Chapter 21

Snakebites, Envenomation, and Treatment of Snakebite Pain with Ketamine

Sabine Himmelseher, Georges Mion, and Christopher V. Maani

Abstract

The global incidence of snakebites is estimated to exceed five million annually. Envenomations are responsible for more than 150,000 deaths and over 400,000 permanent disabilities. Although snakebites are a medical emergency, substantial obstacles frequently impede the provision of effective therapy in regions with limited medical facilities. The treatment of acute snakebite pain is often inadequate, which can contribute to the development of post-traumatic stress disorders (PTSD), depression, psychosocial impairments, and chronic, potentially debilitating pain. The antidepressant, analgesic, and resilience- and PTSD-improving effects of ketamine make it a promising addition to snakebite management. Because ketamine shows a wide safety margin and low costs and is available in most low-resource settings, it is a suitable option for therapy in any location. The aim of this work is to improve our understanding of the challenges and therapeutic principles associated with snakebite envenomation. The positive effects of ketamine on acute snakebite pain, as observed in a prospective observational study in Guinea, will be discussed.

Key words Snakebite, Envenomation, Neglected global health crisis, Ketamine, Pain, Post-traumatic stress disorder, Low-resource setting, Austere wilderness medicine

1 Introduction

A few years ago, Kofi Annan very aptly said that "snakebites are (one of) the biggest public health crisis you have likely never heard of"[1]. Due to a lack of reporting, the true scale of the problem is still unknown. However, estimates suggest that there are more than five million bites each year. Envenomations have been linked to over 150,000 deaths and more than 400,000 instances of permanent disability including paralysis and amputations [1–5]. While the likelihood of exposure to snakes is rather low in North America and Europe, the ongoing climate change may alter this situation [6]. Additionally, the trend of keeping snakes as pets and private collections has increased.

Snakebites are a medical emergency. In impoverished, rural communities and marginalized areas of the world, as well as tropical

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or subtropical regions with limited medical facilities, the obstacles to providing effective treatment are immense. High-risk groups for snakebites include those who engage in outdoor activities and occupations (particularly in agriculture and nature), children, and individuals residing in precarious conditions where environmental factors intersect with snake habitats. Snakebites perpetuate the cycle of poverty, and in their aftermath, victims and families may face substantial financial challenges while bearing a significant medical burden.

After the World Health Organization (WHO) categorized snakebites as a high priority, neglected, potentially life-threatening tropical disease in 2017, international funding increased [3]. In 2021, the Wellcome Trust research fund announced the launch of a £80 million GBP (~$100.560.400 USD) program with the objective of transforming the way snakebite treatments are researched and delivered [7]. In light of the ongoing challenges related to production and international antivenom management [8], the WHO has taken the initiative to enhance quality control measures for antivenom products and target profiles of animal plasma-derived antivenoms [5]. Additionally, the organization has made information campaigns about snakebite prevention and guidance for first aid freely available on official WHO Internet sites. It is well documented that antivenoms are the only effective etiological treatment for snakebites, but accessibility and cost remain significant barriers [9, 10]. There is also a lack of prospective clinical studies and pragmatic trials on snakebite treatment and the course of the disease, and there is an urgent need to reduce morbidity and long-term sequelae for venomous snakebite patients.

Despite the vast, global biodiversity of snake species, the medical principles of care after snakebites are similar across geographical regions [3, 4, 9–13]. For example, in the acute phase after a bite (or spitting), insufficient medical management is frequently observed due to inadequate access to equipped medical facilities, antivenoms, and/or pain medication [3, 4, 11, 12]. Insufficient pain treatment can lead to the development of chronic pain [14], and inadequate analgesia following traumatic injury has been correlated with the onset of post-traumatic stress symptoms in children and adults [15, 16]. After a snakebite, victims frequently experience not only severe pain but also post-traumatic stress disorders (PTSD), depression, and psychosocial impairments [17, 18].

