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SECTION: Cornea
Reviewing Code: 1610 Corneal neuropathy and ocular pain

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Title: Effects of a topical ophthalmic cooling device for chronic ocular surface pain on the ocular surface and corneal nerves

Purpose: A safe and effective treatment for chronic ocular surface pain (COSP) is a major unmet need. This prospective, single-center feasibility trial (clinicaltrials.gov NCT07059754) investigated the effect of a novel topical ophthalmic cooling device (ETX-4143; EyeCool Therapeutics, USA) on ocular surface parameters and corneal nerves, in COSP patients.

Methods: Five adults (mean±SD age 66.4±9.9 yrs; 3 female/2 male) with COSP symptoms for ≥3 months were recruited. The more symptomatic (study) eye was treated with the ETX-4143 Device, involving 2 metallic probes, internally cooled by a -20^{o}C fluid, applied to the conjunctiva over the long ciliary nerves, for 4 mins, with a fellow eye untreated control. Ocular symptoms, visual acuity, tear osmolarity, non-contact corneal esthesiometry, and corneal fluorescein staining were quantified. *In vivo* confocal microscopy (Heidelberg HRT-3 with Rostock Module) was used to image the central epithelial (sub-basal) nerve plexus, from which corneal nerve fiber length [CNFL, mm/mm^2], nerve fiber density [CNFD, fibers/mm^2], nerve branch density [CNBD, branches/mm^2], total branch density [CTBD, branch points/mm^2], nerve fiber area [CNFA, mm^2/mm^2], nerve fiber width [CNFW, mm/mm^2], and nerve fractal dimension [CNFrD] were quantified using ACCMetrics. Stromal nerves were assessed from volume scans of the peripheral cornea and limbus. Measures were taken at baseline and 2-weeks post-treatment. Statistical analyses involved repeated-measures ANOVA.

Results: Clinical ocular surface signs and corneal nerve parameters were similar across visits and between eyes (study vs control); there was no interaction effect for time*condition (Table 1, Figure 1); p>0.05 for all comparisons. Eye pain was lower, relative to baseline, quantified using a Visual Analog Scale (mean change -52 units, 95%CI -99.8 to -4.2, p=0.04) and the Eye Pain Severity Module of the Chronic Ocular Pain Questionnaire (-4.4 units, 95%CI -7.4, -1.4, p=0.02). Corneal stromal nerves were visualized in each eye, at both visits.

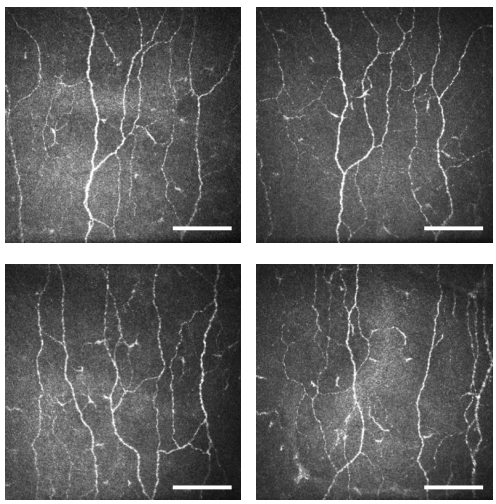
Conclusions: Ocular surface integrity and corneal nerve architecture are maintained 2 weeks after ETX-4143, lending support to its safety as a COSP treatment.

Table 1. Main and interaction effects of time and condition on clinical and corneal nerve parameters

Parameter	Study eye (n=5)	Control eye (n=5)	Time (Visits)	Condition (Study eye and fellow	Time*Condition

							eye)			
	Baseline (Mean ± SD)	2-weeks post-treatment (Mean ± SD)	Baseline (Mean ± SD)	2-weeks post-treatment (Mean ± SD)	F	p-value	F	p-value	F	p-value
Best corrected visual acuity (logMAR)	0.31 ± 0.40	0.24 ± 0.44	-0.03 ± 0.11	-0.04 ± 0.08	2.54	0.19	2.65	0.18	0.93	0.39
Tear osmolarity (mOsm/L)	305.0 ± 13.0	296.6 ± 16.1	297.2 ± 8.3	292.0 ± 7.5	3.25	0.15	5.10	0.09	0.10	0.77
Non-contact corneal aesthesiometry (mBar)	0.29 ± 0.38	0.17 ± 0.14	0.09 ± 0.08	0.19 ± 0.18	0.27	0.63	0.28	0.63	1.20	0.34
Corneal fluorescein staining (Oxford scale, 0 to 5)	1.3 ± 1.1	1.1 ± 0.7	1.3 ± 1.4	1.6 ± 1.2	0.59	0.49	0.03	0.88	1.43	0.30
Corneal nerve fiber length (CNFL, mm/mm^2)	13.2 ± 3.3	12.6 ± 3.7	13.1 ± 2.0	12.5 ± 2.8	0.71	0.45	0.06	0.82	0.90 x 10^{-5}	0.99
Corneal nerve fiber density (CNFD, fibers/mm^2)	22.3 ± 5.2	20.3 ± 6.2	21.5 ± 2.9	21.5 ± 4.7	0.90	0.40	0.03	0.87	4.53	0.10
Corneal nerve branch density (CNBD, branches/mm^2)	27.1 ± 15.6	28.4 ± 22.3	28.3 ± 15.1	23.4 ± 12.9	1.78	0.25	0.40	0.56	1.36	0.31
Corneal nerve total branch density (CTBD, branch points/mm^2)	42.3 ± 18.5	41.7 ± 29.5	38.7 ± 19.3	36.2 ± 21.1	0.19	0.69	1.91	0.24	0.13	0.74
Corneal nerve fiber area (CNFA, mm^2/mm^2)	0.005 ± 0.001	0.005 ± 0.002	0.005 ± 0.001	0.005 ± 0.002	0.02	0.90	0.13	0.74	0.70	0.45
Corneal nerve fiber width (CNFW, mm/mm^2)	0.0202 ± 0.0007	0.0203 ± 0.0004	0.0196 ± 0.0009	0.0198 ± 0.0005	0.36	0.58	2.98	0.16	0.01	0.92
Corneal nerve fractal dimension (CNFrD)	1.48 ± 0.04	1.46 ± 0.06	1.47 ± 0.03	1.47 ± 0.04	0.57	0.49	0.16	0.71	0.96	0.38

Figure 1. Representative central corneal IVCM images



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