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Abstract

Background: The World Health Organization estimates that there are approximately 5.4 million snakebites and 1.8–2.7 million cases of envenomation, with 81 410–137 880 deaths each year worldwide.

Aims: To estimate the prevalence of neurotoxic and haemotoxic snakebite envenomation through a comprehensive systematic review and meta-analysis.

Methods: We searched Medline/PubMed, Scopus and Cochrane Library up to January 2021 using keywords such as snakebite and snake envenomation. Bibliographic and random searches were also performed. Prospective or retrospective observational studies and randomized controlled trials were included for the review.

Results: We included 271 of 9711 studies published between 1963 and 2020. The pooled prevalence of snakebite from 188 studies with a total of 207 235 participants showed the highest prevalence in North America (69.20%; 95% confidence interval, CI: 57.06–81.34%) and lowest in Africa (28.10%; 95% CI: 22.22–33.98%). There was a pooled prevalence of 24.94% (95% CI: 22.84–27.03%) for haemotoxicity, with a highest prevalence of coagulopathy (43.76%;

95% CI: 33.15–54.37%). The overall prevalence of neurotoxicity was 38.20% (95% CI: 31.88–44.53%), with a highest prevalence of ptosis (53.57%; 95% CI: 38.51–68.62%).

Conclusion: There was a higher prevalence of snakebites in North America. The most prevalent haemotoxicity and neurotoxicity were coagulopathy and ptosis, respectively. The overall quality of evidence was good with a non-significant publication bias.

Keywords: snakebite, neurotoxicity, haemotoxicity, prevalence, toxicology

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Introduction

The World Health Organization estimates that there are approximately 5.4 million snakebites and 1.8–2.7 million cases of envenomation, with 81 410–137 880 deaths each year worldwide (1,2). Sub-Saharan Africa, South East Asia and South Asia have the highest number of snake bites with > 100 000 envenomations yearly (3). In South East Asia, India has the highest mortality rate due to snakebite envenomation with 45 900 deaths annually (4). The highest incidence of snakebite in India is found in Uttar Pradesh, Maharashtra, West Bengal, Kerala and Tamil Nadu (5).

Among the 2000 species of snakes globally, 400 are venomous and belong to 4 families: Viperidae (vipers), Elapidae (cobra, krait and coral snake), Hydrophidae (sea snake) and Colubridae (6). Systemic toxicity caused by vipers ranges from vomiting to shock, while local

tissue damage includes swelling and ecchymoses (7). The main haematological toxicity includes coagulopathy and acute kidney injury, which are life-threatening complications. Other complications include myocardial infarction, chronic renal failure, secondary hypopituitarism and rhabdomyolysis (8). Local damage caused by elapids includes wet gangrene necrosis, eventually leading to amputation. Systemic toxicity includes neurotoxic symptoms such as ptosis, ophthalmoplegia, respiratory failure and paralysis (9).

The higher mortality and morbidity in rural and developing regions is due to lack of attention by the people. Initial management by traditional villagers, slow transport facilities, difficulty in reaching doctors at primary healthcare centres, and time taken to identify snakes are multiple factors contributing to mortality. The presenting symptoms, associated complications and unavailability of anti-snake venom also contribute to mortality (10,11). Despite the high frequency of envenomation, physicians do not see snakebite patients very often, unlike for medical toxicologists (12). The substantial incidence of snakebites may be higher than reported due to under-reporting of most cases from villages (6).

Snakebite is an underestimated cause of accidental death globally that needs to be addressed. There are sparsity and diversity in the data on the prevalence and burden of snakebite envenomation which causes a dilemma for decision-makers and guideline providers when planning mitigation strategies, especially in rural areas. Therefore, we attempted, for the first time, to explore the maximum globally available literature on snakebites.

Methods

Study design

The protocol for this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42020208908) and we followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to report the findings.