The pharmacological profile of ketamine, coupled with its low cost and widespread availability even in rural and remote regions, makes it suitable for use in low-resource settings. It can be considered a safe, affordable and often accessible therapeutic option [19, 20]. From a medical perspective, its antidepressant, analgesic, and resilience-improving effects, along with its potential for PTSD treatment, make ketamine a promising agent for inclusion in snakebite therapy [21, 22]. This work will briefly delineate the principles

of medical care in snakebites and will present two lucky patients as illustrative examples of snakebite disease courses to enhance our understanding of the challenges with snakebite envenomations. It will also describe the findings of a prospective observational study on ketamine in snakebite-poisoned patients with acute pain [23].

2 Principles of Care for Snakebite Envenomation

The majority of medically important snakes are classified within two taxonomic families: Elapidae (elapids, including cobras and mambas) and Viperidae (such as vipers, adders, rattlesnakes) [3, 4, 11, 12, 24] (Fig. 1).

Snakes utilize their venom for predatory and defensive purposes. When biting, the venom is injected via grooved or hollow

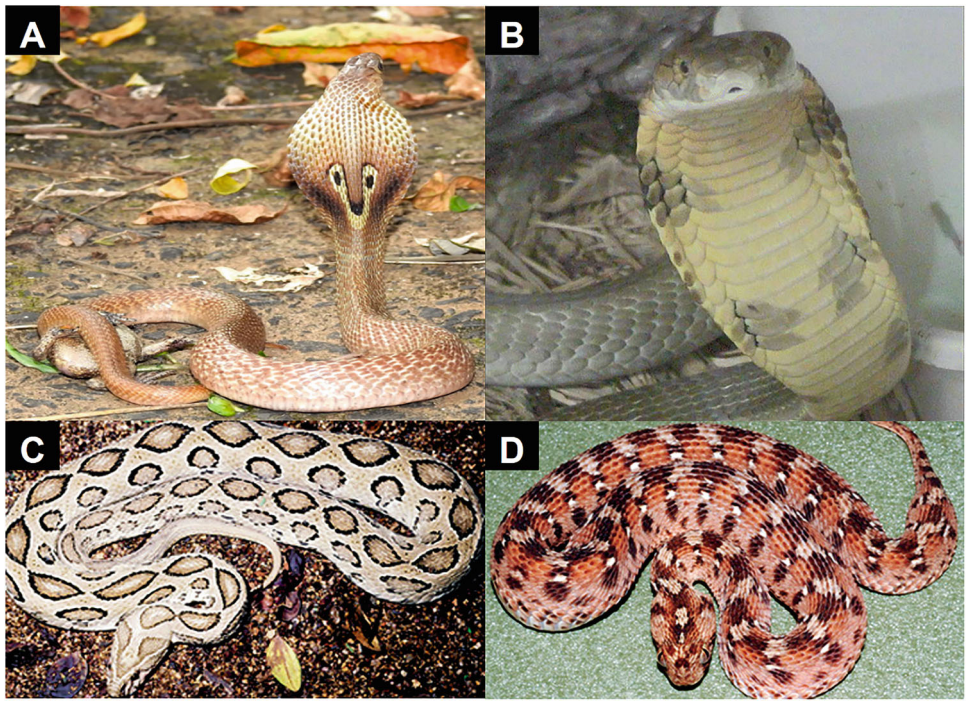

Fig. 1 Snake species responsible for high mortality resulting from envenomation: a spectacled cobra (**a**) and a king's cobra (**b**) (family Elapidae) and a common lancehead viper (**c**) and a saw-scaled viper (**d**) (family Viperidae) (photo **a**) from Martin G [24], image courtesy of Kasambe R, Education Conversation Centre, Bombay Natural History Society, Mumbai, India, under a CC BY-SPA 4.0 license; (**b**) from Veto et al. [28] with permission from John Wiley and Sons conveyed via Copyright Clearance Center, Inc.), and (**c**) and (**d**) from Gutiérezz et al. (2017) [4] with permission from Springer Nature via Copyright Clearance Center, Inc.)

