The Ocular Surface 17 (2019) 822–827

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.elsevier.com/locate/jtos

Original Research

Chronic Electrical Stimulation for Tear Secretion: Lacrimal vs. anterior ethmoid nerve

Andrea L. Kossler[a,*], Mark Brinton[b], Zara M. Patel[c], Roopa Dalal[a], Christopher N. Ta[a], Daniel Palanker[a,b]

[a] Department of Ophthalmology, Stanford University, Stanford, CA, USA
[b] Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, USA
[c] Department of Otolaryngology, Stanford University, Stanford, CA, USA

ARTICLE INFO

Keywords:
Anterior ethmoid nerve stimulation
Dry eye disease
Electrical stimulation
Intranasal stimulation
Lacrimal gland stimulation
Neurostimulation

ABSTRACT

Purpose: To evaluate and compare the effect of lacrimal nerve stimulation (LNS) and anterior ethmoid nerve stimulation (AENS) on aqueous tear secretion, and tissue condition following chronic implantation.

Methods: A neurostimulator was implanted in rabbits adjacent to the (1) lacrimal nerve, and (2) anterior ethmoid nerve. Tear volume was measured with Schirmer test strips after stimulation (2.3–2.8 mA pulses at 30 Hz for 3–5 min), and scores were compared to sham stimulation. Lacrimal gland and nasal septal tissue were evaluated histologically after chronic stimulation (2 weeks–7 months).

Results: LNS increases tear volume by 32% above sham ($p < 0.05$, $n = 5$), compared with 133% for AENS ($p \leq 0.01$, $n = 6$). AENS also significantly increases tear secretion in the fellow, non-stimulated eye ($p \leq 0.01$, $n = 6$), as expected from the tearing reflex pathway. Histologically, chronic LNS is well tolerated by surrounding tissues while chronic AENS results in nasal mucosal fibrosis and implant extrusion within 3 weeks.

Conclusions: AENS is significantly more effective than LNS at enhancing aqueous tear secretion, including the fellow eye. The lacrimal implant is well tolerated, while the nasal implant requires further design optimization to improve tolerability.

1. Introduction

Dry eye disease (DED) is a leading cause of eye discomfort and morbidity and afflicts approximately 20 million Americans [1]. It is estimated that roughly 5 million patients, 50 years and older, have moderate to severe disease [2], which can lead to significant loss of vision. This multi-factorial process is defined as a tear film disorder due to aqueous tear deficiency or excessive evaporation resulting in ocular discomfort, visual disturbance, and tear film instability [3,4]. It is postulated that DED is an immune-mediated disorder and tear secretion is controlled by a neural reflex loop. The ophthalmic division of the trigeminal nerve (V1) is responsible for the afferent branch of this reflex. These axons travel to the midbrain, where they synapse in the pons. The parasympathetic nervous system is largely responsible for the efferent branch of this reflex. Efferent fibers from the superior salivary nucleus pass with the nervous intermedius, synapse in the pterygopalatine ganglion, travel through the inferior orbital fissure to join the lacrimal nerve and innervate the lacrimal gland [5–7]. The lipid and mucin layers of the tear film are also under neural control: sensory, parasympathetic and sympathetic nerves innervate the meibomian glands [8–11]; and goblet cells secrete mucin, controlled by parasympathetic neural signaling [12–14].

Current treatment options for DED fail to effectively increase tear production. Lubricating eye drops and ointments provide temporary relief. Topical cyclosporine and lifitegrast inhibit some of the inflammatory aspects of DED, but only a subset of patients respond to treatment, and many report side effects of burning or an unpleasant taste [15–18]. In 2008, Kossler et al., [19] introduced electrical stimulation of the lacrimal nerve (LN) to increase aqueous tear volume as a potential treatment of DED in a pilot animal study. This study found a significant increase in tear volume in the stimulated eye, compared to baseline and control eye, with no discernible histological damage to lacrimal gland tissue after lacrimal nerve stimulation (LNS). Further LNS studies with chronically implanted neurostimulators in rabbits similarly showed a significant increase in aqueous tear volume [20,21]. In 2017, Brinton et al., [11,21] demonstrated that anterior ethmoid

Abbreviations: DED, dry eye disease; LN, lacrimal nerve; LNS, lacrimal nerve stimulation; AEN, anterior ethmoid nerve; AENS, anterior ethmoid nerve stimulation

* Corresponding author. Byers Eye Institute Stanford University School of Medicine 2452 Watson Court Palo Alto, CA, 94303, USA.
E-mail address: akossler@stanford.edu (A.L. Kossler).

https://doi.org/10.1016/j.jtos.2019.08.012
Received 11 March 2019; Received in revised form 6 July 2019; Accepted 29 August 2019

nerve stimulation (AENS) significantly increases aqueous tear production in rabbits. Additionally, a clinical trial demonstrated reduction in dry eye symptoms using intranasal electrical stimulation of the anterior ethmoid nerve (AEN) at least four times a day [22]. Since then several studies have demonstrated the efficacy of external intranasal stimulation for improved tear production [23–31].

