hydrocortisone injection alone (27.3%). Despite being given pre-medication, adverse reactions of antivenom happened in 54.5% of these patients (n=6), which was comparable to 57.9% of patients (n=11) who did not receive any pre-medication. The Fisher's exact test indicated that the association between the administration of pre-medication and the occurrence of adverse reactions to antivenom was not statistically significant (p=1.00) (Table 2).

Table 1: Characteristics of paediatric snakebite patients receiving antivenom (n=30)

Variable		n	(%)
Age			
	< 2 years old	3	(10.0)
	2-6 years old	8	(26.7)
	7-12 years old	19	(63.3)
Gender			
	Male	21	(70.0)
	Female	9	(30.0)
Race			
	Malay	28	(93.3)
	Indian	1	(3.3)
	Others	1	(3.3)
Antivenom received			
	Pit viper antivenom		
	Cobra antivenom	26	(86.7)
Present of Antivenom Reactions		4	(13.3)
	Yes		
	Mild	10	(33.3)
	Moderate	4	(13.3)
	Severe	3	(10.0)
	No	13	(43.3)
Administration of Pre-medications			
	Yes		
	Hydrocortisone & Chlorpheniramine	6	(20.0)
	Hydrocortisone	3	(10.0)
	Adrenaline	1	(3.3)
	Normal saline bolus, Hydrocortisone & Promethazine	1	(3.3)
	No	19	(63.3)

Figure 1: The frequency of snakebite sites (n=30)

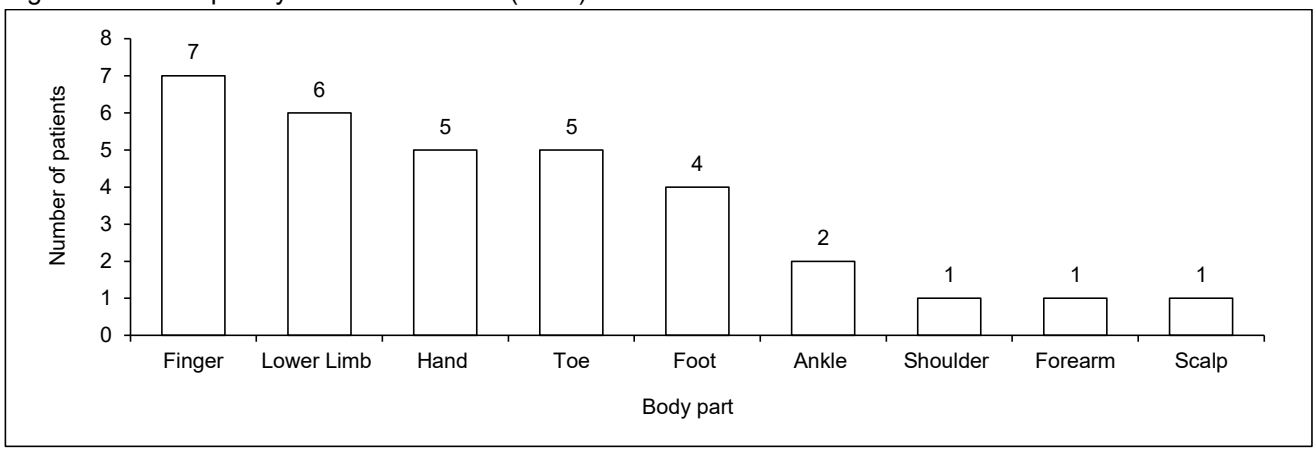

Figure 2: Frequency of adverse reactions to snakebite antivenom (n=17)