teeth, called fangs, which are connected to venomous glands in the upper jaw. The length of the fangs determines whether the venom is introduced subcutaneously or intramuscularly. Snake venoms contain a variety of complex biochemical components, characterized by diversity and interspecies variations. These variations are influenced by a number of factors, the first of which is the snake species. Antivenoms are antibodies that are specific to one (monovalent) or several (polyvalent) species. This is the reason why antivenoms of one species or against snakes at one location may be ineffective in other species or regions [3, 4, 11, 12].

The multifocal toxicity of a venom determines the symptoms of poisoning, which can be classified as either viperine or cobraic syndromes. The volume of venom injected is under the control of the snake and has been associated with a variable degree of clinical effects. Viper venoms mostly induce local tissue damage with necrosis and systemic manifestations such as bleeding, coagulopathies, and hypovolemic shock. Elapide snake venoms predominantly manifest neurotoxic effects, such as neuromuscular paralysis which may result in respiratory failure. After a bite, the adverse effects include edema, cardiotoxicity, rhabdomyolysis, autonomic hyperactivity, local and systemic bleeding, compartment syndrome, superinfection, thrombotic microangiopathy and macrothrombosis, acute kidney injury, shock, and death (for more information, *please see* reviews [3–5, 10–12]). The only effective treatment against snake venoms are antivenoms. Because the prognosis for severely envenomed patients rapidly deteriorates within the first hours, snakebites are always classified as emergencies: Cardiovascular disturbances up to collapse can even develop within seconds and respiratory paralysis within minutes.

First aid focuses on immobilization of a bitten limb and patient transport to the nearest medical facility [3, 4, 11, 12]. Please remove any rings or other tight objects from the affected limb. The use of pressure immobilization is a topic of debate, but research suggests that pressure pads may help to reduce venom spread in viper bites. It is not advisable to use a tourniquet. Any delay in reaching a medical center must be avoided. Reassure patients, who may often be fearful and anxious. Take a medical history. If the situation deteriorates into a life-threatening emergency, resuscitate and stabilize vital signs. At the medical facility, try to identify the causative species. Perform a thorough clinical and laboratory examination (in low-resource settings, use the 20-min whole blood clotting test to detect coagulopathy) [11]. In case of signs of infection, administer appropriate antibiotics [11, 12, 25]. Check for local effects of envenomation, such as severe pain, swelling, blistering, bruising, and lymphangitis, compartment syndrome, and/or venom ophthalmia (Fig. 2).

Check again for systemic effects, such as impaired clotting, shock, muscle dysfunction, paralysis, and kidney injury. In the

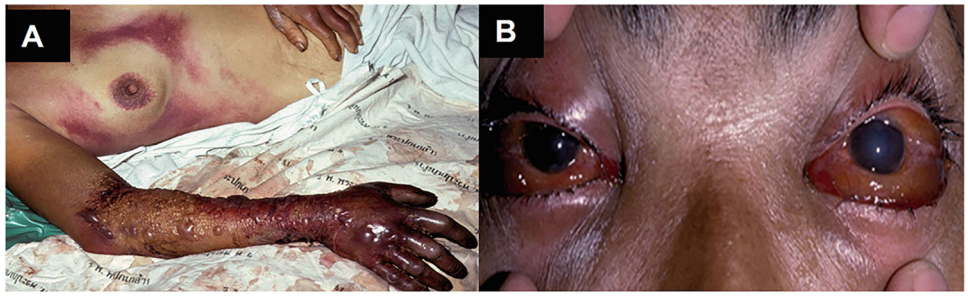

Fig. 2 (**a**) Blistering, swelling, and a gangrenous right hand, which required amputation after a Malayan pit viper bite in Thailand. Extensive ecchymoses (skin discoloration owing to bleeding under the skin) can be seen. (**b**) Bilateral conjunctival edema (chemosis) indicating a generalized increase in capillary permeability after an Eastern Russell's viper bite in Myanmar (from Gutiérezz et al. [4] with permission from Springer Nature via Copyright Clearance Center Inc., images courtesy of DA Williams, WHO Geneva, Switzerland)

event that antivenoms are not available, a prompt decision must be made regarding transfer to a facility with antivenoms.