We hypothesize that stimulation of the afferent nerves in the tearing reflex (AENS) increases aqueous tear production more than the efferent nerve stimulation (LNS). In this study, we evaluate and compare the efficacy and safety of two approaches to increase aqueous tear production using chronic implants: (a) LNS (efferent), and (b) AENS (afferent).

2. Methods

We conducted two chronic experimental animal studies using New Zealand white rabbits (male, 3.5–5 kg; Western Oregon Rabbit Co., Philomath, OR, USA). The right nasal septum mucosa (NS) and right lacrimal gland (LG) were stimulated, while the left lacrimal gland and left nasal septum mucosa served as controls. Animals received intermittent stimulation for 2–3 weeks (AEN, n = 6) or 4–7 months (LN, n = 5) after which the animals were euthanized and tissue collected for histology. The reason for shorter follow-up with nasal devices was the extrusion of the implants through the nasal septum mucosa within 2–3 weeks post implantation. Primary outcome measures included: (1) tear volume measurements with Schirmer test strips during stimulation compared to sham stimulation, and (2) histopathologic evaluation. All animal experimental procedures were conducted in accordance with the Stanford University institutional guidelines, the National Institutes of Health guide for the care and use of Laboratory animals and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

2.1. Surgical procedures

Rabbits were anesthetized with ketamine (35–50 mg/kg, intramuscular), xylazine (3 mg/kg, intramuscular), and glycopyrrolate (0.01 mg/kg, intramuscular). Buprenorphine (0.05–0.1 mg/kg, subcutaneous every 6–12 h) was given for analgesia before and up to 24 h after surgery. After implantation, animals were monitored daily for behavioral habits, such as eating, weight gain and activity. The surgical site was also monitored daily to ensure proper healing.

2.1.1. Implantation beneath lacrimal gland

A 1-cm vertical incision was made inferior to the right medial canthus to expose the inferomedial orbital rim. Blunt dissection extended along the inferior orbital rim periosteum until the extraorbital portion of the inferior lacrimal gland was visualized. A preperiosteal pocket was created between the lacrimal gland and orbital floor. The neurostimulator (Fig. 1A) was placed beneath the gland, adjacent to the lacrimal nerve, within the orbit and the incision was closed with sutures (Fig. 1C).

2.1.2. Nasal septum implantation

Bilateral external nasal incisions opened each nostril to expose the distal septal mucosa. The neurostimulator was placed unilaterally as follows: an 8-mm vertical incision was made in the distal septal mucosa, a Cottle elevator dissected a subperichondrial pocket, approximately 3-cm in depth, along the dorsal rim of the septum. The neurostimulator was inserted with the active electrode facing the mucosa. Finally, a suture was placed through the distal mucosa and septal cartilage to close the incision and secure the device (Fig. 1D). Optimal device placement was correlated with a sneeze reflex at the onset of stimulation. Animals without a sneeze reflex responded to stimulation but required longer pulse durations.

2.2. Electrical stimulation

Electrical stimulation began 4–7 days after implantation. The appropriate pulse duration for each rabbit was selected based on response to stimulus onset by moving its head or sneezing, yet with no observed distress (i.e. pulling away sharply or grinding teeth). The median pulse duration for both AEN and LN stimulation was 170 μs. For AENS, animals received a total of 10 stimulations, spread over 5 days per week, for 2–3 weeks (n = 6). For LNS, stimulations were applied over a 4 (3 animals, 14 total stimulations) or 7 (2 animals, 27 total stimulations) month period, on average animals were stimulated once per week. Occasionally, two stimuli were given on the same day—when this occurred, they were spaced at least 15 min apart.

A radio-frequency (RF) transmitter (Fig. 1B) was placed gently against the skin to wirelessly power the implant to deliver animal specific, bi-phasic, cathodic first charge-balanced pulses of 2.3–2.8 mA and 75–875 μs duration, at 30 Hz for 3–5 min. Continuous stimulation induced the maximum tear secretion for AENS, whereas pulsed stimulation at 50% duty cycle (an equal ratio of on-off time), optimized the response to LNS. Maximum tear responses to AENS and LNS stimulation parameters were used for tear volume comparison. Optimal settings for neural stimulation were selected from a broader set of parameters described in previous publications [11,21]. For sham tear volume measurements, the transmitter was placed gently against the skin but without RF power transmission.