Search strategy

We comprehensively searched Medline/PubMed, Scopus, Cochrane Library, Google Scholar and bibliographic databases from inception to January 2021. Combination of Medical Subject Headings (MeSH) and free-text words to analyse suitable studies related to exposure (snake bites) and outcomes (haemotoxicity and neurotoxicity with clinical presentation) were used to develop the search strategy. References of the selected articles were screened to identify additional eligible studies. A detailed search strategy used in various databases is listed in

Table 1 .

Inclusion criteria

We included English-language prospective or retrospective observational studies (cross-sectional, case–control or cohort) and randomized controlled trials (RCTs) conducted globally that reported the prevalence of snakebite and its toxicity, with clinical presentation among adults. Studies that assessed bites by other animals, dry bites, nonvenomous snake bites, or bites by unidentified snakes or studies that were difficult to interpret were excluded.

Study selection and data extraction

The initially identified studies were screened for titles and abstracts to determine whether they met the eligibility criteria. Full-text articles were retrieved and screened for eligibility. The extracted data consisted of author details, year of publication, country and continent, study design and settings, patient samplings, gender, type of snake, and information on outcomes (type of toxicity, clinical presentation and frequency). The overall prevalence of snakebites according to continent, along with haemotoxic and neurotoxic presentations, was estimated. Two independent reviewers performed the study selection and extracted the relevant data from the included studies. Any disagreements regarding the study selection and data extraction were resolved through discussion, consensus or consultation with other team authors.

Quality assessment

The Cochrane risk of bias assessment tool was used to assess the quality of the RCTs (13). The methodological or reporting quality of included observational studies was assessed using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies) (14). Two independent reviewers were involved in the quality assessment and any discrepancies in the data extraction were resolved by consensus or in consultation with a third reviewer.

Statistical analysis

Review Manager version 5.4 was used to perform the meta-analysis. The pooled prevalence estimates of outcome variables were calculated using total number of participants and those with identified snakebites. The estimated prevalence of overall snakebites, haemotoxicity and neurotoxicity due to snakebite was expressed as a percentage with corresponding 95% confidence interval (CI). Subgroup analysis was performed based on the continent for overall prevalence, types of clinical presentation under haemotoxic and neurotoxic snakebites. The magnitude of heterogeneity between the studies was assessed using the I2 statistic and Tau2 for each of the pooled estimates. A fixed-effect model was applied when there was a nonsignificant level of heterogeneity ($I2 \leq 50$; $P > 0.1$), and a random-effect model in case of

substantial level of heterogeneity (I2 ≥ 50; P **Publication bias and sensitivity analysis**

A funnel plot was used for the visual inspection of publication bias with prevalence rate on the x axis and standard error of prevalence rate on the y axis. Begg's and Egger's tests assessed the statistical significance of publication bias (Comprehensive Meta-analysis Trial version-3). The sensitivity analysis was performed to evaluate the stability of results by omitting studies with high risk of bias from the meta-analysis which may have influenced the effect on overall prevalence.

Results

Study selection

A total of 9711 studies were identified in the search of PubMed/Medline (5726), Scopus (3900) and Cochrane (85), among which, 9541 studies were screened after removal of duplicates. After title and abstract screening, 2699 (28.29%) studies were identified for full-text evaluation, from which 271 (10.04%) studies were included for systematic review (reference of included studies are provided in supplementary file) and 234 (8.67%) for meta-analysis. Figure 1 shows the PRISMA flow diagram for study selection and inclusion.
Figure 2