At present, there is no test that can identify patients with a systemic spread of the venom. When clinically indicated (such as in combined diagnostic, clinical, and systemic envenoming symptoms), antivenoms must be administered as soon as possible (3,4,11,12,26). It is imperative to monitor patients after antivenom treatment for any adverse effects, such as allergic or pyrogenic reactions. Additional medical treatment remains symptom-oriented and supportive. In a "wait-and-see"approach, serial clinical examinations to check for envenomation signs should be repeated for at least 24 h. However, even after several days, delayed manifestations of envenoming have been reported.

Table 1 shows the favorable course of a pregnant patient who correctly identified the snake that had bitten her as a king cobra [27]. Several days after caesarean section delivery, the patient developed a compartment syndrome, necessitating multiple surgical procedures. Table 2 outlines the case of a zoo worker who was also bitten by a king cobra some years ago [28]. The situation was complicated by the development of an anaphylactic shock following the administration of antivenom. Both patients exhibited typical complications associated with snakebites. Antivenoms often are not immediately available, and consultation with poison control and toxicology centers for medical expertise should be sought as early as possible. Additionally, the second course illustrates one of the rare instances where antigenic agents must be reinitiated following anaphylaxis once stability has been restored, and preventive measures have been implemented.

Table 1
Patient report: 26-year-old term pregnant woman with envenomation from spectacled cobra bite complicated by compartment syndrome [27]

Course	Findings, management
Day 1	**Snake bite at dorsal right foot, snake identified as spectacled cobra**
45 min later	**Development of severe pain at bite site**
60 min	**Transport to nearby health facility**
	Administration of 10 vials of polyvalent antivenom
	Referral to All India Institute of Medical Sciences Center at Bhubaneswar
4 h	**Arrival in emergency department, Bhubaneswar**
	Pain in foot: 10/10 NRS—initial treatment with IV paracetamol 1 g
	Pregnancy at 34 weeks 3 days gestational age
	Vitals unremarkable except HR 110 bpm
	Negative "broken neck sign "(snakebite-induced paralysis of neck flexor muscles)
	2 fang marks on dorsal right foot, moderate swelling and tenderness extending to ankle, dorsalis pedis artery pulse present
	Blood tests: Elevated leucocytes ~14,000 x 10^3cumm, neutrophils ~92%, whole blood clotting and coagulation profile within physiological range
	Wound cleaning and dressing (existing tetanus immunization)
	Antibiotic therapy; second dose of 10 vials polyvalent antivenom
	Persistent pain: ultrasound-guided blocks of the superficial peroneal nerve and sural nerve with 3.5 mL 0.375% ropivacaine; result: pain relief, NRS 2/10
Transferral to	Exams: singleton live fetus in longitudinal lie and cephalic presentation
obstetrics	Relaxed uterus, fetal HR 191 bpm; no vaginal bleeding
	Sustained fetal tachycardia: emergency cesarean section
	Uneventful delivery of preterm female baby, 2140 g birth weight
	Managed at neonatal ICU for 48 h because of mild respiratory distress and tachypnea
	Monitoring of mother for changes in foot and limb swelling
Day 3	
	Development of blisters and local tissue necrosis over bite site
	Broad-spectrum antibiotics and anti-inflammatory drugs
Subsequent days	
	Extended foot swelling to below knee and rupture of blisters
	Recording of distal pulses at regular intervals;
	Daily monitoring for compartment syndrome

