Ocular complications of spitting cobra venom

Dear Editor,

The name "spitting cobra" leaves little to one's imagination. Indeed, when threatened, snakes belonging this group can project their venom up to 3 m through the air to defend themselves.[1] The ultimate goal is to hit the opponent's eyes, which causes pain, blindness, and thus confusion, so that the snake can flee.[1-3] This maneuver requires highly developed skills, since it is only effective if the cornea is hit.[4] The snakes do not actually spit but eject venom through a hole in their fangs while making a spitting motion.[3-5] Inoculation of the venom is known as *venom ophthalmia*, a term used for a variety of symptoms. Spitting cobras are a group of elapids that live naturally in Africa and in Asia, including India. Most snakes are of the *Naja* (true cobra) genus. The African *Hemachatus haemachatus* (ring-necked spitting cobra) is not a true cobra, but a close relative.[6]

Corneal damage is theorized to develop in two phases; at first, there is direct injury to the epithelium and stroma caused by the venom itself, after which liberated inflammatory mediators (like prostaglandins and leukotrienes) continue to damage the underlying tissue. Snake venom in general consists of a multitude of proteins, varying among species, with different fractions responsible for different symptoms, for example, a hematotoxic, neurotoxic, or cardiotoxic fraction. The cardiotoxic fraction is found to be responsible for ocular symptoms, but only the compound venom of the spitting cobras can cause corneal damage due to its overall different composition.[7]

Venom dosage correlates to the severity of its effects, as tested in live rabbit models.[8] Low dosages of *Naja nigricollis* venom (0.1 mg) give mild conjunctival and corneal edema, while higher dosages (1.0–2.5 mg) result in corneal erosion, opacification, and scarring. Even higher doses (5.0 mg) result in extensive corneal melting with perforation. One dose of spitting cobra "spit" is estimated to contain 1.2–6.8 mg of venom. While corneal sensitivity correlates with melanin content of the eye, its effects appear to differ per type of spitting cobra.[9] Inoculation of *N. nigricollis* venom in albino rabbits eventually results in corneal neovascularization, whereas pigmented rabbits' corneas get clear over time. Conversely, *H. haemachatus* toxin results in corneal neovascularization in pigmented rabbits, while albino rabbits' corneas get clear in 3 weeks.[6]

Several proposed treatments have been tested in experiments on live and ex-vivo rabbit models, but none is conclusive. Treatment with topical dexamethasone or antivenom made no difference compared to an untreated fellow eye.[8] Topical heparin, theorized to inhibit inflammatory mediators, improved symptoms but could not prevent corneal scarring.[8] An ex-vivo study showed that epithelial and endothelial damage was significantly less after thorough rinsing with tap water 10 min after envenomation but could not prevent corneal swelling.[10] In one study, topical heparin or antivenom gave better results compared to a control group, but only when instilled 1 min after envenomation.[11] Such a quick response, however, is not realistic in a clinical setting. There was no significant difference between the treatments of corneal damage with tetracycline, dexamethasone, or a placebo ointment for 3 days.[11] In another study, topical tetracycline, thought to bind toxins and/or inflammatory mediators, did resolve cloudiness significantly.[6]

When looking at all reported case reports of venom ophthalmia, there seems to be a benefit of rapid irrigation with any, somewhat neutral, substance. Out of nine cases from Nigeria that were treated with irrigation and topical antivenom, only four eyes developed a corneal ulcer. One ulcer perforated, eventually leading to the need for enucleation.[3] An untreated case from the same country presented with a corneal ulcer with a large hypopyon.[12] A Ghanese farmer sustained diffuse punctate corneal epithelial defects which healed completely after irrigation and vitamin A ointment.[13] Four (bilateral) cases of venom ophthalmia were reported in UN soldiers, stationed in Somalia. All eyes were irrigated immediately. They all suffered from a diffuse punctate keratopathy which disappeared within 2 days with topical antibiotics; one eye developed iritis.[14] In a case from South Africa, a woman was spat in both eyes by a Mozambique spitting cobra (*N. mossambica*). She asked her daughter to urinate in her eyes, resulting in an unremarkable clinical course afterward. The subtitle of this paper summarizes this treatment best; it is "a reminder to all that for ocular chemical injury, dilution is the solution."[15] An 83-year-old Chinese woman sustained bilateral injuries while killing a Chinese cobra (*Naja atra*) in her home. Both eyes were irrigated with 1 l of saline. Also, diluted antivenom was instilled in her eyes, which interestingly gave a substantial pain reduction.[16] One herpetologist has been spat in the same eye by three different types of captive spitting cobra (*H. haemachatus*, *N. atra*, and *Naja pallida*) at different occasions. Direct irrigation with tap water for 1–2 h helped in all cases.[5] A Nigerian woman initially rinsed her eyes with milk, and a man from Laos directly immersed his head in a river after being spat. This led to only minor injury.[5] Venom ophthalmia caused by a Sumatran spitting cobra (*Naja sumatrana*) was seen in three Singaporean patients. All recovered after irrigation with tap water on site or saline at the hospital. Multiple corneal punctate epithelial erosions were successfully treated with prophylactic antibiotic drops.[17] In Taiwan, there were 39 reported cases from 1990 to 2016. Most symptoms were mild (59%). Eleven cases were treated with topical or intravenous antivenom. Most cases received immediate irrigation; no long-term ocular conditions were recorded.[18] In the United States, two snake handlers accidentally inoculated venom in their eye themselves after handling a spitting cobra. Direct and copious irrigation with saline resulted in only minimal visual sequalae.[19] A soldier in East Africa was spat in her face by a red spitting cobra (*N. pallida*). This patient, too, had minor corneal injuries and was treated with copious irrigation.[20]

Inoculation with spitting cobra venom causes severe pain, photophobia, and tearing. Roughly one in two patients develops multiple corneal erosions that could progress to a full corneal ulcer or keratitis, with a risk of perforation or secondary bacterial infection.[3] It is hard to predict the individual outcome of an attack, since damage depends on factors like the amount of venom that actually made it into the eye and the type of snake.[6,9] It is unnecessary to kill the animal for identification, since it will not affect treatment and will only higher the changes of facing another spitting attack or worse, being bitten.

In a first-aid setting, venom ophthalmia should be approached as any other chemical injury of the eye.[15,21] The affected eye should be copiously irrigated as soon as possible with any available fluid, like tap water, saline, Ringer's solution, or even milk or urine.[5,15] Pain can be managed with topical

anesthetics and mydriatic drops. Topical anesthetics can also help overcome blepharospasms and thus aid in irrigation of the eye.[21] Currently, there is insufficient evidence for the use of topical antivenom as a treatment.[3,5,6,18] The role of heparin and tetracycline in inhibiting stromal damage and subsequent corneal scarring is unclear.[6,9,11] Prevention of secondary corneal infection with topical antibiotics is useful in patients with epithelial defects. Treatment should continue until all defects have closed.

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Conflicts of interest

There are no conflicts of interest.

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