About the pathways to deliver brimonidine to the Muller's muscle

To the Editor: We read with great interest the case report by Alotaibi et al[1] describing the evaluation of the topical application of brimonidine gel on the upper portion of the eyelid of a patient presenting postbotulinum toxin blepharoptosis. The investigators reported improvement in right eyelid elevation via palpebral fissure measurement 1 hour after application, which persisted for up to 2 hours.[1] We write this letter to challenge the interpretations to guide future reports on the subject.

Although alpha-2 adrenergic agonist ophthalmic eye drops, such as apraclonidine or brimonidine, have been adopted by many clinicians to treat blepharoptosis, more studies are needed to evaluate their efficacy.[2] In a nonrandomized clinical trial measuring margin-reflex distance in healthy subjects after the administration of ophthalmic solutions of brimonidine tartrate 0.2%, phenylephrine hydrochloride 0.12%, or naphazoline nitrate 0.05%, the investigators found that brimonidine and phenylephrine had no effect on the eyelid aperture.[2]

Brimonidine tartrate 0.5% gel (0.33% brimonidine base) has received approval from the United States Food and Drug Administration for use in the topical treatment of erythema of rosacea in adults.[3] Despite the high concentration, brimonidine is unlikely to permeate through epidermis, dermis, orbicularis oculi muscle, 2 fat pads separated by the orbital septum, and the levator aponeurosis to finally reach and contract the Muller's muscle (Fig 1).

Additionally, the photographic documentation shown reveals the following: (1) a null margin-reflex distance before application, instead of 2 mm (no reflex is seen over the pupil, only on the lid margin); (2) One-hour after application, a contralateral upper eyelid elevation was noted, which is suggestive of voluntary contraction of the levator palpebrae superioris muscles. When considering that the systemic absorption could explain the results, it would be unlikely that the drug would achieve systemic levels to cause contralateral contraction of the Muller's muscle without any other systemic side effects.[4] Moreover, accidental conjunctival application would likely only affect the treated eye.

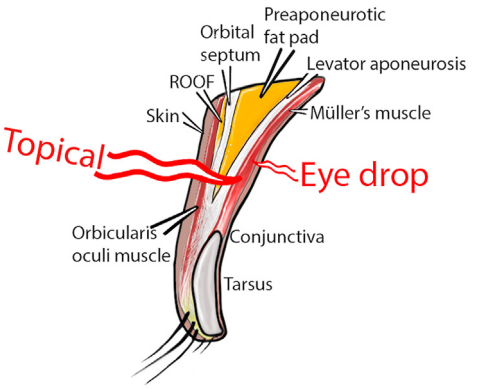

Fig 1. Schematic representation of the pathways to deliver alpha adrenergic agonists to elicit contraction of the Müller's muscle: conventional ophthalmic solutions (eye drops) need to permeate through the conjunctiva, whereas topical gels would need to permeate through multiple layers. *ROOF*, Retroorbicularis oculi fat.

Although eye drops instillation can be cumbersome for some patients, there is evidence for the use of naphazoline nitrate 0.05%[2] to elevate the upper eyelid, and the recently United States Food and Drug Administration-approved oxymetazoline hydrochloride ophthalmic solution 0.1% for the treatment of acquired blepharoptosis in adults.[5] Since 2018, one of the investigators (CGW), has adopted over-the-counter ophthalmic solutions containing naphazoline, such as naphazoline hydrochloride 0.03% (Clear Eyes, MedTech Products Inc.) with anecdotal success.

Continued research is needed to explore different active ingredients and concentrations in ophthalmic solutions, and also in topical products that could benefit patients who are averse to eye drops.

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Conflicts of interest

None disclosed.

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