(continued)

Table 1
(continued)

Course	Findings, management
Day 7	
	Fasciotomy because of fear of compartment syndrome in view of weak peripheral dorsalis pedis artery pulsations
Subsequent days	
	Daily wound dressing changes
Day 14	
Within 1 week	Local pain subsides
Day 21	
Within 2 weeks	**Complete resolution of limb swelling**
21 days after bite	**Uneventful reconstruction of foot defect with free flap from front of thigh**
6 weeks later	
Follow-up	Asymptomatic post-snakebite patient; **mother and baby are doing well**

bpm beats per minute, *cumm* cubic millimeter, *g* grams, h hours, *HR* heart rate, *ICU* intensive care unit, *IV* intravenous, *mL* milliliter, *NRS* numeric rating scale

3 Ketamine in Snakebite Pain Envenomations

In a dedicated snakebite clinic in Guinea, 12 patients, between 14 and 64 years old, were treated by physicians with extensive experience in snakebite therapy in Africa [23]. The protocol implemented for the administration of ketamine was based on standard dose regimens established in high-resource emergency departments, but the doses necessary were lower than those usually needed for out-of-hospital analgesia after severe trauma [29, 30]: on average, 5.75 hours after the snakebite, a dose of 0.05–0.1 mg/kg intravenous ketamine was administered over 2 min in order to treat significant pain, with or without the presence of swelling or blistering of the affected limb. Within 1 min, all patients reported a reduction in pain and felt more comfortable while showing a decrease in hypertension and tachycardia. Nine patients required only a single dose of ketamine. No adverse interactions were observed between ketamine and the applied polyvalent antivenom, which was recently introduced and shown to be effective and well tolerated in Cameroon (Inoserp™ Pan-Africa, Inosan Biopharma, S.A., Spain) [31]. After ketamine and antivenom treatment, paracetamol was the sole analgesic required for the management of

Table 2
Patient report: 22-year-old male zoo shop worker with envenomation from king cobra bite complicated by anaphylactic shock (with a history of asthma treated by inhalers) [28]

Course	Findings, management
Day 1	**Snake bite at lateral aspect of left index finger**
20 min later	**Arrival in accident and emergency room** in Bristol Hospital, United Kingdom
	HR 124 bpm, "dizziness"
	Swollen left index finger with double puncture bite marks, superficial glass lacerations
Within 10 min	**Bilateral eyelid ptosis**
	IV access, 1000 mL saline 0.9%, blood tests
	Contact with Toxbase and Liverpool School of Tropical Medicine:
	Urgent order of specific antivenom from Guy's/St. Thomas's Hospital Poisons Unit, London
	Pressure bandage of entire limb to shoulder for prevention of proximal lymphatic drainage of large molecular weight toxins
20 min later	**Complaints of shortness of breath and inability to swallow saliva**
	Endotracheal intubation per rapid sequence induction
	Sedation and analgesia with propofol and morphine
90 min later	**Transfer to intensive care unit;** arterial BP monitoring, large bore IV access, urinary and nasogastric catheters
	Unremarkable electrocardiography, chest X-ray, and blood tests except for neutrophilia
Intensive care unit	Hypertension (systolic BP 200–220 mm Hg), erratic HR 45–85 bpm
6 h after bite	**20 vials monospecific freeze-dried equine antivenom delivery for *Ophiophagus hannah* envenomation (manufact. by Queen Saovabha Memorial Institute Bangkok, Thailand);** reconstituted in 200 mL water for injection, made up to 500 mL with saline 0.9%, and infused at a rate of 2 mL/h
15 min later	No adverse reactions**; increase in infusion rate to 999 mL/h to administer full dose within 30 min as recommended by manufacturer**
5 min after increase	**Further systolic BP rise up to ~ 250 mm Hg; treated with antihypertensive**
	Development of 2 maculopapular spots on the chest; 200 mg IV hydrocortisone, 10 mg IV chlorphenamine, and 50 mg IV ranitidine
Within 10 min	**Rash progresses to urticaria, finally involving entire chest, flanks, and upper thighs then severe bronchospasm (peak airway pressure 40–50 cm H_2O, maximum tidal volumes 300–350 mL), S_aO_2 drop to 80% with $F_iO_2 = 1$**
Within 1 min	**Systolic BP decrease to 80 mm Hg**
	STOP of antivenom infusion; tentative/probable diagnosis: ANAPHYLAXIS