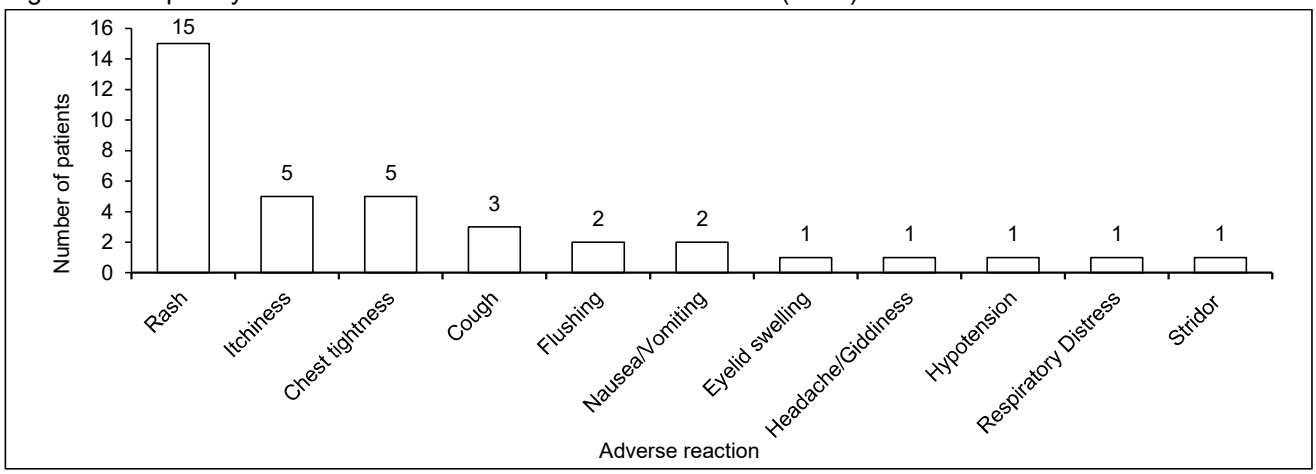

Table 2: The association between the administration of pre-medications and the occurrence of adverse reactions to antivenom (n=30)

	Adverse reaction to antivenom, n (%)		P-value [a]
	Yes	No	
Pre-medication			1.00
Yes (n=11)	6 (54.5)	5 (45.5)	
No (n=19)	11 (57.9)	8 (42.1)	

[a] Fisher's Exact test

Discussion

Currently, all MOH hospitals are using the antivenoms manufactured by the Queen Saovabha Memorial Institute, Thailand. This is attributed to the similarity between snake species between both countries (21). The characteristics of our patients were found to be comparable to those observed in most of the studies. For example, the number of male patients were higher than female patients (8,15,22,23). On the other hand, both local and Asian studies proposed that the most common sites of snakebite were lower and upper limbs with majority of the bites occurred while the patients were working or walking outdoor (24-26).

Owing to antivenom antigenicity, as reported by other researchers, 18.4% to 88.4% of patients developed adverse reactions to antivenom (2,15,22,23). Findings from this study actually fell within the range

published by other researchers. Such a high frequency of antivenom reactions probably result from the lack of advancement in antivenom production technology (27). The production methods used have changed very slowly in the past 50 to 60 years (28). Both types of antivenom used in this study were manufactured by the Queen Saovabha Memorial Institute, Thailand. There was no change of antivenom brand throughout the study period. All antivenoms were given through infusion in a stepwise increment of infusion rate as recommended by Malaysia Management Guideline of Snakebites (18).

Most patients with adverse reactions to antivenom in this study presented with rash, itchiness and chest tightness or bronchospasm. Similar presentations of antivenom reactions were observed in Bangladeshi and Australian patients (23, 29). In contrast, Deshpande *et al*. showed that the most common presentation of reaction were chills and rigors in Indian patient (24). In addition, more patients developed tachycardia and tachypnoea in Papua New Guinea, as compared to our study (15). The differences of antivenom reactions reported among patients were likely due to the administration and type of pre-medications used in different countries. There are multiple mechanisms involved in the development of adverse antivenom reactions (30).

