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Mini Review

A Perspective to Stinging Nettles from Emergency Department, Snakebites Worldbite

Sönmez BM*
University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey

***Corresponding author:** Bedriye Müge Sönmez, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey

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Introduction

Epidemiology

Venomous snakes are responsible for approximately 1.5-3 million bites as well as perhaps more than 100.0000 fatalities annually worldwide [1]. Although exist 3000 venomous snake species in a global scale, only 200 of them pose a life threat for humans due to venom properties and tooth pattern. The venomous species include Elapidae, Viperidae, Hydrophiidae, Colubridae, and Antractaspididae families [2].

Progressive urban development and degradation of wild life have not resulted in lower rates of attacks of humans by wild animals. On the contrary, animals like snakes pose public health problems due to their venoms [3]. Humans residing in rural environments are reportedly more prone to snakebites than people living in urban centers [4-6]. Such a disparity may result from larger snake populations in rural areas but also people making a living through agriculture, which is reportedly a risk factor for snakebite [7]. People suffering from snakebite are generally adult males actively taking part in professional life [5,8].

General distribution of venomous snakes

Venomous snakes have a habitat distributed throughout the planet but are especially an important public health problem in the rural tropical areas of sub-Saharan Africa, Asia, and Latin America. They are especially numerous in Africa, Asia and South America [9-11]. WHO guidelines indicate two major categories in relation to the relative risk of each species. Category 1 is the most medically important group and encompasses snakes with a great potential for threatening life or causing major morbidity, disability, of injury. Category 2 is of secondary importance medically but also includes highly venomous snakes that may well cause disability, morbidity, or mortality; the difference of the snakes in this category is that clear epidemiological or clinical information may not exist and/or these snakes are responsible for less snakebite incidents owing either to their activity cycles, behavior, or habitats that are remote from human settlement [9].

Myanmar has the world record for venomous snakebites [12]. Regionally speaking, the leading country in the Central America region is Panama, where 1800 snakebite records occur annually, causing a fatality rate of 0.5/100.000 people [13]. In Asia, Kerala is one of the places that have the lead in this category, along with West Bengal, Tamil Nadu, Maharashtra, and Andhra Pradesh, and hosts about 37 venomous snake species, [14]. In South America, Brazil suffers most from snakebites (approximately 26,000-29,000 cases annually), which is followed by Venezuela (7,000), Colombia (3,000), Ecuador (1,400-1,600), Peru (1,400-1,500), and Bolivia (1,000) [15]. Although snakebite incidences in African continent vary considerably as a result of differing hospitalization rates, Kenya has the most extensive record [8]. In Caribbean, snakebite incidents largely remain unrecorded [16]. Snakebites are less a cause of medical concern in Europe than the other parts of the planet; European snakebite incidents are usually caused by Malpolon monspessulanus and the sub-family of Viperidae [17]. The latter is also the most common snake species in rural Turkey [18].

Mechanisms/Pathophysiology

Venom-antivenom characteristics

Each species has its own venom composition, and snake's age and geographical region also affects it. Venom composition usually dictates clinical presentation [19,20]. Some components of typical venom act together and form protein complexes; toxin content and composition of venom should be well known to cover the geographical differences of fatality potential of and clinical signs and symptoms associated with various venoms [21,22]. Snake venoms contain abundant amounts of phospholipase A2 (PLA2), B, C and D enzymes, hemorrhaging, transaminase, hyaluronidase, phosphodiesterase, acetyl cholinesterase, cytolytic, necrotic toxins. The major protein families in snake venom with a discussion of their toxic activities can be found below [23,24]:

- Phospholipases A2: local and systemic myotoxicity, pain, damage to lymphatic vessels, edema, neurotoxicity, nephrotoxicity and hemolysis.
- Metalloproteinases: hemorrhage, myonecrosis, extracellular matrix degradation, blistering, pain, edema and cardiovascular shock, nephrotoxicity and coagulopathy.
- Hyaluronidases: extracellular matrix degradation.
- Three-finger toxins: Cytotoxicity, necrosis and neurotoxicity.
- Dendrotoxins: Neurotoxicity.
- Serine proteinases: Coagulopathy, edema and hypotension.
- Vasoactive peptides (for example, bradykinin-potentiating

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peptides): Hypotension.

