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TOXICOLOGY OBSERVATION

Local Antivenom Treatment for Ophthalmic Injuries Caused by a *Naja atra*

Hin Tat Fung · Ka Keung Lam · Oi Fung Wong · Tommy Shing Kit Lam

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Abstract We report a case of local antivenom therapy for ocular exposure to the venom of *Naja atra*. An 83-year-old woman sustained conjunctival and corneal injuries by the venom of a spitting *N. atra*. Local instillation of *N. naja* antivenom quickly relieved the pain as measured by visual analog scale, and she recovered uneventfully. Good recovery ensuing topical antivenom administration for ocular exposure to the venom of spitting *N. atra* and *Naja nigricollis* has been described in literature, but the pain response was not thoroughly documented. The mechanism of antivenom for pain relief remains to be established. In light of the associated positive outcome observed in human, the role of ocular antivenom therapy merits further study.

Keywords Antivenom · Cobra · Eye · *Naja atra* · Snake

Introduction

Ocular exposure to snake venom is rare and it is uncertain what the appropriate treatment is, although topical application of antivenom has been used. We report a case of the use of topical antivenom for ocular exposure to *Naja atra* venom detailing the serial pain scores before and after the antivenom administration.

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H. T. Fung (✉) · K. K. Lam · O. F. Wong · T. S. K. Lam
Accident and Emergency Department, Tuen Mun Hospital, Hong Kong, China
e-mail: oifungwong@yahoo.com.hk

Case

An 83-year-old woman, in good past health, was sprayed by the venom of a Chinese cobra (*N. atra*) at 1-m distance during an attempt of killing the snake found outside her house. She experienced immediate pain of the eyes and photophobia. She attended the emergency department with the dead snake at 30 min post-exposure.

On arrival, she was noticed to have bilateral conjunctivitis and visual acuity of 20/20 in both eyes. Slit lamp examination revealed bilateral multiple corneal abrasions but clear anterior chambers. Iritis and blepharospasm were absent. The pain score on visual analog scale was 8/10 and 1/10 for the right and left eyes, respectively. At 1 h post-exposure, she received 1 L of normal saline irrigation and immediately afterwards one drop of 1% amethocaine for each eye. However, the pain score was not altered throughout the next 3 h.

The snake was confirmed on site to be *N. atra* by a biologist of Kadoorie Farm and Botanic Garden. In view of the exquisite right eye pain with persistent pain score of 8/10, we decided to treat her with antivenom. The *N. naja* antivenom, a specific antivenom manufactured by Shanghai Institute of Biological Products against *N. atra*, was diluted in 1:2 fashion with normal saline and 0.1 mL of the diluted solution was instilled onto the right eye at 4 h post-exposure. This was ensued by substantial pain reduction, with post-antivenom pain score of 6/10 at 5 min, 2/10 at 10 min, and 2/10 at 1.5 h. Further antivenom was not given because of satisfactory pain relief. Analgesics were not prescribed all along.

She was discharged with 0.5% chloramphenicol eye drops and ophthalmologist follow-up on next day when she received additional chloramphenicol eye ointment and

0.12% prednisolone eye drops. The left and right eyes were pain-free 3 and 7 days later, respectively. Reexamination of the corneal abrasions was not arranged, but phone follow-up 2 months later did not reveal any residual symptoms.

Discussion

Spitting *N. atra* was reported incurring ophthalmic injuries [1, 2]. A case series of Mainland China described eight patients attending the emergency department from 15 to 50 min post-exposure with eyelid swelling, conjunctivitis, and keratitis without corneal ulcers. Topical *N. naja* antivenom from the same manufacturer of our case, without any dilution mentioned, was applied to all of them under the regimen of four to six drops every 5 min until a total of 30 min. They all had pain relief within 20 min and resolution of keratitis within 3 days. Other details of the response to treatment including the pain score were not depicted. The authors commented that the outcome was superior to previous cases without antivenom treatment [2].