Characteristics of included studies

All the included studies were published between 1963 and 2020. Sample size varied from 7 to 70 816 participants. Gender was specified in 96 studies, with higher numbers of male than female participants. Most studies were prospective (122) and retrospective (112) followed by randomized controlled trials (23), cross-sectional studies (7) and ambispective studies (7). Globally, India (48) had the highest number of studies, followed by Brazil (37), United States of America (33) and Sri Lanka (30). The other countries were Australia (14), Chinese Taipei (11), Thailand (10), Nigeria (6), France (5), Nepal (5), Israel (5), Colombia (5), Myanmar (8), VietNam (4), Papua New Guinea (3), Venezuela (Bolivarian Republic of) (3), Japan (3), Pakistan (3), Saudi Arabia (3), Mexico (2), Malaysia (2), Islamic Republic of Iran (2), China (2), Croatia (2), Czech Republic (2), Argentina (2), Hong Kong SAR (1), California (1), Sweden (1), Spain (1), Philippines (1), Suriname (1), Morocco (1), Panama (1), Bangladesh (1), Liberia (1), Djibouti (1), Costa Rica (1), Zimbabwe (1), Alabama (1), South Africa (1), Lao People's Democratic Republic (1), Ecuador (1), Cameroon (1), United Kingdom of Great Britain and Northern Ireland (UK) (1), Greece (1) and Finland (1).

Clinical presentation of snakebite envenomation

A total of 122 studies reported haemotoxicity (103) and neurotoxicity (59) caused by snakebite. The common haemotoxic presentations were bleeding (62), coagulopathy (29), thrombocytopenia (26), haematuria (27), haematemesis (13), haemorrhage (12), haemolysis (4)

and hypofibrinogenemia (3). Neurotoxic presentations included ptosis (30), weakness in any part of the body (13), paralysis (9), dizziness (9), diplopia (9), dyspnoea/respiratory difficulty (9), blurred vision (8), variation in consciousness (8), dysphagia (5), drowsiness (5), palsy (4), fasciculations (3) and convulsions (2).

Quality assessment of observational studies

STROBE was used to assess the quality of observational studies. Three studies gave a complete satisfactory score of 22, 12 a score of 21, 31 a score of 20, 61 a score of 19, 46 a score of 18, 54 a score of 17 and 30 a score of 16. Lowest scores were for 4 studies giving a score of 15, 3 a score of 14 and 2 a score of 13.

Assessment of risk of bias in RCTs

RevMan for Windows version 5.4 (Cochrane Collaboration, Oxford, UK) was used to assess the quality of RCTs. Twenty-three RCTs were assessed for risk of bias, and high risk was found in 8 studies for detection bias, followed by 7 studies for performance bias. Nineteen studies showed medium risk for attrition bias followed by 15 studies for selection bias in allocation concealment. Low risk was found for reporting bias (23 studies) followed by performance bias (11 studies).

Prevalence of snakebite

The pooled prevalence of snakebite from 188 studies with a total of 207 235 participants showed highest prevalence in North America (69.20%; 95% CI: 57.06–81.34%; I2 = 100%; 26 studies), followed by Europe (59.66%; 95% CI: 44.04–75.28%; I2 = 100%; 9 studies); South America (57.07%; 95% CI: 35.09–79.04%; I2 = 100%; 33 studies); Asia (49.24%; 95% CI: 42.80–55.69%; I2 = 100%; 98 studies); Australia (31.39%; 95% CI: 22.49–40.29%; I2 = 100%; 16 studies); and lowest in Africa (28.10%; 95% CI: 22.22–33.98%; I2 = 89%; 6 studies). As there was high heterogeneity among studies (I2 = 100%; P **Prevalence of haemotoxicity**

The meta-analysis of 177 studies with 35 637 participants showed a pooled prevalence of 24.94% (95% CI: 22.84–27.03%) for haemotoxicity. Highest prevalence of haemotoxic presentation was coagulopathy (43.76%; 95% CI: 33.15–54.37%; I2 = 99%; 5934 participants in 36 studies), followed by systemic bleeding and haemorrhage (23.77%; 95% CI: 21.15–26.39%; I2 = 97%; 22 253 participants in 71 studies), thrombocytopenia (18.65%; 95% CI: 14.41-22.89%; I2=90%; 11351 participants in 25 studies) and hematuria (14.09%; 95% CI: 11.16-17.03; I2=95%; 5685 participants in 30 studies). Least prevalence was for haematemesis (4.09%; 95% CI: 2.49–5.68%; I2 = 62%; 1783 participants in 15 studies). A random-effect model was used as there was high heterogeneity among the studies (I2 = 99%) .