- Disintegrins: Inhibition of platelet aggregation.
- C-Type lectin-like proteins: Inhibition or promotion of platelet aggregation and thrombocytopenia.
- Cysteine-rich secretary proteins: smooth muscle paralysis.
- Small basic myotoxic peptides: Muscle contracture.
- Natriuretic peptides: Hypotension.
- Sarafotoxins: Cardiotoxicity.

In 1984 Albert Calmette, with the collaboration of Pierre Paul Émile Roux, readied antisera production on rabbits against venom-induced death. At the same time, Physalix and Bertrand showed hyperimmune serum-induced effective neutralization of snake venoms. The first human use of an antivenom was carried out by Lépinay, a colleague of Calmette. The first anti-venom against Indian Cobra was introduced in 1895 [25,26].

In order to guarantee neutralization of venoms by antivenoms, a preclinical test should be conducted in compliance with internationally-accepted protocols and guidelines; of these, neutralization of venom potency, also known as ED50, is the major preclinical test. It refers to an effective antivenom dose that makes 50% of test animals survive a 3×to 5×LD50 challenge dose (where the LD50=lethal dose of venom that results in killing 50% of test animals in a given interval) [26,27].

Nevertheless, antivenoms differ with respect to the rate of adverse reactions, which range from early anaphylactic reactions to later serum sickness type reactions; furthermore, no antivenom has been proven safe in this sense when adverse reactions are carefully scrutinized after their use [28]. Antivenoms also carry some major disadvantages including access problems in rural regions where they are needed the most; geographical and taxonomic differences between snake species resulting in a diverse venom composition and antigenic reactivity; and potential allergic reactions associated with antivenoms [29]. Nevertheless, people in rural and remote places still perform folk medicine using herbal products for most of their medical problems including snakebites. Medicinal herbs are used to extract a wide range of bioactive medicines that can be either directly utilized for the treatment if snakebites or, as vital supplements, for production of anti-venoms. These compounds can thus be make of use as efficacious alternative agents in two main areas, namely as the sole therapy when antivenom immunotherapy is not urgently available, or in supplement form on top of existing therapy [30]. Alkaloids, acids, steroids, flavonoids, coumestans, pterocarpans, terpenoids and some miscellaneous compounds can be mentioned as herbal compounds used to treat snakebite victims [23].

Pathophysiology

Pharmacologically, snake venom incorporates various pharmacologically active proteins and peptides with pivotal roles in the pathophysiology of snakebite [31]. The venomous snake superfamily Colubroidae is the largest venomous animal family. Vipers (family Viperidae) and elapids (family Elapidae) are responsible for the majority of envenomations and fatal cases from snakebite among Homo Sapiens and domestic animals [32].

A venomous snake injects its venom through its fangs, modified teeth that are connected to a venom gland through a duct [24]. The size of the fangs determines whether a snake's venom is released into subcutaneous or intramuscular compartments. Some components of a venom act locally in the immediate vicinity of the area it has been released while others are transported to distant body sites *via* lymphatics or blood vessels and act systemically [33].

Snake venom is a highly complex and biochemically diverse compound with a wide range of toxicological effects that result in highly diverse clinical signs and symptoms. Some compounds in venoms inflict local tissue injury with resulting long-term sequelae but others act systemically resulting in signs of neurotoxicity (e.g. respiratory paralysis), hemorrhage, acute renal injury, rhabdomyolysis (that is, diffuse muscle breakdown), cardiovascular effects, autonomic hyperactivity or thrombus formation [34].