The implanted stimulator (Fig. 1A) included a gold coil for inductive power transfer and an active 3-mm diameter, platinum black electrode, held in place with platinum cured silicone. Electronics that convert transmitted power into charge balanced bi-phasic pulses of current were encapsulated in a titanium case—which also served as the return electrode. The implant was gently curved to fit in the human lacrimal gland fossa, but has also been used in rabbit studies [11,21]. The battery-operated, external transmitter delivers power to the implant using an external coil tuned to the same resonance as the implanted coil. The user can increase the strength of stimulus using an external remote control (Fig. 1B).

2.3. Tear volume measurements

The cornea and conjunctiva were anesthetized with 1–2 drops of proparacaine administered 5 min prior to the Schirmer test. Proparacaine was removed from the conjunctival sac prior to stimulation. Schirmer tests were performed during electrical or sham stimulation for 5 min with LN and 3 min with AEN. Collection time was reduced in the latter case due to much higher volume of the secreted tear.

2.4. Preparation of samples for histopathology

All rabbits were euthanized under full anesthesia by an intravenous injection (ear vein) of Beuthanasia-D (0.22 ml kg^{-1}). The right and left orbits of the LNS group and the nasal septum of the AENS group were harvested and fixed in 10% formalin. Samples were then processed and embedded in paraffin. The 5 μm thick sections were stained with hematoxylin and eosin to evaluate the lacrimal gland and nasal mucosa after chronic stimulation.

2.5. Statistical analysis

Multiple Schirmer scores from each animal were averaged together and significance determined using a one-way ANOVA ($F(3,18) = 16.28$) and the one-sided paired or unpaired (as appropriate) *t*-test with the Holm-Sidak Bonferroni correction for multiple comparisons ($p < 0.05$). Error bars shown are the standard deviation.

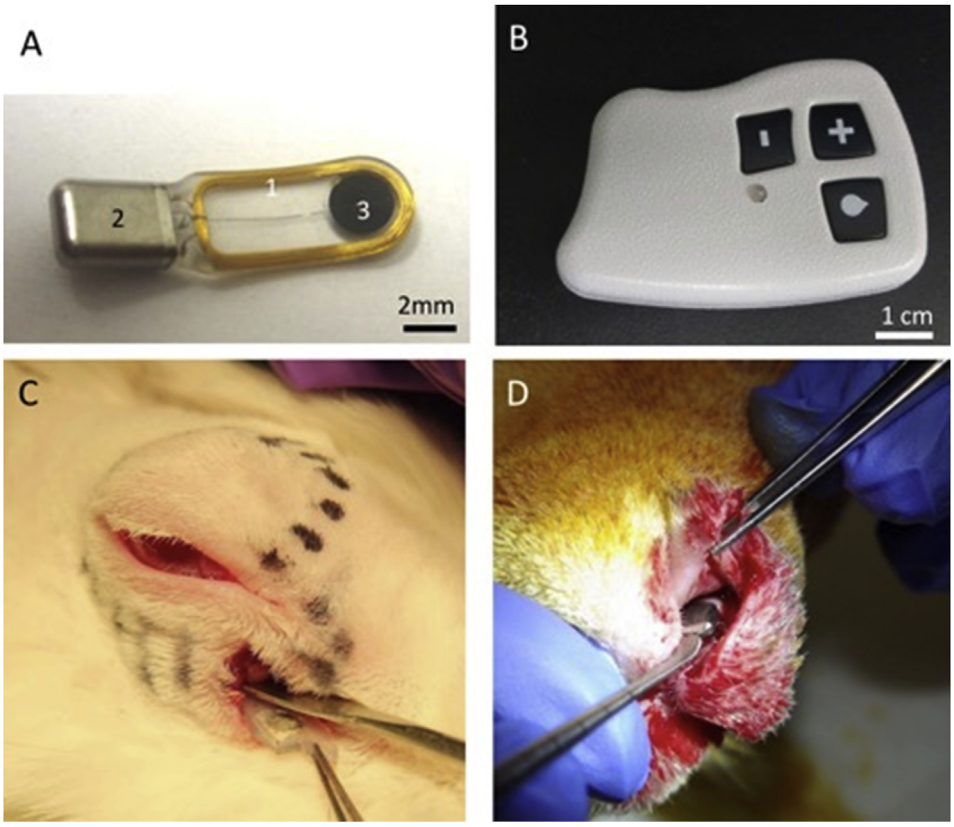

Fig. 1. A. Implant composed of the RF receiving coil (1), case with electronics serving as a return electrode (2), and an active electrode (3). B. RF power transmitter with adjustable pulse duration. C. Implantation near the lacrimal gland. D. Implantation into the nasal septum.