Prevalence of neurotoxicity

The summary estimate from 57 studies with 9266 participants observed an overall prevalence of 38.20% (95% CI: 31.88–44.53%) neurotoxicity due to snakebite. The highest prevalence of neurotoxic presentation was ptosis (53.57%; 95% CI: 38.51–68.62%; I2 = 99%; 3184 participants in 21 studies), followed by ophthalmoplegia (40.16%; 95% CI: 26.26–54.06%; I2 = 99%; 2495 participants in 12 studies), Blurred vision (27%; 95% CI: 16.34-37.65; I2: 98%; 2513 participants in 8 studies) and Diplopia (25.34%; 95% CI: 13.82-36.86; I2: 94%; 1025 participants in 7 studies). The least prevalence was observed for dizziness (12.54%; 95% CI: 5.40-19.68; I2: 99 %; 930 participants in 8 studies). The overall heterogeneity among studies was high (I2 = 99%; P **Publication bias assessment**

Visual examination of the funnel plots showed symmetrical distribution of studies, indicating chances of nonbias, which was statistically confirmed through Egger's test (P = 0.321) and Begg's test (P = 0.371) for overall survival from snakebite.

Sensitivity analysis

Due to the large number of studies, sensitivity analysis was performed by omitting observational and RCTs with low-quality and high-risk of bias from the pooled prevalence of overall survival. Two observational studies of low quality (15-16) and 5 RCTs of high-risk bias (17-21) were omitted and the meta-analysis was repeated. The sensitivity analysis showed prevalence to be 51.83% (95% CI: 43.81–59.85%) and 52.29% (95% CI: 44.10–60.48%) before and after removal of the studies, respectively, indicating high stability of the results.

Discussion

Our study predominantly focused on haemotoxicity and neurotoxicity from snakebite and elucidated their overall prevalence and clinical presentations. Due to the existing overlap of clinical features with haemotoxic and neurotoxic snakebite, our study tried to pool the most commonly occurring clinical manifestations. A total of 271 studies were included that provided deeper insight into the prevalence of overall snakebite in North America, South America, Europe, Asia, Africa and Australia.

Traditionally, it has been oversimplified that Viperidae are haemotoxic and Elapidae are neurotoxic, but there is a considerable overlap in their clinical presentations and complications. This results in a conundrum regarding their identification and treatment in clinical settings. A qualitative study by Malik et al. among a group of allopathic practitioners in India showed that most of them found it hard or could not differentiate between a viperine and elapid bite due to overlapping symptoms (22-23). Our meta-analysis dealt with major clinical presentations of toxicity from reported families of snakes.

Under haemotoxicity, the clinical presentations chosen were coagulopathy, systemic bleeding and haemorrhage, thrombocytopenia, haematuria and haematemesis on the basis of frequency of reporting. Similarly ptosis, ophthalmoplegia, diplopia, dizziness and blurred vision were chosen under neurotoxic manifestations. Bleeding and haemorrhage irrespective of the site were common symptoms. The prevalence of haemotoxic presentations in descending order was coagulopathy (43.76%), systemic bleeding and haemorrhage (23.77%), thrombocytopenia (18.65%), haematuria (14.09%) and haematemesis (4.09%). A study by Thang et al. presented haematuria (27.44%), followed by coagulopathy (23.46%), thrombocytopenia (21.89%) and haematemesis (6.97%) (24).