At present, there is no strong evidence to support the use of hydrocortisone and antihistamines as pre-medications for snake antivenom (31). Therefore, the routine use of pre-medications is not recommended by our local guidelines unless there are signs of antivenom reactions (2,18). Nevertheless, approximately one third of our study cohort still received pre-medications prior to antivenom infusion. Hydrocortisone, either given alone or in combination with other agents, appeared to be the most preferred agent in our study. Similar practice was observed in Sri Lanka and Australia (22,29). On the other hand, a study in Papua New Guinea found that the combination of adrenaline and promethazine were commonly used to prevent antivenom reactions (15).

In contrast to our local guidelines, the WHO advocated the routine use of adrenaline as pre-medication since 2016 except in older patients with underlying cerebrovascular disease (3). A systematic review and meta-analysis had also demonstrated that adrenaline plays a positive role in the prevention of early adverse reactions following antivenom administration (32). In addition, a randomised double-blind placebo-controlled trial by Silva *et al*. comparing the effectiveness of pre-medications in adult snakebite victims had reported that pre-treatment with low dose adrenaline significantly reduced the risk of acute adverse reactions to antivenom by 43% at one hour compared to placebo; hydrocortisone or promethazine did not give the same benefit as adrenaline (22). Unlike antihistamine and glucocorticoids which interfere with the mechanisms of antivenom adverse reactions, adrenaline works by directly counteracting the effects produced by mast cell and basophil activation (30). Acting as both α and β adrenoceptors agonist, adrenaline results in the arterial and venous vasoconstriction, increase in cardiac output as well as bronchodilation, hence rapidly reversing bronchospasms, angioedema and severe hypotension observed in anaphylactic shocks (30).

Adrenaline may be effective in reducing antivenom reactions but its safety concern should be addressed before it is used as routine pre-medication in snakebites management. Study on the safety of adrenaline as pre-medication by Dassanayake *et al*. (33) reported a death from suspected intracranial bleeding following adrenaline injection. Furthermore, children, patient aged over 70 years old, patient with hypertension, ischaemic heart disease, arrhythmias or cerebrovascular disease were excluded from the study. This raised the concern on the safety of adrenaline when used as pre-medication in the paediatric population.

In our study, pre-treatment with adrenaline was only observed in one patient and hence the effectiveness of adrenaline as premedication could not be analysed. The different types of pre-medication used among our study population might explain the lack of association between the administration of pre-medications and occurrence of antivenom reactions. Many studies showed that non-adrenaline-containing pre-medications such as hydrocortisone, promethazine or chlorpheniramine alone failed to demonstrate protective role against antivenom reactions (19,22,32,34). Gawarammana *et al*. (19) reported the reduction of antivenom reactions rate among patients treated with the combinations of hydrocortisone and chlorpheniramine, compared to patients treated with hydrocortisone alone and placebo but this study was deemed low statistical power due to small sample size (n=52).

There were a number of limitations faced when carrying out this study. The study was limited by small sample size. Therefore, it may be the reason that the result did not reach any statistical significance. Thus, we need a larger sample size to demonstrate the effectiveness of antivenom pre-medications. Most patients were receiving different combinations of pre-medications and this was potentially the factor for statistical comparisons between individual pre-medication. On top of that, retrieval of patients' record involved both electronic and hand-

written copy that were sometimes inconsistent with each other. Our retrospective design further restricted the assessment of the data accuracy when this happened. As this study was conducted in one centre only, the findings may not truly reflect the trend in Malaysia as a whole.

Conclusion

In conclusion, the adverse reactions to antivenom were high among the children regardless of the administration of pre-medication. Future studies are recommended to explore the effectiveness of pre-medications in the local population in preventing antivenom reactions especially among the children. The adoption of pre-medication recommendations into local snakebite management guideline based on local evidence should be carried out to optimise the therapeutic efficacy of antivenom. Meanwhile, the development of better quality and safer antivenoms are warranted.

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Conflict of Interest Statement

This research was independent of all funding sources. The authors declare there is no conflict of interest.