(continued)

Table 2
(continued)

Course	Findings, management
	10 µg IV adrenaline boluses up to 100 µg and start of 0.1 µg/kg/min adrenaline infusion
	Rapid infusion of 500 mL hydroxyethyl starch and administration of bronchodilators
After 25 min	**Continued anaphylaxis therapy; resolution of bronchospasm and hypotension, rash invisible**
	Further advice from Liverpool; re-start of antivenom infusion at lower rate of 100 mL/h and additional 200 mg hydrocortisone in 24 h
	Result: Rash reappeared, but no more serious adverse reactions occurred
9.5 h post-bite	**Antivenom infusion finished; cessation of adrenaline**; removal of pressure dressings
17 h post-bite	Clinical examinations after reducing sedation**: regain of motor function, head lift from pillow, no ptosis, strong limb power, tidal volumes > 10 mL/kg, good cough reflex**
	Stop of sedation and tracheal extubation
Day 2	
	Discharge from intensive care unit
	Transferral to plastic surgery for care of isolated ischemia of bitten finger

BP blood pressure, *bpm* beats per minute, *cumm* cubic millimeter, F_iO_2 fraction of inspired oxygen, *kg* kilograms, *h* hour (s), *HR* heart rate, *IV* intravenous, *mL* milliliter, S_aO_2 oxygen saturation

residual pain in all patients. Apart from a slightly sedative effect at a dose of 0.1 mg/kg, no other ketamine-related adverse effects were observed. The authors conclude that ketamine can be employed as an efficacious analgesic for the management of pain associated with snakebites. They also propose that it can be administered as a bridge for pain treatment until antivenom therapy is available [23]. In addition to providing adequate analgesia, ketamine may reduce the development of post-bite PTSD, depression, and other neuropsychiatric problems. In non-snakebite settings, ketamine has been shown to improve such disorders in diverse populations when they have become chronic as well [22, 32, 33].

In impoverished areas, snakebite victims may not seek help in medical centers out of fear of high treatment costs. However, in certain regions, even traditional healers are nowadays open for collaboration with health services to administer antivenom to snakebite victims [34]. When it comes to ketamine, the cost is relatively low in many low- to low-middle-income countries. At the clinic in Guinea where the pain study patients were treated, the average costs per effective ketamine dose were $0.03–0.06 USD

[23]. The lead study author from the United States, who utilizes ketamine in everyday emergency medicine, therefore stated that he believes that "withholding a safe and effective (analgesic) therapy despite availability at the local pharmacy at an affordable price, might be considered as dereliction of professional duty as a physician" [23].

4 Take-Home Message

Antivenoms represent the primary treatment against venomous snakebites. Snakebite envenomation constitutes a medical emergency that requires immediate treatment. The initial symptoms of envenomation may manifest as severe, localized pain, which can result in significant, long-term complications. In addition to the physical disabilities that often result from snakebites, victims frequently develop serious psychological problems, with a high incidence of PTSD and depression. Ketamine is a safe, effective, and affordable analgesic for the management of pain associated with snakebites. It is often available even in resource-poor settings. In addition to providing acute pain control, ketamine may prevent post-snakebite psychological disorders and may be useful for the prevention of pain chronification. Further scientific investigation is required to clarify the role of ketamine in physical and psychological snakebite traumas.

Conflicts of interest

The authors declare no conflicts of interest.

Disclaimer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense of the USA.

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