Local tissue injury mainly occurs through the effects of myotoxic phospholipases A2 (PLA2s), which are connected to and damage the cellular membrane of muscle fibers; this event leads to calcium influx to the cytosol, resulting in myofilament hypercontraction, mitochondrial dysfunction and other degenerative consequences, irreversibly injuring muscle cell [35-37]. This mechanism leads to chronic musculoskeletal sequelae as long-term health complications of snakebites [38]. Metalloproteinases in Snake Venom (SVMPs) cause degradation of important components of capillary basement membrane, which gives rise to reduced mechanical stability of micro vessels and dermal injury due to injury to dermal–epidermal interface, which eventually form blisters [39,40].

Neurotoxicity occurs by the actions of two major neurotoxins: α-neurotoxins and β-neurotoxins, which cause descending flaccid neuromuscular paralysis, and can induce a fatal blockade of bulbar (oral and laryngeal muscles responsible for speech and swallowing) and respiratory muscles [24]. α-Neurotoxins are connected to cholinergic receptors at the motor end plate of muscle fibers; these inhibit acetylcholine binding and provoke flaccid paralysis. In contrast, β-neurotoxins are PLA2s that affect presynaptic nerve terminal of neuromuscular junctions and cause enzymatic hydrolysis of phospholipids [41,42].

Cardiovascular and hemostatic disturbances mainly occur through SVMPs impairing the coagulation cascade or hydrolyze fibrinogen and fibrin [39, 43, 44]. Venom-induced systemic bleeding represents a major pathway leading to hemodynamic disturbances and may culminate in to cardiovascular shock [33].

Acute renal injury occurs due to renal ischemia secondary to reduced renal blood flow, and results from hemodynamic alterations caused by systemic bleeding and vascular leakage; proteolytic degradation of the glomerular basement membrane by SVMPs; deposition of microthrombi in the renal microvasculature, direct cytotoxic action of venom components, inducing systemic myotoxicity (that is, rhabdomyolysis), accumulation of large amounts of myoglobin in renal tubules, with consequent toxicity [45,46].

Rhabdomyolysis is due to the action of myotoxic PLA2s at the systemic level as a result of the binding of these toxins to receptors in muscle fibers [37].

Table 1: Grading the severity of envenomation.

0	no envenomation	Fang marks, minimal pain, swelling and erythema around the fang marks <2.5cm, no systemic symptoms.
I	Minimal envenomation	Fang marks, immediate pain, swelling and erythema of 2.5-15 cm during the first 12 hours, no systemic signs.
II	Moderate envenomation	Fang marks, immediate severe pain, swelling and erythema of 15-40 cm during the first 12 hours, mild systemic signs.
III	Severe envenomation	Fang marks, immediate severe pain, swelling and erythema >40 cm in the first 12 hours with systemic signs.
IV	Very severe envenomation	Fang marks, immediate severe pain, severe systemic signs including shock and coma.

Clinic

Snakebite envenomation manifests with local and systemic symptoms [47]. The former is pain, swelling, hemorrhagic blistering, bruising, and regional lymphadenopathy while the latter are headache, nausea, vomiting, and abdominal pain [14]. Snakebites may sometimes cause minimal or no symptoms and called as 'dry bites' (that is, transcutaneous bites without envenoming) [48]. Specific snakebites may result in specific symptoms. To conclude, pathophysiology and the toxins are the determinants of the clinical presentation.

Diagnosis

Bite site should be definitely well examined; time of envenomation, prehospital treatments if any, culprit snake species and other relevant questions about snakebite should be thoroughly questioned and recorded [24]. Patients' clinical condition should be assessed using complete blood cell count, biochemistry parameters including renal and hepatic functions, coagulation parameters, serum electrolytes, and myocardial enzymes. Electrocardiography and imaging tests including computed tomography and magnetic resonance should be performed as necessary [1]. Although venom antigens can be detected and quantified in body fluids with enzyme immunoassays, kits utilizing the latter are not widespread on a global scale [24].

Management

Treatment is based on the severity of envenomation; it is divided into field care and hospital management.