3. Results

Eleven New Zealand white rabbits were used for this study: five for LNS, and six for AENS. All rabbits tolerated surgery and chronic stimulation without evidence of infection or behavioral changes. There was no significant difference in body weight change among rabbits after chronic stimulation, suggesting that stimulation did not alter feeding patterns or activity. The overall growth was otherwise normal and there were no other demonstrable gross adverse effects to stimulation. Of note, the AENS group demonstrated histopathologic changes to the nasal septum and mucosa due to chronic implantation.

3.1. Tear volume increase

As shown in Fig. 2, the average tear production from LNS (14.74 mm ± 2.29) increased by 32%, compared with sham stimulation in the same eye (11.16 mm ± 2.02, $p < 0.05$). Tearing in the fellow eye (9.71 mm ± 1.20) was not significantly affected by LNS, compared with sham stimulation (12.35 mm ± 3.32). LNS was delivered with 2.3–2.8 mA pulses (170–680 μs) at 30 Hz, repeated for 1 s on, 1 s off throughout the 5 min Schirmer test.

As shown in Fig. 3, AENS increased tear volume in the stimulated eye by 133% (20.75 mm ± 4.87) and in the fellow eye by 64% (14.63 mm ± 1.80, $p < 0.01$), compared with sham (8.92 mm ± 1.16 and 8.90 mm ± 1.30, respectively; $p < 0.01$). Tear volume in the stimulated eye was significantly higher (42%, $p < 0.05$) than in the fellow eye. AENS was delivered with 2.3–2.8 mA pulses (75–875 μs) at 30 Hz continuously for 3 min throughout the Schirmer test.

When comparing the tear volume increase above sham (Fig. 4), AENS demonstrated significantly higher efficacy in tear secretion in both the stimulated and fellow eyes (11.83 mm ± 5.57 and 5.73 mm ± 2.57, respectively; $p < 0.05$), compared with LNS (3.58 mm ± 2.36 and −2.64 mm ± 2.12). Unlike LNS, AENS resulted in a bilateral increase in tear production.

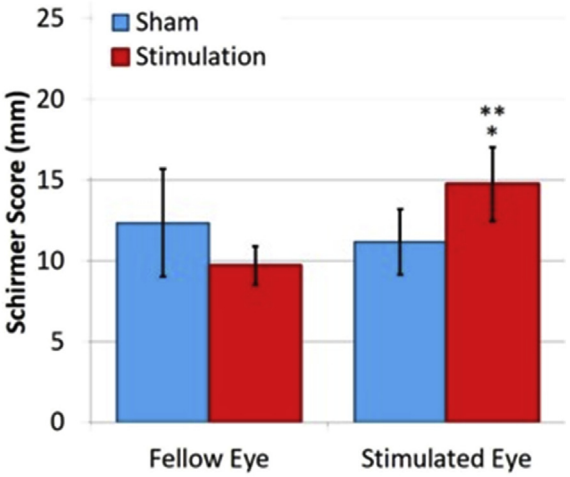

Fig. 2. Chronic LN Stimulation: 2.3–2.8 mA pulses (170–680 μs) at 30 Hz, repeated for 1 s on, 1 s off throughout the 5 min Schirmer test (mean ± stdev, n = 5). Animals received 14 (over 4 months, n = 3) or 27 total stimulations (over 7 months, n = 2). ** and * indicate significance ($p < 0.05$) compared with sham (same eye) and fellow eye.

