Ultrasound features of Cytotoxic venomous snake bite and implications for surgical management — A systematic review

Karundat Bhola[a], Samson Mashele[b], Yoshan Moodley[b,*]

[a] *Department of Radiology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, 719 Umbilo Road, Congella, 4013, Durban, South Africa.*

[b] *Faculty of Health and Environmental Sciences, Central University of Technology, Bloemfontein, South Africa.*

Abstract

Background:

Snake bite is an important, yet often neglected health problem in many regions of the world. Cytotoxic venomous snake bites (VSB) have the potential to induce significant tissue injury, resulting in compartment syndrome. This research sought to provide a summary of ultrasound features of VSB, with the aim of improving management in afflicted patients.

Methods:

A systematic review of 2 electronic medical literature databases was performed. Pre-defined eligibility criteria were used to identify relevant published case series (sample size 10 or more) which reported on ultrasound features of VSB. Screening of the reference lists of eligible manuscripts was also performed.

Results:

Two case series reporting on ultrasound studies of cytotoxic VSB were included in this review. One study was from the United States and the other study was from South Africa. Children under 12 years comprised a large proportion of VSB victims (92.3% in the American study and 33.3% in the South African study). The majority of VSB victims were male (76.9% in the American study and 57.1% in the South African study). Snake species involved were Crotaline/rattlesnakes (American study) and adders or cobras (South African study). In both studies, VSBs were located on the upper limbs. The most common ultrasound finding in both studies was subcutaneous oedema. The deep muscular appears to be minimally affected in cytotoxic VSB.

Conclusion:

Ultrasound features of cytotoxic envenomation were consistent between studies. Ultrasonography provides useful information which can be used to supplement the information obtained during the external clinical examination of cytotoxic VSB and can be used to identify patients with a risk of compartment syndrome who might require surgery.

Recommendation:

Ultrasonography should be performed as one of the primary investigations when patients present with VSB.

Keywords: Venomous snake bite, snake envenomation, cytotoxic, ultrasound features, systematic review, Date submitted: 5th/10/2022 Date accepted: 18th/10/2022

1. INTRODUCTION

Despite the high levels of morbidity and mortality associated with venomous snake bites (VSB)

*Corresponding author.

Email address: ymoodley@cut.ac.za (Yoshan Moodley)

in many regions of the world, this condition continues to be overlooked as a global public health issue [1, 2]. In high-burden regions such as Africa and Asia, there are several snake species that possess cytotoxic venom [3, 4]. Cytotoxic VSB is characterized by painful swelling on external examination and may occur with or without significant watery blood leaking from the bite wound, shock, blistering, or tissue discoloration [5]. Ultrasound equipment is amongst the most accessible pieces of healthcare equipment in regions of the world most severely impacted by cytotoxic VSB [6], and ultrasonography can be used to supplement the information gained through the external clinical examination of the injury with information related to internal aspects of the injury [7].

A summary of the published literature which describes the most frequently encountered ultrasound features of cytotoxic VSB would therefore be useful in assisting healthcare workers managing afflicted patients, particularly in high-burden settings. However, there are currently no published systematic reviews which describe the most common ultrasound features of cytotoxic VSB. This research sought to address this paucity in the literature through a systematic review. The research question developed using the Population-Exposure-Control-Outcome (PECO) framework for systematic reviews was: What are the ultrasound features of cytotoxic VSB?

2. METHODS

This was a qualitative, evidence-based systematic review. No meta-analysis component was included in this research. The titles and abstracts of manuscript records indexed in the PubMed and Scopus electronic medical literature databases were searched from the date of database inception until 23 February 2019 using the following electronic search strategy: ("Snakebite*" OR "Snake-bite*" OR "Snakebite*") AND ("Envenom*" OR "Venom") AND ("Ultrasound*" OR "Ultrasonography*" OR "Sonograph" OR "Sonogram*" OR "Radiology*" OR "Radiograph*" OR "Doppler"). An asterisk indicates the use of the truncation function in the electronic medical literature database. All database fields were searched. This included the record title and abstract, keywords, and database-controlled vocabulary.

Following the exclusion of duplicates, the abstracts of records returned from this search were then screened using a set of eligibility criteria. To be included in the full-text screening process, abstracts must have fulfilled all of the following criteria: a) Describe observational studies of VSB in humans; b) Described studies with sample size $\geq$10; c) Abstract in the English language. Following the full-text screening process, only manuscripts that reported ultrasound features of cytotoxic VSB at the site of the bite (or within proximity) were included in the final systematic review. The reference lists of manuscripts included in the final systematic review were also screened to identify additional manuscripts of interest which might have been missed during the electronic search.