Field care

The therapeutic goals include total body immobilization, with particular care to immobilize the affected limb to prevent the venom from disseminating through veins and lymph vessels, airway management, checking breathing and circulation, eliminating any ring or tight object from around the affected limb, and putting a pressure pad or pressure bandage over the bite site [7,44]. Incision of the bite site, suction of the venom, and applying tourniquets are ineffective, potentially harmful, and should thus be discouraged [7]. First aid should delay systemic dissemination of a venom, prevent fatal complications, and transport a patient to a healthcare facility [49].

Hospital management

The initial assessment in the emergency department should include an examination of the airway, respiration, circulation, and level of consciousness. Patients in shock due to cardiovascular compromise should be urgently resuscitated, as those with respiratory failure due to neurotoxicity and cardiac arrest secondary to hypoxia, cardiac toxicity, or rhabdomyolysis-induced hyperkalemia [49,50]. Clinical severity of envenomation determinates the therapy. Table 1 provides the grading of system of signs indicative of severity. Observation should be done at least 24 hours with frequent clinical checks [24]. A "dry bite" that lacks signs of envenomation requires a watchful observation in the emergency service for a period of 8-10 hours against the possibility of the progression of symptoms [50].

At the first contact, signs of local injury (edema, petechiae, bullae, oozing from the wound, etc.) should be sought in the bitten area. The severity of swelling should be determined, and the affected extremity's circumference should be measured every 15 minutes to ensure that the progress of swelling halts and compartment syndrome does not occur. The affected limb should be taken to rest in a well-padded splint for a minimum of 24h. [51,52].

Antivenom administrations should be primarily pursued for venomous snakebites. Antivenoms contain heterologous antibodies directed to snake venoms that are derived from sera of animals that are immunized against the target venom. The antibodies in antivenoms are capable of binding and neutralizing venoms [1]. There are a number of commercially available antivenom products globally. Antivenoms can antagonize venoms' hemorrhagic, hypotensive, and postsynaptic neurotoxicity actions; they are also capable of preventing or minimizing presynaptic neurotoxicity, rhabdomyolysis and local tissue necrosis provided that they are administered early enough. This suggests that in the management of snakebites, a major clinical decision is whether antivenom will be administered [24].

Antivenom should be appropriately used and thus a patient should be evaluated thoroughly. Its use is not universal for all venomous snakebites. It is associated with heightened risks of severe untoward effects; furthermore, it is a costly treatment which is limited in stocks. Hence, it is essential to counterbalance risks of antivenom treatment against its benefits [50].

Antivenom treatment is recommended if and when a patient with proven or suspected snake-bite develops one or more of the following signs [53]:

- Systemic involvement: Heametologic abnormalities, Neurotoxicity (ptosis, external ophthalmoplegia, paralysis); Cardiovascular abnormalities: Hypotension, shock, cardiac arrhythmia, abnormal electrocardiography (ECG), Acute renal failure signs, Evidence of intravascular haemolysis or generalised rhabdomyolysis.

- Local involvement: Extensive and rapid local swelling within 48 hours of the bite, High risk of tissue necrosis or compartment syndrome.

Additional to antivenom treatment some drugs can be used for additional supportive care. Approved drugs for supportive care of patients with snakebite envenoming in addition to antivenom

are adrenaline and antihistaminics for anaphylactic reaction due to antivenom or envenomation, pain killers, antibiotics for necrotic envenomation or proven infection signs and symptoms, Acetylcholinesterase inhibitors for neurotoxic effects, blood products for heamotologic failure or systemic bleeding, Vasopressor drugs hypotension, shock and anaphylactic reactions, tetanus toxoid to boost immunity against tetanus toxin and corticosteroids for suspected adrenal failure [24].

Disposition and follow-up

A normal physical examination and initial laboratory test results do not guarantee significant envenomation. Patients with dry bites may be discharged after an observation period of 6 to 8 hours only to return should pain, swelling, or bleeding occur. Patients with severe or life-threatening bites or patients who are administered antivenom should be admitted to an intensive care unit; patients with mild or moderate envenomation who have received adequate doses of antivenom therapy with no further requirement can be admitted to general ward. Discharge should be considered upon regression of swelling and coagulopathy, provided that patient can be freely ambulated. The bitten body region (especially the hand) should be administered physical therapy upon resolution of edema and coagulopathy. Outpatient follow-up is recommended to prevent any delayed infection or serum sickness with all antivenoms; for this purpose, all patients should be instructed about the symptoms of serum sickness and be able to return when these symptoms develop [1,24].