3.2. Histopathologic evaluation

3.2.1. Lacrimal gland

Histopathologic examination of the lacrimal glands following 4–7 months of chronic stimulation revealed no discernible tissue damage, suggesting the implant and the stimulation protocol were well tolerated

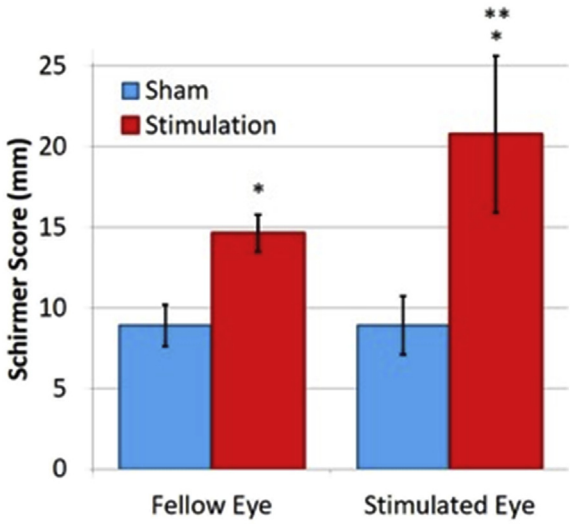

Fig. 3. AEN Stimulation: 2.3–2.8 mA pulses (75–875 μs) at 30 Hz continuously for 3 min during the Schirmer test (mean ± stdev, n = 6). Animals received 10 total stimulations (n = 6) over a 2–3 week period. ** and * indicate significance ($p < 0.05$) compared with sham (same eye) and fellow eye.

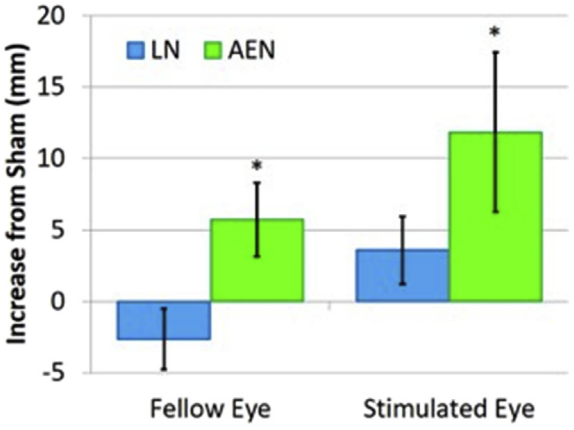

Fig. 4. AEN vs. LN stimulation: increase in Schirmer score, compared to sham. Data presented as mean ± stdev. * indicates significance ($p < 0.05$) between AEN and LN stimulation in same eye.

(Fig. 5A and B). There was no evidence of atypical lymphocytic or inflammatory cell infiltration, atrophy of the stroma or acini, or atypical foreign body reaction, hemorrhage, fungi or bacteria in the surrounding orbital tissues.

3.2.2. Nasal septum

Mucosal thinning, fibrosis and inflammation were present in all the nasal mucosa specimens on the side of the implant. Four out of five specimens (80%) demonstrated mucosal erosion. One specimen was not included in histologic evaluation due to complete erosion of the implant through the mucosa. Three specimens (60%) had erosion at the superior most edge of the mucosa adjacent to the titanium portion of the implant (Fig. 6A). The non-operated left nasal mucosa also showed evidence of mucosal thinning in 4 (80%) specimens and fibrosis and inflammation in 4 (80%) specimens (Fig. 6C and D). Septal thinning was noted in 4 (80%) samples.

4. Discussion

Chronically implanted LNS and AENS stimulators significantly increase tear production in healthy rabbits. AENS is much more effective than LNS and results in a bilateral increase in tear volume, unlike LNS, which produces a unilateral effect.

Our earlier pre-clinical studies [11,21] led to the development of the implantable LN stimulator and non-implantable AEN stimulator by Oculeve Inc. The first clinical studies have similarly shown a significant increase in tear volume in patients with DED following nasal stimulation of AEN [22]. After acquisition of Oculeve by Allergan Plc (Dublin, Ireland), and following two pivotal studies [23], AENS (TrueTear) was approved to provide temporary increase in tear production during neurostimulation in adult patients.

Although an external stimulator is minimally invasive, it may not be appropriate for patients who are non-compliant, have a significant tremor, or prefer an automatically programmable hands-free option. These patients may benefit from an implantable nasal stimulator. While LNS has not been adequately studied in humans, this concept should be investigated further for patients with unilateral aqueous tear deficiency with a functioning lacrimal gland, intranasal pathology that would interfere with AEN function, trigeminal ganglion injury, or facial nerve dysfunction above the geniculate ganglion where the efferent branch of the tearing reflex would be affected. The present study evaluates an implantable neurostimulator adjacent to the AEN and LN in efficacy of tear production and in tolerability by adjacent tissues in rabbits.

