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Systematic Review Protocol

Role of Immune Mediators in Pathophysiology of Snakebite Envenoming: A Scoping Review Protocol

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Abstract

Introduction: Snakebite is a neglected tropical disease and a common medical emergency in the tropics. Envenoming in humans activates both innate and adaptive immune responses, which play a pivotal role in host defence against venom toxins. On the other hand, a dysregulated immune response triggers devastating pathophysiological effects related to venom-induced, immune-mediated host damage, causing tissue injury or organ damage, oxidative stress, angiogenesis, and fibrosis in diverse target tissues. While there is evidence of an association between immune dysregulation and the clinical features of severe envenoming, the role of immune mediators in the pathophysiology of snakebite envenoming, contributing to the development of severe clinical features, remains to be elucidated. Our scoping review aims to summarise the role of immune mediators in pathophysiological events following snakebite envenoming and antivenom treatment**.**

Method and analysis: The scoping review will follow Arksey and O'Malley's scoping review framework and the guidance recommended by the Joanna Briggs Institute (JBI). MEDLINE/PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases will be searched using predefined keywords to gather the peer-reviewed, English-language articles reporting original data from 2000 to the present. All reviews will involve two or more reviewers. Data will be presented in a descriptive manner, and tables and figures will be used when necessary.

Ethics and dissemination: A scoping review does not require ethics approval since it will rely on secondary data. Once the review is completed, we anticipate submitting it for publication in a peer-reviewed journal.

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Introduction

Snake envenoming

Snakebite is a neglected tropical disease that causes a significant public health burden in South and Southeast Asia, Sub-Saharan Africa, and Latin America [1,2]. The most affected are poor farming communities in rural areas of these regions [2–5]. Snake venoms are complex mixtures of different toxins belonging to various protein

families. Snake venom toxins cause various pharmacological properties capable of causing both local and systemic effects in envenomed humans [6,7]. The clinical manifestations of snake envenoming could vary depending on the inter and intra-specific variations of the toxin composition of the snake venoms and the host defence responses [8]. Once the venom is delivered into a human during a snakebite, some toxins may exert toxic effects in the tissues around the bite site locally, while other toxins are distributed through lymph and blood and act at distant target sites such as the neuromuscular junction, skeletal muscles and clotting cascade, causing neuromuscular paralysis, coagulopathy, thrombotic microangiopathy, acute kidney injury, myotoxicity, and cardiovascular collapse [8–11]. Most of the medically important snakes belong to the families Elapidae and Viperidae. In general, both true vipers (Subfamily Viperinae) and pit vipers (Subfamily Crotalinae) of the family Viperidae cause local tissue injury, coagulopathy, myotoxicity, thrombotic microangiopathy, acute kidney injury [12–14]. Cobras, kraits, mambas, coral snakes, some sea snakes of the family Elapidae, and some viperid snakes induce neurotoxic effects, such as neuromuscular paralysis [15–19].

Pathophysiology of snake envenoming

Venom-induced consumption coagulopathy (VICC) is the most common systemic effect of snake envenoming [20]. The activation of the clotting cascade by snake venom procoagulant toxins triggers VICC, which is characterised by the rapid consumption of blood clotting factors, mainly fibrinogen and also factors V, VII, and X [20,21]. Haemorrhagins in snake venom damage the vascular endothelium and induce spontaneous systemic bleeding [20,21]. The combined effect of VICC and vascular wall damage may result in severe haemorrhage, sometimes leading to fatal outcomes [21,22].

Acute kidney injury (AKI) is another clinically significant systemic complication in envenoming secondary to snakebite by snakes belonging mostly to the family Viperidae [23,24]. A subset of snakebite patients with VICC develops an uncommon severe complication called thrombotic microangiopathy (TMA). TMA is characterised clinicopathologically by microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and microvascular thrombotic occlusion leading to organ ischemia, often resulting in AKI [21,25–31]. Tubular necrosis, cortical necrosis, interstitial nephritis and glomerulonephritis are the main pathological alterations associated with AKI, with the background of TMA. The AKI due to the snakebite envenoming is usually reversible unless acute cortical necrosis occurs [32–38].