Conclusion

Snake bites are a major public health problem whole over the world but with regard to their mortality and morbidity risks. Management of these medical emergencies requires a multidisciplinary approach. Particularly emergency care physicians should be familiar with but most importantly excel in the management of snake bites.

References

1. Richard CD, Julian W. Reptile Bites. In: Judith E. Tintinalli, editor. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th ed. McGraw-Hill Education. 2016: 1379-1383.
2. Dehghani R, Mehrpour O, Shahi MP, Jazayeri M, Karrari P, Keyler D. Epidemiology of venomous and semi-venomous snakebites (Ophidia: Viperidae, Colubridae) in the Kashan city of the Isfahan province in Central Iran. J Res Med Sci. 2014; 19: 33-40.
3. Nogalski A, Jankiewicz L, Cwik G, Karski J, Matuszewski Ł. Animal related injuries treated at the Department of Trauma and Emergency Medicine, Medical University of Lublin. Ann Agric Environ Med. 2007; 14: 57-61.
4. Chippaux JP. Estimate of the burden of snakebites in sub-Saharan Africa: a meta-analytic approach. Toxicon. 2011; 57: 586-599.
5. Halesha BR, Harshavardhan L, Lokesh AJ, Channaveerappa PK, Venkatesh KB. A study on the clinico-epidemiological profile and the outcome of snake bite victims in a tertiary care centre in southern India. J Clin Diagn Res. 2013; 7: 122-126.
6. Feitosa ES, Sampaio V, Sachett J, Castro DB, Noronha M, Lozano JL, et al. Snakebites as a largely neglected problem in the Brazilian Amazon: highlights of the epidemiological trends in the State of Amazonas. Rev Soc Bras Med Trop. 2015; 48: 34-41.
7. Avau B, Borra V, Vandekerckhove P, De Buck E. The Treatment of Snake Bites in a First Aid Setting: A Systematic Review. PLoS Negl Trop Dis. 2016; 10: e0005079.
8. Vaiyapuri S, Vaiyapuri R, Ashokan R, Ramasamy K, Nattamaisundar K, Jeyaraj A, et al. Snakebite and its socio-economic impact on the rural population of Tamil Nadu, India. PLoS One. 2013; 8: e80090.
9. WHO. Venomous snakes distribution and species risk categories. 2010.
10. Bhaumik S, Jagadesh S, Lassi Z. Quality of WHO guidelines on snakebite: the neglect continues. BMJ Glob Health. 2018; 3: e000783.
11. Ochola FO, Okumu MO, Muchemi GM, Mbaria JM, Gikunju JK. Epidemiology of snake bites in selected areas of Kenya. Pan Afr Med J. 2018; 29: 217.
12. Mahmood MA, Halliday D, Cumming R, Thwin KT, Kyaw MMZ, White J, et al. Snakebite incidence in two townships in Mandalay Division, Myanmar. PLoS Negl Trop Dis. 2018; 12: e0006643.
13. Pecchio M, Suárez JA, Hesse S, Hersh AM, Gundacker ND. Descriptive epidemiology of snakebites in the Veraguas province of Panama, 2007-2008. Trans R Soc Trop Med Hyg. 2018; 112.