The prevalence of neurotoxic symptoms was 53.57% for ptosis, 40.16% for ophthalmoplegia, 27% for blurred vision, 25.34% for diplopia and 12.54% for dizziness. In a prospective cohort study by Phillips et al. with 23 victims envenomated by Russell's viper, systemic neurotoxicity was seen in all patients, and ptosis was the most common symptom observed (73.9%) (25). Silva et al. conducted a study of 245 confirmed bites from Russell's viper and 130 patients developed neurotoxic manifestations, and bilateral partial and complete ptosis was seen at a rate of 44.89% (26). Similarly, studies conducted by Silva et al. (26), Johnston et al. (27) and Kularatne et al. (8) reported a prevalence of 48.16%, 48.48% and 54.55% for ophthalmoplegia, respectively. Blurred vision was reported by Silva et al. (26) and Kumar et al. (28), which was similar to our study. A study by Bucaretchi et al. in Brazil had a similar prevalence of diplopia to our study (29), and Burch et al. recorded a similar prevalence in dizziness (30).

Apart from neurotoxicity and haemotoxicity, all snake venoms are capable of inducing cytotoxicity, causing cell necrosis and apoptosis. Snake venom cytotoxicity manifests clinically as local necrosis, haemolysis, cardiotoxicity, myonecrosis and kidney injury, either through direct action or in combination with other pathogenic activities of the venom (31).

Our study had some limitations. All our studies used electronically linked databases, thus we were unable to determine the validity of identification of snakebite in a given patient population. Confounders and covariates were not uniform across the studies. Studies were limited to English language and full-text availability, and exclusion of conference abstracts, editorials and commentaries could have resulted in missing some important data.

Conclusion

A higher prevalence of snakebite was observed in North America, followed by Europe. Coagulopathy and ptosis were major symptoms of haemotoxic and neurotoxic snakebites, respectively.

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Competing interests: None declared.

Prévalence mondiale de l'envenimation neurotoxique et hémotoxique par morsure de serpent : analyse systématique et méta-analyse

Résumé

Contexte : L'Organisation mondiale de la Santé estime qu'il y a environ 5,4 millions de morsures de serpents, 1,8 à 2,7 millions de cas d'envenimation et 81 410 à 137 880 décès dus à ces morsures chaque année dans le monde.

Objectifs : Estimer la prévalence de l'envenimation neurotoxique et hémotoxique par morsure de serpent au moyen d'une analyse systématique et d'une méta-analyse.

Méthodes : Nous avons effectué des recherches dans Medline/Pub Med, Scopus et Cochrane Library jusqu'en janvier 2021 à l'aide de mots-clés tels que snakebite et snake envenomation. Des recherches bibliographiques et aléatoires ont également été réalisées. Des études observationnelles prospectives ou rétrospectives et des essais contrôlés randomisés ont été inclus dans l'analyse.

Résultats : Nous avons inclus 271 des 9711 études publiées entre 1963 et 2020. La prévalence cumulée des morsures de serpents provenant de 188 études comprenant un total de 207 235 participants était la plus élevée en Amérique du Nord [69,20 % ; intervalle de confiance (IC) à 95 % : 57,06-81,34 %] et la plus faible en Afrique (28,10 % ; IC à 95 % : 22,22-33,98 %). La prévalence cumulée de l'hémotoxicité était de 24,94 % (IC à 95 % : 22,84-27,03 %), avec une prévalence maximale de la coagulopathie (43,76 % ; IC à 95 % : 33,15-54,37 %). La prévalence globale de la neurotoxicité était de 38,20 % (IC à 95 % : 31,88-44,53 %), la prévalence la plus élevée étant celle du ptosis (53,57 % ; IC à 95 % : 38,51-68,62 %).

Conclusion : La prévalence des morsures de serpents était plus élevée en Amérique du Nord.

L'hémotoxicité et la neurotoxicité les plus fréquentes étaient respectivement la coagulopathie et le ptosis. La qualité globale des données probantes était bonne, avec un biais de publication non significatif.

