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Botulinum toxin A for the treatment of photophobia and dry eye

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Photophobia is a chronic debilitating condition that, in severe cases, causes individuals to become prisoners in their own homes. Despite diminishing quality of life, few studies have evaluated therapies for photophobia. Anecdotally, botulinum toxin A (BoNT-A) was reported effective in the treatment of 3 patients with medication refractory photophobia.[1] In this cross-sectional retrospective study we evaluate the effect of BoNT-A on photophobia and dry eye symptoms in individuals with chronic migraine (CM) and evaluate factors predictive of a positive treatment response. The Miami Veterans Affairs (VA) Institutional Review Board approved the study, which was conducted in accordance to the principles of the Declaration of Helsinki and complied with the United States Health Insurance Portability and Accountability Act. Informed consent was obtained from patients surveyed.

117 patients undergoing treatment with BoNT-A for CM between August 22, 2016 and November 28, 2016 at the Miami VA Medical Center were included. All patients had a diagnosis of CM (≥15 headaches or headache days/month) and failed a trial of at least 2

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prophylactic medications or had contraindications to these medications. 68 patients (58.1%) were male with a mean age of 47.0 years, standard deviation (SD) 11.3. The mean total number of BoNT-A treatments was 10.2 SD 7.7 which had been received over an average time of 3.0 years SD 2.4. Using the date of chart review as an anchor, mean time since last injection was 64.2 days SD 54.2 with 114.4 SD 24.5 mean total units injected at that time.

After reviewing the medical records, standardized phone questionnaires were delivered to 91 (77.8%) of individuals. Patients were asked to rate photophobia severity during and between migraine episodes using a numerical rating scale (NRS) anchored at “0” for no photophobia and “10” for the worst photophobia imaginable. All patients reported photophobia during migraine with mean severity ratings of 8.59 SD 1.53. Approximately half (54.9%) reported interictal photophobia with mean severity ratings of 5.48 SD 2.59, n=50.

Patients were asked to recall symptoms prior to and since initiating BoNT-A and rate migraine pain, photophobia, and dry eye symptom severity using the same NRS. The majority of patients rated their pre-BoNT-A photophobia score as severe (80%, n=72 with a score≥7; mean 7.91 SD 2.05, n=90). 36 patients rated their pre-BoNT-A dryness score as severe (44.4% score≥7; mean 5.40 SD 3.41, n=81). As supported by the literature, we found significant associations between migraine pain, photophobia, and dry eye severity scores.[1] (Available at www.aaojournal.org)

Using paired t-test analysis, we found that migraine pain, photophobia, and dry eye symptoms all significantly improved with BoNT-A ($p<0.005$ for all). This pattern remained when only those individuals without a diagnosis of dry eye were included. (Table 1) Clinical response to BoNT-A injections was also assessed subjectively with the options given as “worse”, “no change”, “a little better”, “better” or “much better” for migraine pain, photophobia and dry eye symptoms since beginning treatment. 66 patients (72.5%, n=91) reported at least some improvement in photophobia (27 a little better, 16 better, and 23 much better) and 24 patients (29.3%, n=82) reported at least some improvement in dry eye symptoms (10 a little better, 10 better and 4 much better). Finally, using univariable logistic regression analysis we determined that older individuals were more likely to report improvement in photophobia with BoNT-A. (Available at www.aaojournal.org)

The associations between migraine pain, photophobia, and dry eye, and their improvement with BoNT-A may be due to shared neural mechanisms. In migraine, first-order nociceptive impulses from the meninges and dural vessels travel through the ophthalmic division of the trigeminal nerve and synapse in the trigeminal cervical complex (TCC). Second-order neurons then synapse in the posterior thalamus, giving off third-order neurons that terminate in the somatosensory cortex producing sensations of pain.[2] These pathways are also critical in photophobia.[1, 3] Retinal ganglion cell impulses exert an indirect parasympathetic vasodilatory effect on ocular blood vessels that is sensed by ocular trigeminal afferents that signal to the TCC, posterior thalamus, and higher cortical centers. A second pathway mediated by melanopsin-containing intrinsically photosensitive retinal ganglion cells sends sensory input directly to the posterior thalamus.[3] Finally, in relation to the ocular surface, corneal nociceptive signals also synapse in the TCC. These pathways demonstrate

convergence of nociceptive signaling, sensitization, and signal amplification in migraine pain, photophobia, and dry eye.