Acute neuromuscular paralysis is a lower-motor neuron type, flaccid paralysis due to the blockade of neurotransmission in skeletal muscles by venom neurotoxins [16]. The severity of the neuromuscular paralysis ranges from mild paralysis, limited to facial muscle weaknesses, to lethal respiratory and limb paralysis, depending on the neurotoxin type or degree of envenoming [39–46]. The two dominant toxins, phospholipase A2 toxins (β-neurotoxins) act presynaptically [47,48] and three-finger α-neurotoxins (α-3FNTx) act postsynaptically [49,50].

Although Previous studies have well described the underlying pathophysiology associated with neuromuscular paralysis and VICC [20,21,47–50], the exact pathophysiology associated with TMA, AKI, severe tissue complications, and multi-organ failure in snakebite envenoming is poorly understood [11,20,21,30,31].

Immune response following snakebite

In an envenomed human, both innate and adaptive immune responses play a pivotal role in the host's defence against the toxins present in the injected venom [51–53]. The acute immune response is mediated by the barriers and cellular defences of the innate immune system, which provides the initial protective mechanism against venom toxins [54–56]. Further, it stimulates adaptive immune responses through the presentation of antigens by antigen-presenting cells like dendritic cells, macrophages, and monocytes. Innate immunity to deleterious microbes or materials relies upon germline-encoded receptors called pattern recognition receptors (PRRs), which permit a limited range of immune cells to recognise and respond rapidly to (i) pathogens that share microbial non-self'–conserved molecular structures, known as 'pathogen-associated molecular patterns' (PAMPs) and (ii) common metabolic consequences of infection and inflammation denoted by 'damage-associated molecular patterns' (DAMPs) [54–56]. Recognition of DAMPs, which are formed early in the envenoming, and 'venom-associated molecular patterns' (VAMPs) by PRRs, especially toll-like receptors (TLRs), plays a key role in the activation of immune responses, which are important in host protection, venom neutralisation, and the resolution of symptoms [57,58]. Production of cytokines, chemokines, antimicrobial peptides, phagocytosis, destruction of foreign substances, generation of reactive oxygen and nitrogen intermediates, and release of protective enzymes are

some proinflammatory responses resulting from the recognition of DAMPs and VAMPs by PRRs [56].

Rapid recruitment of immune cells to the sites of injury, enabling local inflammation to eliminate the deleterious microbes or materials, is achieved mainly through the secretion of the cytokines and chemokines [55,59]. Stimulation of adaptive immune responses through the antigens presented by antigen-presenting cells [60] results in T cell activation and differentiation to induce various effector immune responses and differentiation of B cells into plasma cells to produce antibodies [55,61]. Thus, following envenoming, regulated host immune response results in detoxification or neutralisation of the venom and resolution of clinical manifestations through tissue repair and homeostasis [58]. On the other hand, a dysregulated immune response can trigger an uncontrolled inflammatory response, causing tissue injury, oxidative stress, angiogenesis, and fibrosis in diverse target tissues [62].

Role of immune response in the pathophysiology of snake envenoming

Following a snakebite, the clinical features of local envenoming range from swelling to blistering and tissue necrosis at the bite site [7]. Snake venom myotoxic and cytolytic factors contribute to local tissue necrosis. Local tissue disruption is primarily induced by zinc-dependent metalloproteinases and myotoxic phospholipases A2, which disrupt the plasma membrane integrity of muscle fibers, causing tissue necrosis [63–65]. Further, the toxic compounds in venom and damaged tissues activates the immune system of the victim. Though the regulated immune response neutralizes the venom toxins limiting the tissue damage caused by envenomation, dysregulated immune response can increase the symptom severity of the clinical manifestations described above [66–69].