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[illegible] 207235 [illegible] 188 [illegible] (57.06-81.34% :95% [illegible] 69.20%) [illegible] .(33.98%–22.22 :95% [illegible] 28.10%) [illegible] (22.84-27.03% :95% [illegible]) 24.94% [illegible] .(54.37%–33.15 :95% [illegible] 43.76%) [illegible] (31.88-44.53% :95% [illegible]) 38.20% [illegible] .(68.62%–38.51 :95% [illegible] 53.57%) [illegible]

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References

1. Snakebite envenoming [website]. Geneva: World Health Organization; 2021 (https://www.who.int/health-topics/snakebite#tab=tab_1, accessed 24 August 2022).

2. Suraweera W, Warrell D, Whitaker R, Menon G, Rodrigues R FS et al. Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. Elife. 2020 Jul 7;9:e54076. https://doi.org/10.7554/eLife.54076 PMID:32633232

3. Sankar J, Nabeel R, Sankar MJ, Priyambada L, Mahadevan S. Factors affecting outcome in children with snake envenomation: a prospective observational study. Arch Dis Child. 2013 Aug;98(8):596–601. DOI: 10.1136/archdischild-2012-303025 PMID: 23716133

4. Mohapatra B, Warrell DA SW et al. Snakebite mortality in India: a nationally representative mortality survey. PloS Negl Trop Dis. 2011;5(4):e1018. https://doi.org/10.1371/journal.pntd.0001018

5. Ahmed SM, Ahmed M, Nadeem A, Mahajan J CA et al. Emergency treatment of a snakebite: Pearls from literature. J Emerg Trauma Shock. 2008;1(2):97–105.

6. Monteiro FNP, Kanchan T, Bhagavath P, Kumar GP, Menezes RG, Yoganarasimha K. Clinico-epidemiological features of viper bite Envenomation: A study from Manipal, South India. Singapore Med J. 2012;53(3):203–7.

7. Domanski K, Kleinschmidt KC, Greene S, Ruha AM, Bebarta VS, Onisko N, et al. Cottonmouth snake bites reported to the ToxIC North American snakebite registry 2013–2017. Clin Toxicol. 2020;58(3):178–82.

8. Kularatne SAM, Silva A, Weerakoon K, Maduwage K, Walathara C, Paranagama R, et al. Revisiting Russell's Viper (Daboia russelii) bite in Sri Lanka: Is abdominal pain an early feature of systemic envenoming? PLoS One. 2014;9(2):1–8.

9. Warrell DA, Cox TN, Firth JD BJ. Injuries, envenoming, poisoning and allergic reactions caused by animal. Oxford textbook of Medicine; Oxford university press. 2003. 923–45 p.

10. Kharat R, Kedare R. Epidemiological profile of snake bites over 1-year period from tertiary care centre in maval region of Maharashtra, India: Original research article. Indian J Forensic Med Toxicol. 2020;14(1):44–9.

11. 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(4):309–20.

12. WHO. The clinical management of snake bite in the southeast region Asia. Regional office for South East Asia. 2005. p. http://www.searo.who.int/LinkFiles/SDE_mgmt_snake-.

13. Lundh A, Gøtzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008 Dec;8(1):1-9.

14. Elm EV, Altman DG, Egger M, Pocock S GP et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–9.

15. Majumdar S, Biswas A, Chowdhuri S. An epidemiological study of snake bite cases attending at mortuary in tertiary district level medical college. Indian J Forensic Med Toxicol. 2019;13(4):7–11.

16. Namal Rathnayaka RMMK, Ranathunga PEAN, Kularatne SAM. Venom-Induced

Consumption Coagulopathy Following Hump-Nosed Pit Viper (Genus: Hypnale) Envenoming in Sri Lanka: Uncertain Efficacy of Fresh Frozen Plasma. Wilderness Environ Med [Internet]. 2020;31(2):131–43. Available from: https://doi.org/10.1016/j.wem.2019.12.006

17. Mendonça-da-Silva I, Magela Tavares A, Sachett J, Sardinha JF, Zaparolli L, Gomes Santos MF, et al. Safety and efficacy of a freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: An open randomized controlled phase IIb clinical trial. PLoS Negl Trop Dis. 2017;11(11):1–21.