On a molecular level, hyperstimulation of peripheral nociceptors, as is seen in migraine, leads to the release of inflammatory mediators, such as CGRP, with subsequent sensitization of peripheral and central neurons.[4] CGRP–related hypersensitivity is also a critical component of photophobia and light-aversion.[3] In addition to its effects at the neuromuscular junction, BoNT-A exerts antinociceptive effects by inhibiting the release of neuroinflammatory substrates, including CGRP.[4] We believe this action to be of greatest relevance to this study. BoNT-A also inhibits unmyelinated C-fiber nociceptors in the meninges[4] which may also play a role in diminishing other sensations (photophobia and dryness). Prevention of peripheral nerve activation and subsequent inhibition of central nerve stimulation may, over time, stabilize the afferent processing system and reverse the changes of sensitization.[5] We hypothesize that reductions in photophobia and dry eye severity scores secondary to BoNT-A injection for CM are a consequence of a less active neuronal network connecting these pathways.

Limitations to this study include recall bias, a unique patient population, reliance of chart review for co-morbidities and medications, and varied injection protocol by provider. Furthermore, we do not know whether we can generalize our findings to individuals with photophobia and sensations of dryness without chronic migraine. Finally, without a control group, we cannot rule out that our findings represent a regression to the mean. Based on our pilot data and limitations, this manuscript supports a future randomized placebo-controlled trial to investigate the use of BoNT-A in the treatment of photophobia and recalcitrant dry eye symptoms in patients with and without CM. The co-occurrence of debilitating photophobia in numerous ocular diseases and the prevalence of dry eye symptoms in the population warrant further exploration of these treatment modalities and their applicability to comprehensive ophthalmology practices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparison of symptoms severity scores before and after botulinum toxin A injections

	Before injections, mean (SD)	After injections, mean (SD)	Mean Δ (SD)	95% CI	p-value
Migraine n=90 *	9.34 (0.91)	5.90 (2.48)	−3.43 (2.46)	[−3.95, −2.92]	<0.001
Photophobia n=90 *	7.91 (2.05)	5.27 (2.73)	−2.64 (2.56)	[−3.18, −2.11]	<0.001
Dry eye symptoms n=81 *	5.40 (3.41)	4.68 (3.34)	−0.716 (2.11)	[−1.18, −0.249]	0.003
No self-reported or documented diagnosis of dry eye					
Migraine n=63	9.17 (0.959)	5.89 (2.65)	−3.29 (2.63)	[−3.95, −2.62]	<0.001
Photophobia n=63	7.68 (1.93)	5.10 (2.60)	−2.59 (2.53)	[−3.23, −1.95]	<0.001
Dry eye n=57	4.40 (3.33)	3.74 (3.20)	−0.667 (2.29)	[−1.27, −0.060]	0.032
Self-reported or documented diagnosis of dry eye					
Migraine n=27	9.70 (0.669)	5.93 (2.07)	−3.78 (2.03)	[−4.58, −2.98]	<0.001
Photophobia n=27	8.44 (2.24)	5.67 (3.03)	−2.78 (2.68)	[−3.84, −1.72]	<0.001
Dry eye symptoms n=24	7.75 (2.29)	6.92 (2.55)	−0.833 (1.66)	[−1.53, −0.133]	0.022

* 90 individuals responded to the pre/post injection migraine and photophobia severity questions while only 81 individuals responded to the pre/post injection dry eye symptoms severity questions.

SD = standard deviation