"Grey" literature was excluded from the literature search. Although this might have introduced publication bias, we had concerns regarding the peer-review process for "grey" literature and the possibility that some "grey" literature (such as conference abstracts) would not provide sufficient information to be included in the final systematic review. The screening of abstracts and full texts, as well as the study quality assessment process, was performed independently by the two authors. The opinion of an external expert was sought in the event of a dispute regarding the inclusion or exclusion of manuscripts in the final systematic review, or the quality of studies reported in eligible manuscripts.

Information related to article authors, year of publication, the country where the study was conducted, sample size, VSB victim age and gender, snake species involved, site of VSB, and ultrasound features of VSB was extracted from each eligible manuscript and entered into an electronic spreadsheet. The quality of studies reported in the eligible manuscripts was evaluated using the quality assessment tools developed by the National Heart, Lung, and Blood Institute [8].

Basic descriptive statistics were used to present

the most common patient characteristics and ultrasound features of VSB. The electronic spreadsheet was imported into the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, USA), which was then used to perform the descriptive statistical analysis. Results for the descriptive statistical analysis are presented as frequencies and percentages.

This research was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (Protocol EXM050/19).

3. RESULTS

The flow of information through the different phases of this systematic review is shown in Figure 1.

The electronic search yielded a total of 302 records. Of these 302 records, 5 (1.7%) were duplicates. Of the remaining 297 unique records, only 18 (6.1%) were selected to undergo full-text review. Reasons for excluding the 279 records from the full-text screening process included: Not observational studies of VSB in humans (195, 69.9% of excluded records following abstract screening); Sample size <10 (83, 29.7% of excluded records following abstract screening); Abstracts not in the English language (1, 0.4% of excluded records following abstract screening). Following the full-text screening of the 18 manuscripts, there were 16 (88.9% of full-text manuscripts reviewed) were found to be ineligible as they did not report ultrasound features of cytotoxic VSB at the site of the bite or within close proximity to the site of the bite. Screening the reference lists of the remaining 2 eligible manuscripts did not yield any additional manuscripts of interest. Therefore, the final systematic review was comprised of 2 manuscripts [9, 10].

A description of the 2 manuscripts included in this systematic review is shown in Table 1. These 2 manuscripts each reported on a single study of cytotoxic VSB. One of the 2 studies was conducted in Africa (South Africa), while the other study was conducted in North America (United States). Both studies were deemed to be of good quality. Sample sizes were modest in both studies.

All but one of the patients from the American study were >12 years old, while one-third of patients in the African study were aged >12 years old. More males than females presented with VSB in both studies. The American study reported on crotaline/rattlesnake bites. While it was unclear which specific snake species were responsible for the VSB in the African case series, the authors suggest that these species were most likely adders or cobras. In both American and African studies, most patients were bitten on the upper limbs. Subcutaneous oedema was the most common ultrasound finding in bitten limbs. Involvement of the deeper musculature, as evidenced by ultrasonography, was rare.

4. DISCUSSION

Subcutaneous oedema is a common ultrasound feature observed in patients presenting with cytotoxic VSB. This finding was consistent between settings and snake species and was not impacted by the age or gender composition of the 2 studies reviewed [9, 10]. Oedema results from the collection of intracellular fluids in the extracellular matrix [11]. It is likely that subcutaneous oedema noted on ultrasound following cytotoxic VSB is a consequence of the cytolytic actions of the toxins and enzymes present in the venom [12]. Cytotoxins are non-enzymatic components that may comprise up to 70% of the venom in some cytotoxic snake species [12]. These protein molecules form pores in cell membranes which promote the leakage of intracellular contents into the extracellular matrix. Internalized cytotoxin might also disrupt surface membrane permeability through its interaction with lysosomes [12]. The venom of many cytotoxic snake species is also rich in the enzyme Phospholipase A2. This enzyme displays hydrolytic activity and has an affinity for the phospholipid groups in cell membranes. The hydrolytic activity of Phospholipase A2 at the cell surface not only increases cell membrane permeability but can also initiate other signalling processes which culminate in cytolysis [12]. This