The significant bilateral effect of AENS suggests stimulation of the afferent branch of the tearing reflex bilaterally activates main lacrimal glands and accessory glands of Wolfring and Krause; whereas, efferent stimulation of the lacrimal nerve entering the gland stimulates the main lacrimal gland unilaterally. This explains the larger, bilateral effect of AENS on tear production. Furthermore, the afferent pathway has been shown to stimulate lipid and mucin secretion from meibomian glands and goblet cells [8–14]. Brinton et al., demonstrated a significant increase in lipid secretion after AENS [11]. Gumus et al., reported a significantly higher granulation of goblet cells after external intranasal stimulation compared to sham and baseline [24,31]. Another intranasal

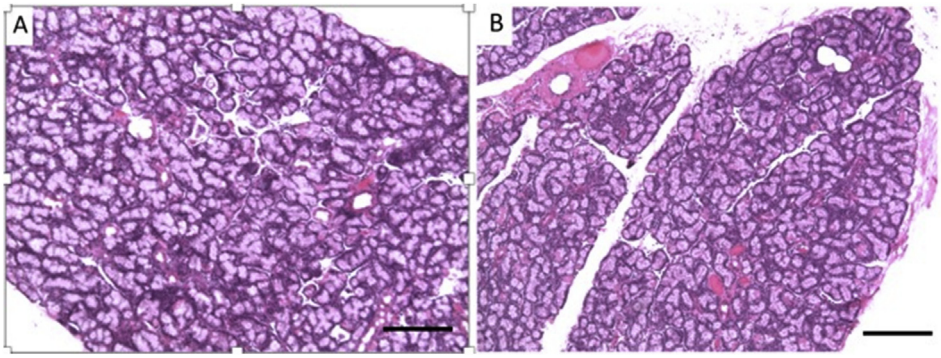

Fig. 5. Lacrimal gland histology. A. Stimulated gland with no evidence of atypical lymphocytic or inflammatory cell infiltration, atrophy of the stroma or acini, or atypical foreign body reaction, B. Control lacrimal gland. Scale bars are 200 μm.

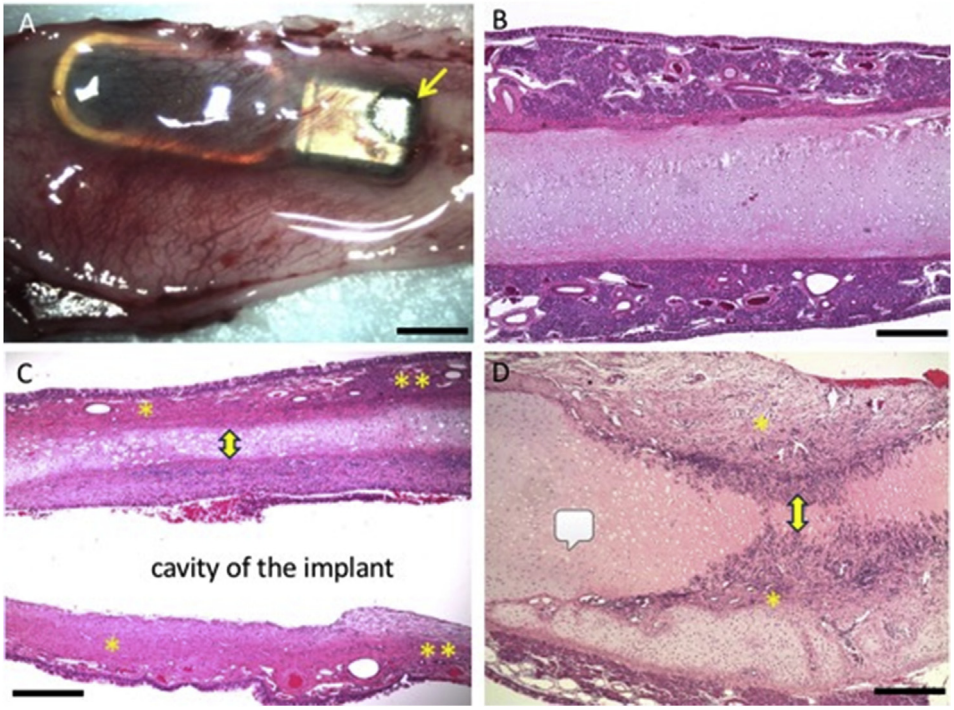

Fig. 6. Nasal tissues. A. Mucosal erosion adjacent to the titanium portion of the implant (arrow), B. Control nasal septum (no implant). C. Bilateral mucosal thinning (**), fibrosis (*) and septal thinning (↔), D. Bilateral fibrosis (*) and septal thinning (↔). Scale bars are 200 μm.