Acute adverse reactions, particularly the anaphylaxis, to antivenoms, are a serious problem in managing snakebite patients in developing settings [70–75]. The exact mechanisms that trigger the adverse reactions to antivenom is also uncertain [70,73,76,77]. Immune dysregulation following envenoming is a result of the complex interplay between multiple factors associated with the host, antivenom treatment and venom toxins, and can be associated with the pathophysiology of severe tissue complications [78,79], VICC [80], AKI [81,82], organ damage [83] and the anaphylaxis [77]. Thus, in-depth understanding of the role of host immune responses in the pathophysiology of envenoming and adverse effects following antivenom therapy is pivotal in the identification of markers for early detection of severe complications of envenoming and antivenom treatment as well as the possible therapeutic targets [84]. This scoping review comprehensively describes and summarises the available literature pertaining to the immunological response in snakebite envenoming and antivenom treatment. This will be important in identifying the knowledge gaps in the literature regarding the role of immune mediators in the pathophysiology of snakebite envenoming and its clinical manifestations.

Methods

Scoping review design

Through conducting this scoping review, we will focus on addressing multiple questions pertaining to the role of immune mediators in pathophysiological events following snakebite envenoming and antivenom therapy. Our scoping review will be performed adhering to the framework proposed by the Jonna Briggs Institute (JBI) Scoping Review Methodology Group on conducting scoping reviews [85–87], based on the previous guidance developed by Arksey and O'Malley [88], and Levac et al. [89]. Additionally, this will be carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) checklist [90]. Arksey and O'Malley's framework consists of five stages, namely; 1) identification of the research question, 2) identification of relevant studies, 3) selection of eligible studies, 4) charting the data, and 5) collating and summarising the results.

Stage 1: Identification of the research question

The central research question for our scoping review is: 'What is the role of immune mediators in pathophysiological events following snakebite envenoming and antivenom treatment?' Following are the specific sub-questions.

1. What are the types of study designs used to describe the immunological responses to snakebite envenoming and antivenom treatment?

2. What are the potential immune mediators associated with the development of clinical features of snakebite envenoming?

3. What is the association between immune mediators and the development of clinical features of snakebite envenoming?

4. How does antivenom influence the dynamic expression of immune mediators in snakebite envenoming?

5. What are the potential immune mediators which can be used as markers for the early detection of severe envenoming events in snakebite?

Stage 2: Identification of relevant studies, search strategy

The search strategy for our scoping review intends to explore published and peer-reviewed articles. The search strategy will be designed following the three-step search strategy recommended by JBI Scoping Review Methodology Group [85]. The unique medical subject headings (MeSH terms) will be used for evidence search, while unique terms will be combined using Boolean operators 'OR' or 'AND'. As an initial step, a limited preliminary search will be conducted in MEDLINE/PubMed database using simple terms such as, ('immune marker*' OR 'immune mediator*' OR 'inflammatory mediator*' OR 'inflammatory marker*') AND ('Snakebite envenoming' OR snakebite) to identify the keywords given in the title and abstract of the retrieved papers and the index terms used to describe those retrieved studies. The final list of keywords and index terms selected from the above process will be used to search across all selected databases, namely MEDLINE/PubMed, Embase, Cochrane Library, Scopus, and Web of Science. Lastly, gray literature will be sought through manual screening of the lists of references in all the included studies for additional sources.

Stage 3: Selection of eligible studies

This review will follow the Population, Concept, and Context (PCC) framework described by Tricco et al. and Peters et al. [87,90]. Therefore, the studies meeting the following criteria (inclusion and exclusion criteria) will be included.

Participants:

The inclusion criteria for participants will involve snakebite patients and healthy individuals of any age or gender. No inclusion or exclusion criteria will be considered for the severity of the envenoming. Participants required records of immune mediator(s) from blood or serum or plasma. In-vitro studies involving human cell lines that describe the expression of soluble immune mediators in snakebite envenoming, with or without treating the antivenom will be included, while animal studies (both in-vivo and in-vitro) will be excluded.

Concept:

The concept being explored will describe the expression of soluble immune mediators across various clinical manifestations following snakebite envenoming with or without the antivenom treatment.