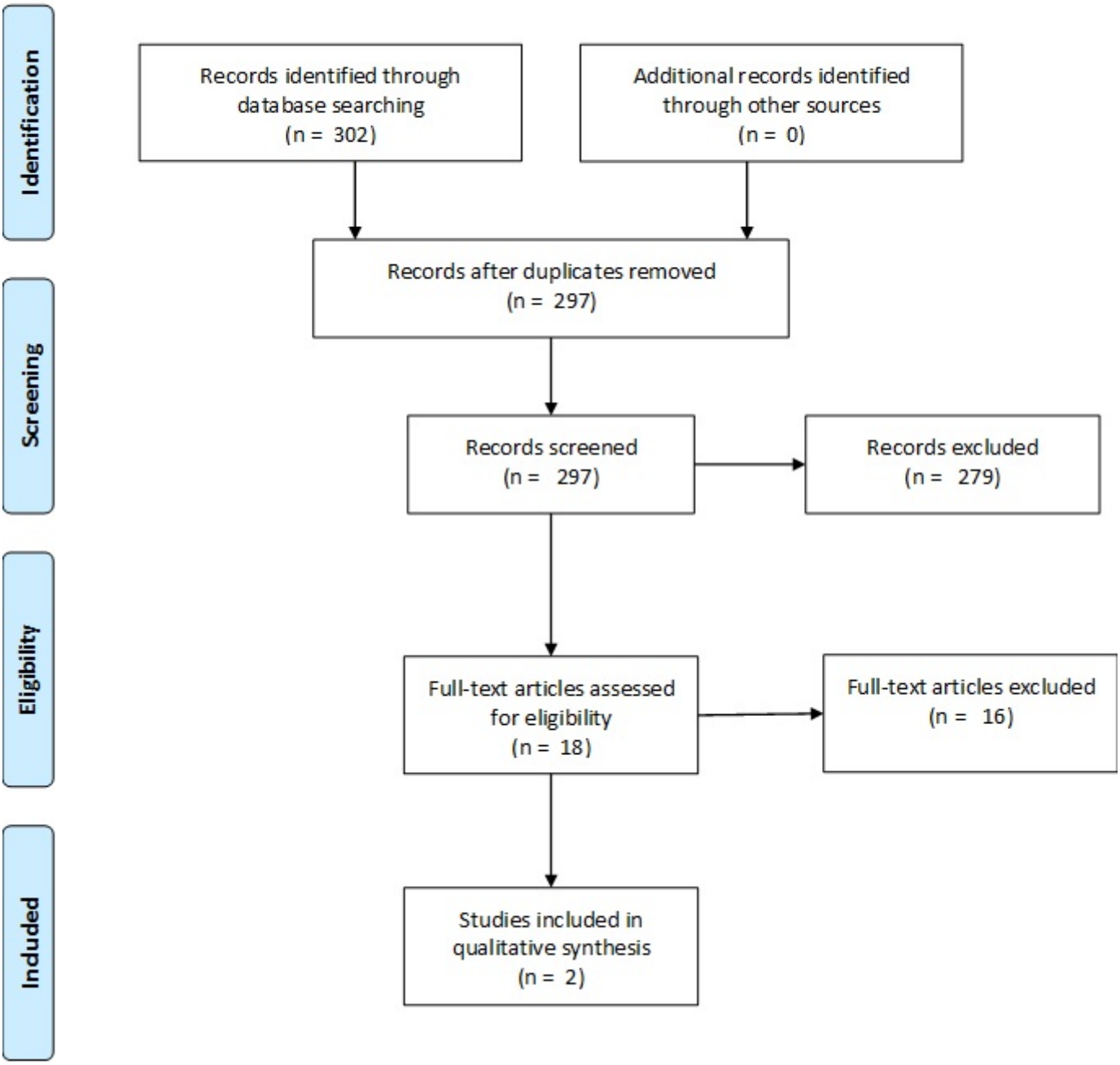

Figure 1: Flow of information through the different phases of this systematic review

Table 1: Description of the studies included in this systematic review

Author & year	Country	Study quality	Sample size	Age	Gender	Snake species	Site of bite	Ultrasound findings
Vohra et al., 2014 [9]	United States	Good	13	<12 years: 12/13 (92.3%).	Male: 10/13 (76.9%).	Crotaline/ Rattlesnake	Upper limbs: 7/13 (53.8%). Lower limbs: 6/13 (46.2%).	Subcutaneous oedema: 12/13 (92.3%). Finger pulp disruption – Finger bite: 2/13 (15.4%). Blister: 1/13 (7.7%). Tendon sheath fluid: 1.13 (7.7%). Deep musculature: No findings.
Wood et al., 2016 [10]	South Africa	Good	42	<12 years: 14/42 (33.3%).	Male: 24/42 (57.1%).	Unclear, but authors suggest adders and cobras.	Upper limbs: 27/42 (64.3%). Lower limbs: 15/42 (35.7%).	Subcutaneous oedema: Increase in expansion coefficient. Deeper musculature: Minimal involvement (1 patient had fasciotomy).

would further contribute to the collection of intracellular fluid in the extracellular matrix at the site of the cytotoxic VSB.