stimulation study reported a significant increase in tear volume and claimed that subjective patient data revealed an improvement in ocular comfort lasting ~ 3 h after the application [22]. The authors suggest the duration of comfort may be explained in part by the endogenous nature of elicited tears, including mucins, proteins and lipids [22]. These studies suggest that AENS increases not only aqueous tear volume but also the lipid and mucin secretion to improve tear film composition for longer lasting relief. This further supports our hypothesis that AENS stimulates the afferent branch of the tearing reflex, i.e. the ophthalmic division of the trigeminal nerve (VI), and is more effective than efferent LNS in both the volume and quality of secreted tears. This field would benefit from deeper quantitative analysis of lipid, mucin, osmolarity and protein composition of stimulation-induced tears to better understand the complex interplay between neuronal stimulation and tear physiology.

Histological analysis of the tissues adjacent to chronic implants demonstrated that, unlike well-tolerated implants near the lacrimal gland, nasal septum near the implant revealed significant tissue damage. One problem was the curved rigid shape of the implant initially designed for placement in the human lacrimal gland fossa. The 2 mm thick profile and curved shape of the implant was not appropriate for the rabbit nasal mucosa, as evidenced by mucosal thinning and erosion adjacent to the curved titanium portion of the implant. The mucosal thinning, fibrosis and inflammation found on the non-operated side of the nasal mucosa suggests that foreign body reaction and/or electrical stimulation may affect even the opposite side of the nasal septum. A flat, low profile implant intended for the nasal septum will be required for future AENS studies to help determine if such an implant is feasible and if chronic electrical stimulation is well tolerated by the nasal mucosa.

Studies in rabbits are limited by their anatomy: nasal septum cartilage is too thin to remove and replace with our implant. Therefore, the implant was placed between the septum and mucosa in a pocket that may have been too tight for our implant. Additionally, stimulation was confirmed with a sneezing effect which may have dislodged our implant from the target location. Both techniques could have resulted in suboptimal implant placement and variable neuronal stimulation. A reduced response to stimulation may also have occurred with repeated daily stimulation. However, our experimental design intentionally avoided repetitive daily stimulation to minimize desensitization and animal stress. Further studies should be performed to determine if desensitization occurs and at what stimulation parameters.

Finally, our animal study may not directly translate to human patients with diseased lacrimal glands, such as Sjögren's syndrome, graft-versus-host disease, severe meibomian gland dysfunction, or any other injury to the afferent or efferent branch of this reflex. Patients with intranasal pathology, injury to the trigeminal ganglion, or damage to the parasympathetic division of cranial nerve seven may benefit from efferent LNS.

In conclusion, electrical stimulation of the AEN and LN both significantly increase aqueous tear secretion, however AENS is much more effective and produces a bilateral increase in tear volume. While a LN stimulator could be implanted, nasal implants would require further design optimization and additional studies to validate their tolerability. Clinical studies are necessary to verify the benefits of AENS and LNS in patients with various forms of DED, diseased glands and damage to the tearing reflex.

Financial support

This work was supported in part by: National Institute of Health (NIH)/National Eye Institute (NEI) Center Core Grant P30EY026877; Research to Prevent Blindness, RBP Challenge Grant, United States and National Institutes of Health (NIH)/National Eye Institute (NEI). R01 Grant. R01EY023259. The sponsor or funding organization had no role in the design or conduct of this research.

Disclosure/conflict of interest statement

D.P. is a co-inventor on a patent describing neural stimulation for tear secretion, licensed by Stanford University to Allergan. No conflicting relationships exist for other authors.

Acknowledgements

None.