References

1. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! Journal of Venomous Animals and Toxins including Tropical Diseases. 2017 Dec;23(1):38.
2. Muhammad Ismail HI, Ng HP, Thomas T. Paediatric protocols for Malaysian hospitals.
3. World Health Organization. Guidelines for the Management of Snake-bites 2nd Edition. World Health Organization Regional Office for South-East Asia. 2016.
4. World Health Organization. United Nations Children's Fund. World Report on Child Injury Prevention. Geneva, Switzerland: World Health Organization, United Nations Children's Fund, 2008.
5. Ariaratnam CA, Sjöström L, Raziek Z, Abeyasinghe S, Kularatne M, Arachchi RK, Sheriff MR, Theakston RD, Warrell DA. An open, randomized comparative trial of two antivenoms for the treatment of envenoming by Sri Lankan Russell's viper (Daboia russeliirusselii). Transactions of the Royal Society of Tropical Medicine and Hygiene. 2001 Jan 1;95(1):74-80.
6. Kularatne SA. Reactions to snake venom antisera: study of pattern, severity and management at General Hospital, Anuradhapura. Sri Lanka Journal of Medicine. 2000;9(1):8-13.
7. Seneviratne SL, Opanayaka CJ, Ratnayake NS, Kumara KS, Sugathadasa AM, Weerasuriya N, Wickrama WA, Gunatilake SB, De Silva HJ. Use of antivenom serum in snake bite: a prospective study of hospital practice in the Gampaha district. Ceylon Medical Journal. 2000 Jun;45(2):65-8.
8. Smalligan R, Cole J, Brito N, Laing GD, Mertz BL, Manock S, Maudlin J, Quist B, Holland G, Nelson S, Lalloo DG.Crotaline snake bite in the Ecuadorian Amazon: randomised double blind comparative trial of three South American polyspecific antivenoms. BMJ. 2004 Nov 11;329(7475):1129.
9. Cardoso JL, Fan HW, França FO, Jorge MT, Leite RP, Nishioka SA, Avila A, Sano-Martins IS, Tomy SC, Santoro ML, Chudzinski AM. Randomized comparative trial of three antivenoms in the treatment of envenoming by lance-headed vipers (Bothrops jararaca) in São Paulo, Brazil. QJM: An International Journal of Medicine. 1993 May 1;86(5):315-25.
10. Moran NF, Newman WJ, Theakston RD, Warrell DA, Wilkinson D. High incidence of early anaphylactoid reaction to SAIMR polyvalent snake antivenom. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998 Jan 1;92(1):69-70. 4th Edition. Malaysian Paediatric Association; 2018.606-615.
11. Sutherland SK. Antivenom use in Australia: premedication, adverse reactions and the use of venom detection kits. Medical journal of Australia. 1992 Dec;157(11):734-9.
12. Sutherland SK. Serum reactions an analysis of commercial antivenoms and the possible role of anticomplementary activity in de-novo reactions to antivenoms and antitoxins. Medical Journal of Australia. 1977 Apr;1(17):613-5.
13. Theakston RD, Phillips RE, Warrell DA, Galagedera Y, Abeysekera DT, Dissanayaka P, de Silva A, Aloysius