18. Isbister GK, Buckley NA, Page CB, Scorgie FE, Lincz LF, Seldon M, et al. A randomized controlled trial of fresh frozen plasma for treating venom-induced consumption coagulopathy in cases of Australian snakebite (ASP-18). J Thromb Haemost. 2013;11(7):1310–8.

19. Isbister GK, Shahmy S, Mohamed F, Abeysinghe C, Karunathilake H, Ariaratnam A. A randomised controlled trial of two infusion rates to decrease reactions to antivenom. PLoS One. 2012;7(6).

20. de Oliveira Pardal PP, Souza SM, da Costa Monteiro MR de C, Fan HW, Cardoso JLC, França FOS, et al. Clinical trial of two antivenoms for the treatment of Bothrops and Lachesis bites in the north eastern Amazon region of Brazil. Trans R Soc Trop Med Hyg. 2004;98(1):28–42.

21. Ariaratnam CA, Sjöström L, Raziek Z, Abeyasinghe S, Kularatne M, Arachchi RWKK, et al. An open, randomized comparative trial of two antivenoms for the treatment of envenoming by Sri Lankan Russell's viper (Daboia russelii russelii). Trans R Soc Trop Med Hyg. 2001;95(1):74–80.

22. Wijewantha, H. S and Sellahewa, K. H.. Hump nosed viper bite in Sri Lanka-descriptive observational study of 1543 cases. Asian Pac J Trop Med. 2010;902–5.

23. K, Malik AS and Chatterjee. Awareness of Indian medical practitioners about snakebite and its management-Is there a need to re-evaluate medical training? Med J Dr patil vidyapeeth.

2020;13(5):519.

24. Thang V Van, Bao TQQ, Tuyen HD, Krumkamp R, Hai LH, Dang NH, et al. Incidence of snakebites in can tho municipality, mekong delta, South Vietnam— evaluation of the responsible snake species and treatment of snakebite envenoming. PLoS Negl Trop Dis. 2020;14(6):1–9.

25. Phillips RE, Theakston RDG, Warrell DA, Galigedara Y, Abeysekera DTDJ, Dissanayaka P, et al. Paralysis, rhabdomyolysis and haemolysis caused by bites of Russell's viper (Vipera russelli pulchella) in Sri Lanka: Failure of Indian (Haffkine) antivenom. Qjm. 1988;68(3–4):691–715.

26. Silva A, Maduwage K, Sedgwick M, Pilapitiya S, Weerawansa P, Dahanayaka NJ, et al. Neurotoxicity in Russells viper (Daboia russelii) envenoming in Sri Lanka: A clinical and neurophysiological study. Clin Toxicol. 2016;54(5):411–9.

27. Johnston CI, Ryan NM, O'Leary MA, Brown SGA, Isbister GK. Australian taipan (Oxyuranus spp.) envenoming: clinical effects and potential benefits of early antivenom therapy–Australian Snakebite Project (ASP-25). Clin Toxicol. 2017;55(2):115–22.

28. Kumar KGS, 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;11:209–16.

29. Bucaretchi F, Herrera SRF, Hyslop S, Baracat ECE, Vieira RJ. Snakebites by Crotalus durissus ssp in children in Campinas, São Paulo, Brazil. Rev Inst Med Trop Sao Paulo. 2002;44(3):133–8.

30. Jon M. Burch, Rita Agarwal, Kenneth L. attox, David V. Feliciano GLJ. The treatment of crotalid envenomation without antivenin. J Trauma. 1988;28(1):35–43.

31. Tan NH, Tan CH. Cytotoxicity of snake venoms and toxins: mechanisms and applications. Arcadius V. Krivoshein YNU, editor. Snake Venoms and Envenomation: Modern Trends and Future Prospects. Medicine and Biology Research Developments. New York: Nova Science Publishers. 2016:215-54.