References

[1] Market ScopeReport on the global dry eye market. St. Louis, MO. 2004.
[2] Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318–26.
[3] Lemp MA. Report of the national eye institute/industry workshop on clinical trials in dry eyes. CLAO J 1995;21:221–32.
[4] Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S, et al. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international dry eye work shop. Ocul Surf 2007:75–92. 2007.
[5] Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. Cornea 1998;17:584–9.
[6] Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the Pathophysiology of dry eye. Exp Eye Res 2004;78:409–16.
[7] Smith JA, Albeitz J, Begley C, Caffery B, Nichols K, Schaumberg D, et al. The epidemiology of dry eye disease: report of the epidemiology subcommittee of the international dry eye WorkShop. Ocul Surf 2007:93–107. 2007.
[8] LeDoux MS, Zhou Q, Murphy RB, Greene ML, Ryan P. Parasympathetic innervation of the meibomian glands in rats. Investig Ophthalmol Vis Sci 2001;42:2434–41.
[9] Kirch W, Horneber M, Tamm ER. Characterization of Meibomian gland innervation in the cynomolgus monkey (Macaca fascicularis). Anat Embryol 1996;193. 365.
[10] Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Investig Ophthalmol Vis Sci 2011;52:1938–78.
[11] Brinton M, Kossler AL, Patel ZM, Loudin J, Franke M, Ta CN, et al. Enhanced tearing by electrical stimulation of the anterior ethmoid nerve. Investig Ophthalmol Vis Sci 2017;58:2341–8.
[12] Dartt DA. Control of mucin production by ocular surface epithelial cells. Exp Eye Res 2004;78:173–85.
[13] Kessler TL, Dartt DA. Neural stimulation of conjunctival goblet cell mucous secretion in rats. Adv Exp Med Biol 1994;350:393–8.
[14] Kessler TL, Mercer JH, McCarthy DM, Dartt DA. Stimulation of goblet cell mucous secretion by activation of nerves in rat conjunctiva. Curr Eye Res 1995;14:985–92.
[15] Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005;112:1790–4.
[16] Sall K, Stevenson OD, Mundorf TK, Reis BL. CsA Phase 3 Study Group. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. Ophthalmology 2000;107:631–9.
[17] Sheppard JD, Torkildsen GL, Lonsdale JD, D'Ambrosio Jr. FA, McLaurin EB, Eiferman RA, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology 2014;121:475–83.
[18] Tauber J, Karpecki P, Latkany R, Luchs J, Martel J, Sall K, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 Study. Ophthalmology 2015;122:2423–31.
[19] Kossler AL, Tse DT. Lacrimal nerve stimulation by a neurostimulator for tear production- a pilot study. oral presentation. Am Soc Ophthalmic Plast Reconstr Surg Fall Sci Symp November 2008.
[20] Kossler AL, Tse DT. Chronic stimulation of the lacrimal gland for enhanced tear production. Poster, association for research in vision and ophthalmology (ARVO). May 2009.
[21] Brinton M, Chung JL, Kossler AL, Kook KH, Loudin J, Franke M, et al. Electronic enhancement of tear secretion. J Neural Eng 2016;13:016006.
[22] Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. Clin Ophthalmol 2016;10:795–804.
[23] Sheppard JD, Torkildsen GL, Geffin JA, Dao J, Evans DG, Ousler GW, et al. Characterization of tear production in subjects with dry eye disease during intranasal tear neurostimulation: results from two pivotal clinical trials. Ocul Surf 2019;17:142–50.
[24] Gumus K, Schuetzle KL, Pflugfelder SC. Randomized, controlled, crossover trial comparing the impact of sham or intranasal neurostimulation on conjunctival goblet cell degranulation. Am J Ophthalmol 2017;177:159–68.
[25] Orrick B, Watson M, Angjeli E, Franke M, Holdbrook M, Ousler GW, et al. Quantitation of tear production by tear meniscus height following acute use of the intranasal tear neurostimulator. Investig Ophthalmol Vis Sci 2017;58. 2692.
[26] Cohn GS, Corbett D, Tenen A, Coroneo M, McAlister J, Craig JP, et al. Randomized, controlled, double masked, multicenter, pilot study evaluating safety and efficacy of intranasal neurostimulation for dry eye disease. Investig Ophthalmol Vis Sci 2019;60:147–53.
[27] Woodward A, Senchyna M, Franke M, Holdbrook M, Argueso P. Effect of intranasal neurostimulation on tear protein content in patients with dry eye. Investig Ophthalmol Vis Sci 2017;58. 2673.
[28] Dieckmann G, Kataguiri P, Pondelis N, Jamali A, Abbouda A, et al. In vivo confocal microscopy demonstrates intranasal neurostimulation-induced goblet cell alterations. Investig Ophthalmol Vis Sci 2017;58. 2694.
[29] Pondelis N, Dieckmann G, Kataguiri P, Abbouda A, Zeina S, Franke M, et al. Intranasal neurostimulator induces morphological changes in meibomian glands in patients with dry eye disease. Investig Ophthalmol Vis Sci 2017;58. 2235.
[30] Watson M, Angjeli E, Orrick B, Baba S, Franke M, Holdbrook M, et al. Effect of the intranasal tear neurostimulator on meibomian glands. Investig Ophthalmol Vis Sci 2017;58. 4387.
[31] Gumus K, Pflugfelder SC. Intranasal tear neurostimulation: an emerging concept in the treatment of dry eye. Int Ophthalmol Clin 2017;57:101–8.