DJ. Envenoming by the common krait (Bungaruscaeruleus) and Sri Lankan cobra (Najanajanaja): efficacy and complications of therapy with Haffkineantivenom. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1990 Mar 1;84(2):301-8.
14. Warrell DA, Looareesuwan S, Theakston RD, Phillips RE, Chanthavanich P, Viravan C, Supanaranond W, Karbwang J, Ho M, Hutton RA, Vejcho S. Randomized comparative trial of three mono specific antivenoms for bites by the Malayan pit viper (Calloselasmarhodostoma) in southern Thailand: clinical and laboratory correlations. The American journal of tropical medicine and hygiene. 1986 Nov 1;35(6):1235-47.
15. Williams DJ, Jensen SD, Nimorakiotakis B, Müller R, Winkel KD. Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea. Toxicon. 2007 May 1;49(6):780-92.
16. Chippaux, J.P., 2010. Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Biologieaujourd'hui, 204(1), pp.87-91.
17. Nikapitiya, B. and Maduwage, K., 2018. Pharmacodynamics and pharmacokinetics of snake antivenom. Sri Lanka Journal of Medicine, 27(1).
18. Ministry of Health. Guideline: Management of Snake Bite. Malaysia. 2017.
19. Gawarammana IB, Kularatne SA, Kumarasiri RP, Senanayake N, Dissanayake WP, Ariyasena H. Parallel infusion of hydrocortisone ± chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. Medical Journal of Australia. 2004 Jan;180(1):20-3.
20. Brown SG. Clinical features and severity grading of anaphylaxis. Journal of Allergy and Clinical Immunology. 2004 Aug 1;114(2):371-6.
21. Tan CH, Tan NH. Toxinology of snake venoms: the Malaysian context. Snake Venoms.2015:1-37.
22. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwatthage W, Aronson JK, Armitage JM. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS medicine. 2011 May 10;8(5):e1000435.
23. Amin MR, Mamun SM, Rashid R, Rahman M, Ghose A, Sharmin S, Rahman MR, Faiz MA. Anti-snake venom: use and adverse reaction in a snake bite study clinic in Bangladesh. Journal of Venomous Animals and Toxins including Tropical Diseases. 2008;14(4):660-72.
24. Deshpande RP, Motghare VM, Padwal SL, Pore RR, Bhamare CG, Deshmukh VS, Pise HN. Adverse drug reaction profile of anti-snake venom in a rural tertiary care teaching hospital. Journal of Young Pharmacists. 2013 Jun 1;5(2):41-5.
25. Chew KS, Khor HW, Ahmad R, Rahman NH. A five-year retrospective review of snakebite patients admitted to a tertiary university hospital in Malaysia. International journal of emergency medicine. 2011 Dec;4(1):41.
26. Karunanayake RK, Dissanayake DM, Karunanayake AL. A study of snake bite among children presenting to a paediatric ward in the main Teaching Hospital of North Central Province of Sri Lanka. BMC research notes. 2014 Dec;7(1):482.
27. Tan KY, Tan CH, Fung SY, Tan NH. Venomics, lethality and neutralization of Najakaouthia (monocled cobra) venoms from three different geographical regions of Southeast Asia. Journal of proteomics. 2015 Apr 29; 120:105-25.
28. Williams DJ, Faiz MA, Abela-Ridder B, Ainsworth S, Bulfone TC, Nickerson AD, HabibAG, Junghanss T, Fan HW, Turner M, Harrison RA. Strategy for a globally coordinated response to a priority neglected tropical disease: Snakebite envenoming. PLoS neglected tropical diseases. 2019 Feb 21;13(2):e0007059.
29. Isbister GK, Brown SG, MacDonald E, White J, Currie BJ. Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis. Medical Journal of Australia. 2008 Apr;188(8):473-6.
30. Morais V. Antivenom therapy: efficacy of premedication for the prevention of adverse reactions. Journal of Venomous Animals and Toxins including Tropical Diseases. 2018 Dec;24(1):7.
31. Yong Soh S, Rutherford G. Evidence behind the WHO guidelines: hospital care for children: should s/c adrenaline, hydrocortisone or antihistamines be used as premedication for snake antivenom? Journal of tropical pediatrics. 2006 May 15;52(3):155-7.
32. Habib AG. Effect of pre-medication on early adverse reactions following antivenom use in snakebite. Drug safety. 2011 Oct 1;34(10):869-80.
33. Dassanayake AS, Karunanayake P, Kasturiratne KT,Fonseka MM, Wijesiriwardena B, Gunatilake SB, de Silva HJ. Safety of subcutaneous adrenaline as prophylaxis against acute adverse reactions to anti-venom serum in snakebite. Ceylon Medical Journal.2011 Aug 25;47(2).
34. Fan HW, Marcopito LF, Cardoso JL, França FO, Malaque CM, Ferrari RA, Theakston RD, Warrell DA. Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. Bmj. 1999 May 29;318(7196):1451-2.