The high frequency at which subcutaneous oedema is observed in patients with cytotoxic VSB has several implications with regard to the clinical management of cytotoxic VSB. In some cases the actual site of the VSB might be difficult to determine on external examination, and thus the presence of oedema can be used to assist physicians in identifying the specific location of a VSB for further assessment. The presence of oedema on an ultrasound could also be used to rule out the possibility of cytotoxic VSB, especially in high-burden settings when a patient is unable to provide physicians with a description of how the injury occurred and there are no other witnesses who can provide this information. There may be occasions when the patient confirms a snake bite but is unable to identify the snake species involved, or the dead snake was not brought to the hospital. Subcutaneous oedema could potentially be used as an indicator of a bite from a cytotoxic species, which would assist in narrowing down the suspected snake species for the administration of species-specific anti-venom.

Involvement of the deep musculature on ultrasound examination was rare in the two studies of cytotoxic VSB reviewed [9, 10]. Wood et al., suggest that the involvement of the deep musculature is due to the diffusion of venom from the subcutaneous tissue into the musculature [10]. Nevertheless, involvement of the deep musculature often heralds compartment syndrome and the requirement for surgical intervention, which further contributes toward morbidity and mortality in afflicted patients [7, 10]. Therefore, ultrasound evidence of deep musculature involvement can be useful in identifying which patients are most at risk of compartment syndrome and are most likely to require subsequent surgical intervention. This strategy could also reduce some of the morbid-

ity and mortality in patients with cytotoxic VSB, by ensuring that patients who are at low risk for compartment syndrome (i.e. those patients who do not demonstrate the involvement of the deeper musculature on ultrasound) are not unnecessarily subjected to invasive surgical interventions.

In both studies reviewed, the pathology of cytotoxic VSB viewed on ultrasound was primarily restricted to the subcutaneous tissue [9, 10]. There are several explanations for this. Firstly, some of the snake species which possess cytotoxic venom have relatively short fangs, and these shorter fangs are unable to directly deliver venom into the deep musculature during a bite [13]. The angle at which the bite was made would also be a determinant of how deep the snake's fangs would penetrate into the limb. In most bites on humans, the snake bites a vertical target (i.e. the lower limb of a standing human or the upper limb of a human who is reaching downwards) and the penetration of the target with the fangs might not be as successful as when the snake bites a horizontal target during predatory activity [14]. The shorter duration of fang contact during defensive versus predatory bites must also be considered. Some researchers also suggest that defensive bites are often executed with the aim of deterring an attack from a potential threat through the infliction of pain, rather than the delivery of venom which might not be in effect for some time after encountering the threat [14]. This hypothesis is supported by statistics that report that no venom is released in up to 25% of VSBs [15]. Venom is also an important resource to the snake, and there is research that suggests that the release of venom is metered according to whether the bite is executed for defense or predatory activity [14, 16]. It is possible that in most defensive bites on humans, a lower quantity of venom is released which might not be sufficient to diffuse through the subcutaneous tissue and into the deeper musculature where it can exert significant toxic effects.

This systematic review was not without limitations. Two eligible case series were identified for inclusion in this systematic review, and only 1 of these studies was from a setting with a high burden of VSB. Eligible studies from Asia, a region reporting over 100000 VSBs a year [2], were noticeably absent in the published literature. The findings of this systematic review should be interpreted with caution, as although ultrasound features of cytotoxic VSB appeared to be consistent between African and North American settings, there is no guarantee that bites from Asian snake species would share the same ultrasound presentation. Lastly, a meta-analysis of ultrasound findings could not be performed due to the expected heterogeneity between the two studies reviewed.

5. CONCLUSIONS

The ultrasound features of cytotoxic VSB appear to be primarily confined to the subcutaneous tissue, with oedema being the most frequently observed ultrasound feature. Involvement of the deeper musculature is rare but has potentially devastating consequences. Ultrasound features of cytotoxic VSB were consistent between studies reviewed in this research, irrespective of the difference in location of the studies, snake species involved, and patient-related characteristics. This systematic review also highlights the versatility and potential importance of ultrasound in the management of cytotoxic VSB. Several limitations of this systematic review are acknowledged, and further research is recommended to address these limitations.

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7. List of abbreviations:

VSB - venomous snake bites; PECO - "Population-Exposure-Control-Outcome"; SPSS -

Statistical Package for the Social Sciences.

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Author biography

Karundat Bhola is a former Master of Medicine (Radiology) student at the University KwaZulu-Natal, South Africa. He is now a practicing radiologist at a public hospital in Durban, South Africa.

Samson Mashele is a professor and acting Deputy Vice-Chancellor: Research, Innovation and Engagement at the Central University of Technology, Bloemfontein, South Africa. He has a

strong background in basic science research, with a particular interest in enzymology.

Yoshan Moodley is an epidemiologist and public health researcher. He is currently a research associate at the Faculty of Health and Environmental Sciences, Central University of Technology, Bloemfontein, South Africa.