Warrell DA described nine patients with ocular exposure to *Naja nigricollis* venom. Six of them presented early within 2.5 h with conjunctivitis, keratitis, corneal ulceration, or iritis. They all received local antivenom and completely recovered in 1 to 15 days, but the pain response was not documented. The other three patients presented late, the first on the next day with diffuse keratitis which improved 9 days later, the second on day9 with severe pain deteriorating to necrotic eye globe requiring enucleation, and the third 5 years later with dense corneal leucoma and complete blindness as incidental finding. None of them underwent antivenom therapy [3].

Intraocular venom exposure occurs when the forceful contraction of the masseter muscles ejects the venom of the cobra from its anterior-facing apertures at the tip of the fangs. Examples of spitting cobra are *N. atra* in Asia and *N. nigricollis* in Africa. The basic cardiotoxins in cobra venom are polypeptides interfering with the integrity of cellular membrane and are largely responsible for the ocular toxicity [4]. Another toxin, phospholipase A_2, works synergistically with the cardiotoxins, but phospholipase A_2 alone is free from visible ocular effects [4]. Besides conjunctival and eyelid inflammation, cobra venom may produce corneal injury that is of particular concern because of the potential visual impairment. Corneal edema is caused by the combination of sodium potassium pump inhibition by the cardiotoxins and release of histamine and acetylcholine by the venom, resulting in fluid influx, vasodilation, and absorption of excessive hypotonic tears [4, 5]. The progression of corneal edema to liquefaction and opacification is due to the release by the venom of collagenase or proteinase [5].

Probably by means of removing the cardiotoxins not yet tightly bound to the cell membrane, early fluid irrigation was deemed beneficial in alleviating the ocular symptoms of victims subjected to cobra venoms [4]. Irrigation was carried out for our patient for the dilution and removal of the residual venom. This was followed by topical amethocaine in consideration of the severe pain on presentation. Amethocaine, a fast-acting topical anesthetic, was unsuccessful in pain reduction as evident by the unresponsive pain score in the subsequent 3 h of its application. With regard to the failed pain response to irrigation and amethocaine, we moved to local antivenom treatment. Despite late commencement at 4 h post-exposure, the *Naja naja* antivenom achieved rapid pain relief quantified by a fall of pain score from 8/10 to 2/10 in 10 min. This dramatic improvement in contrast to the preceding static pain level after amethocaine supported that the agent contributory to pain relief was antivenom, but not the prior amethocaine.

There are several possible explanations for the resolution of pain following topical administration of antivenom. Firstly, in vitro incubation of IgG isolated from Antivenin Crotalidae Polyvalent and crotalid venom for 15 min has been successful in neutralizing the venom's platelet aggregation activity on human blood extract [6]. Based on the extrapolation of the in vitro result, it is plausible that in human ocular exposure, interaction effects may also take place within a comparable time frame provided there is adequate physical contact between the antivenom and venom solutions. Secondly, antivenom may bind free residual venoms as well as venoms already adhered to cell surface. As a result, the progress of toxicity is stopped.

A rabbit trial compared the effect of various therapeutic agents on the ocular damages caused by topical *Naja sumatrana* venom. Topical Haffkine snake antivenom and heparin (5,000 IU/mL) significantly ameliorated the inflammation, scarring, and healed corneal epithelial defects, while 0.1% dexamethasone ointment and 1% tetracycline ointment did no better than the control [7]. To date, there is no human report of the utilization of heparin for ocular envenomation by snake venom.

Our patient did not manifest features of systemic envenomation. From our literature search, ocular snake venom exposure producing systemic envenomation has not been reported. It does not appear that there is a role for intravenous antivenom following this route of exposure.

Conclusion

Ocular exposure to *N. atra* venom may produce damage of the conjunctiva and cornea. The reduction in pain temporally associated with instillation of antivenom in our case and the Chinese series suggests topical *N. naja* antivenom an appropriate treatment, and this should be evaluated by future studies.

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