Context:

Despite the geographical locations, this scoping review will include studies pertaining to both institutional and community care settings, where patients receive healthcare services, as well as in laboratory settings where in vitro research on snakebite envenoming and antivenom treatment is carried out. Database search will be limited to sources published from 1st January 2000 to the present. Studies published in languages other than English and articles lacking full text will be excluded.

Type of sources:

All peer-reviewed primary articles of original studies that describe the role of immune mediators in pathophysiological events following snakebite envenoming and antivenom treatment will be considered. Articles not reporting original data, such as reviews, book chapters, congress proceedings, or abstracts (no full text available), will be excluded.

Source selection:

Following the database search, all the identified citation records from the evidence search will be collated and exported to reference manager software Mendeley reference manager (Elsevier, UK), and duplicates will be removed. The initial stage of the selection process will involve screening the titles and abstracts of the remaining articles by two independent reviewers following the inclusion and exclusion criteria of this scoping review. The full text of the screened studies will be retrieved and further assessed for eligibility, and only the studies which fulfil the inclusion criteria will be retrieved in the final analysis. Any discrepancies will be resolved by either a discussion between the two authors or referral to a third investigator if necessary. Authors of studies will also be consulted if any additional information is required during the study selection process. The final search results and the complete study inclusion process will be reported in the final scoping review and presented using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram [90,91]. The findings from all the studies will be described narratively in the scoping review.

Stage 4: Charting the data

Data extraction aims to tabulate a descriptive summary of the included literature. It will be carried out independently by two reviewers, using a modified data extraction table (Table 1), adapted from JBI template

source of evidence details, characteristics and results extraction instrument [85]. Data to be extracted will include general details of the study, study characteristics, reported outcomes of the study, conclusion of the study and limitations of the study as stated by the author (Table 1). Any discrepancies in the extracted data will be resolved by either discussion between the two authors or referral to a third investigator, if necessary, before finalising a single form comprising extracted data. The draft data extraction table will be revised and modified, if necessary, during the data extraction process.

Table 1: Overview of the data extraction table

Category	Description
General details of the study	
Author	
Year	
Study title	
Journal	
Country	
Study characteristics	
Study design	case-control study, cross-sectional study, clinical trial, case report
Purpose of the study	Study objectives and question posed
Population/Subject	Characteristics of population (human), Characteristics of cell line
Participants	Age, Gender, Number
Patient classification	Classification of patient groups based on illness severity
Sample type	Sample or fluid subjected to measure the immunological mediator level
Sampling duration	Time lapse considered for sampling
Snake type/ Venom toxin type	Particular snake species/ venom toxin type used in *in-vivo* or *in-vitro* studies
Immune mediator(s)	Immune mediator (s) evaluated
Method of analysis	Method used for evaluating the immune mediator(s) level
Reported outcomes	
Changes in immune mediator(s) concentration	Changes among different groups/ changes occur at different time laps, clinical outcomes or interventions
Key finding	Summary of the key findings
Conclusion	Conclusion of the study as stated by author
Limitations	Limitations of the study as stated by author

Stage 5: Collating and summarizing the results

The search results will be presented in accordance with JBI methodological guidance for the conduct of the scoping review, using PRISMA flowchart and an appended PRISMA-ScR checklist [90,91]. This scoping review does not aim to perform formal data analysis, such as meta-analysis [87,90]. In line with the design types of the selected studies, we will present the quantitative results using descriptive statistics and qualitative results thematically. This will involve in mapping of extracted data in one or more tables and/or figures. Tabulated results will be supplemented with a narrative summary, providing an explanation of how these findings correspond to the principal scope of the study.

Ethics and dissemination

A scoping review does not require ethics approval since the review will rely on secondary data and primary data is not used. The results of our scoping review will provide a comprehensive overview of the current literature pertaining to the immunological response in snakebite envenoming and antivenom treatment. In addition, this scoping review will contribute to identifying the knowledge gaps that exist in the literature regarding the role of immune mediators in pathophysiological events following snakebite envenoming and antivenom treatment. Once the review is completed, we anticipate submitting it for publication in an international, peer-reviewed open-access journal.

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