14. Kumar KS, Narayanan S, Udayabhaskaran V, Thulaseedharan NK. Clinical and epidemiologic profile and predictors of outcome of poisonous snake bites - an analysis of 1,500 cases from a tertiary care center in Malabar, North Kerala, India. Int J Gen Med. 2018; 11: 209-216.
15. Roriz KRPS, Zaqueo KD, Setubal SS, Katsuragawa TH, Silva RRD, Fernandes CFC, et al. Epidemiological study of snakebite cases in Brazilian Western Amazonia. Rev Soc Bras Med Trop. 2018; 51: 338-346.
16. Resiere D, Mehdaoui H, Gutiérrez JM. Snakebite envenomation in the Caribbean: The role of medical and scientific cooperation. PLoS Negl Trop Dis. 2018; 12: e0006441.
17. Chippaux JP. Epidemiology of snakebites in Europe: a systematic review of the literature. Toxicon. 2012; 59: 86-99.
18. Karakus A, Zeren C, Celik MM, Arica S, Ozden R, Duru M, et al. A 5-year retrospective evaluation of snakebite cases in Hatay, Turkey. Toxicol Ind Health. 2015; 31: 188-192.
19. Cao D, Domanski K, Hodgman E, Cardenas C, Weinreich M, Hutto J, et al. Thromboelastometry analysis of severe North American pit viper-induced coagulopathy: A case report. Toxicon. 2018; 151: 29-33.
20. Kalita B, Singh S, Patra A, Mukherjee AK. Quantitative proteomic analysis and antivenom study revealing that neurotoxic phospholipase A2 enzymes, the major toxin class of Russell's viper venom from southern India, shows the least immuno-recognition and neutralization by commercial polyvalent antivenom. Int J Biol Macromol. 2018; 118: 375-385.
21. Mukherjee A.K. Non-covalent interaction of phospholipase A(2) (PLA(2)) and kaouthiotoxin (KTX) from venom of Naja kaouthia exhibits marked synergism to potentiate their cytotoxicity on target cells. Journal of venom research. 2010; 1: 37-42.
22. Mukherjee AK, Mackessy SP. Pharmacological properties and pathophysiological significance of a Kunitz-type protease inhibitor (Rusvikunin-II) and its protein complex (Rusvikunin complex) purified from Daboia russelii russelii venom. Toxicon. 2014; 89: 55-66.
23. Singh P, Yasir M, Hazarika R, Sugunan S, Shrivastava R. A Review on Venom Enzymes Neutralizing Ability of Secondary Metabolites from Medicinal Plants. J Pharmacopuncture. 2017; 20: 173-178.
24. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017; 3: 17063.
25. Shrikanth VM, Janardhan B, More SS, Muddapur UM, Mirajkar KK. *In vitro* anti snake venom potential of Abutilon indicum Linn leaf extracts against Echis carinatus (Indian saw scaled viper). J Pharmacogn Phytochem. 2014; 3: 111-117.
26. Williams DJ, Habib AG, Warrell DA. Clinical studies of the effectiveness and safety of antivenoms. Toxicon. 2018; 150: 1-10.
27. Gutiérrez JM, Solano G, Pla D, Herrera M, Segura Á, Vargas M, et al. Preclinical Evaluation of the Efficacy of Antivenoms for Snakebite Envenoming: State-of-the-Art and Challenges Ahead. Toxins (Basel). 2017; 9: E163.

28. Alirol E, Sharma SK, Ghimire A, Poncet A, Combescure C, Thapa C, et al. Dose of antivenom for the treatment of snakebite with neurotoxic envenoming: Evidence from a randomised controlled trial in Nepal. PLoS Negl Trop Dis. 2017; 11: e0005612.

29. Soares AM, Ticli FK, Marcussi S, Lourenço MV, Januário AH, Sampaio SV, et al. Medicinal plants with inhibitory properties against snake venoms. Curr Med Chem. 2005; 12: 2625-2641.

30. Singh P, Yasir M, Tripathi MK, Shrivastava R. A review on in vitro screening assay for inhibitory effect against venom enzymes using medicinal plants. Toxicol. Int. 2017; 23: 173-178.

31. Ghezellou P, Garikapati V, Kazemi SM, Strupat K, Ghassempour A, Spengler B. A perspective view of top-down proteomics in snake venom research. Rapid Commun Mass Spectrom. 2019; 33.

32. Warrell DA, Gutiérrez JM, Calvete JJ, Williams D. New approaches & technologies of venomics to meet the challenge of human envenoming by snakebites in India. Indian J. Med. Res. 2013; 138: 38-59.

33. Warrell DA. Snake bite. Lancet. 2010; 375: 77-88.

34. Calvete JJ. Proteomic tools against the neglected pathology of snake bite envenoming. Expert Rev. Proteomics. 2011; 8: 739-758.

35. Dixon RW, Harris JB. Myotoxic activity of the toxic phospholipase, notexin, from the venom of the Australian tiger snake. J. Neuropathol. Exp. Neurol. 1996; 55: 1230-1237.

36. Montecucco C, Gutiérrez JM, Lomonte B. Cellular pathology induced by snake venom phospholipase A2 myotoxins and neurotoxins: common aspects of their mechanisms of action. Cell. Mol. Life Sci. 2008; 65: 2897-2912.

37. Gutiérrez JM, Ownby CL. Skeletal muscle degeneration induced by venom phospholipases A2: insights into the mechanisms of local and systemic myotoxicity. Toxicon. 2003; 42: 915-931.

38. Jayawardana S, Arambepola C, Chang T, Gnanathasan A. Long-term health complications following snake envenoming. J Multidiscip Healthc. 2018; 11: 279-285.

39. Escalante T, Rucavado A, Fox JW, Gutiérrez JM. Key events in microvascular damage induced by snake venom hemorrhagic metalloproteinases. J. Proteomics. 2011; 74: 1781-1794.

40. Jiménez N, Escalante T, Gutiérrez JM, Rucavado A. Skin pathology induced by snake venom metalloproteinase: acute damage, revascularization, and re-epithelization in a mouse ear model. J. Invest. Dermatol. 2008; 128: 2421-2428.

41. Barber CM, Isbister GK, Hodgson WC. Alpha neurotoxins. Toxicon. 2013; 66: 47-58.

42. Paoli M, Rigoni M, Koster G, Rossetto O, Montecucco C, Postle AD. Mass spectrometry analysis of the phospholipase A(2) activity of snake pre-synaptic neurotoxins in cultured neurons. J Neurochem. 2009; 111: 737-744.

43. Del Brutto OH, Del Brutto VJ. Neurological complications of venomous snake bites: a review. Acta Neurol. Scand. 2011; 125: 363-372.

44. Kini RM. The intriguing world of prothrombin activators from snake venom. Toxicon. 2005; 45: 1133-1145.

45. Sitprija V, Sitprija S. Renal effects and injury induced by animal toxins. Toxicon. 2012; 60: 943-953.

46. Pinho FMO, Zanetta DM. T Burdmann EA. Acute renal failure after Crotalus durissus snakebite: a prospective survey on 100 patients. Kidney Int. 2005; 67: 659-667.

47. Ruha AM, Kleinschmidt KC, Greene S, Spyres MB, Brent J, Wax P, et al. The Epidemiology, Clinical Course, and Management of Snakebites in the North American Snakebite Registry. J Med Toxicol. 2017; 13: 309-320.

48. Silveira PV, Nishioka S de A. Venomous snake bite without clinical envenoming ('dry-bite'). A neglected problem in Brazil. Trop Geogr Med. 1995; 47: 82-85.

49. Ahmed SM, Ahmed M, Nadeem A, Mahajan J, Choudhary A, Pal J. Emergency treatment of a snake bite: Pearls from literature. J Emerg Trauma Shock. 2008; 1: 97-105.

50. Brian J Daley, Sneha Bhat. Snakebite Treatment & Management. 2018.

51. Pe T, Myint AA, Han KE, Ha T, Swe TN. Local compression pads as a first-aid measure for victims of bites by Russell's viper (Daboia russelii siamensis) in Myanmar. Trans R Soc Trop Med Hyg. 1995; 89: 293-295.

52. Warrell DA. WHO/SEARO Guidelines for the clinical management of snakebite in the Southeast Asian Region. SE Asian J Trop Med Pub Hlth. 1999; 30: 1-85.

53. WHO/Guidelines for the management of snakebites, 2nd edition.