INTRODUCTION

The cornea is the most densely innervated tissue in the body. Corneal nerves play a pivotal role in maintaining ocular surface health by detecting noxious stimuli, inducing the blink reflex, promoting tear secretion, supporting limbal stem cell function, and releasing neurotrophic factors for epithelial integrity, proliferation, and wound healing.1,2 A variety of
ocular and systemic conditions can adversely impact corneal nerves, including dry eye, infectious keratitis, glaucoma, ocular surgery, and diabetes mellitus.1–5 Regardless of the etiology, reduced corneal sensitivity (or corneal hypoesthesia) can lead to serious detrimental effects such as aqueous tear deficiency and neurotrophic keratopathy, a vision-threatening condition in which persistent corneal erosions/ulcerations can rapidly progress to stromal melting or corneal perforation.1

Transscleral cyclophotocoagulation (TSCPC) is a surgical modality commonly used in human and veterinary patients for management of glaucoma. The procedure reduces aqueous humor production by targeting the ciliary body, and is generally indicated when medical management fails to control intraocular pressure (IOP) in painful visual eyes.6–8 Standard diode laser with continuous-wave emission at 810 nm (CW-TSCPC) is successful in lowering IOP in canine patients,6–8 but adverse effects often develop post-operatively given pronounced tissue disruption and collateral damage from the laser procedure. Such complications affect the inside of the globe (eg, uveitis, hyphema, cataract formation, retinal detachment)6–8 but also the ocular surface (eg, corneal ulcers, dry eye). The latter is explained by disruption of corneal nerves, a finding demonstrated clinically and histologically by Weigt and colleagues on healthy canine eyes undergoing Nd:YAG CW-TSCPC.9 Micropulse transscleral cyclophotocoagulation (MP-TSCPC) offers a “gentler” alternative to standard diode laser in patients with glaucomatous.10–16 The pulsatile nature of the micropulse laser theoretically reduces collateral damage by allowing surrounding tissues to cool during “off-cycles”.12 Corneal sensitivity was measured in a recent canine study10 and a case report of two human patients,17 but this information is lacking in the majority of reports describing MP-TSCPC for glaucoma management.12–16

The main purpose of the study was to describe the incidence of corneal hypoesthesia and related complications (ie, aqueous tear deficiency, neurotrophic keratopathy) following MP-TSCPC in dogs. A secondary objective was to identify potential risk factors for developing post-operative ocular surface complications, in order to guide clinicians with patients’ selection and owners’ education. In particular, we investigated the effects of age, skull conformation, glaucoma duration, and laser energy given their presumed influence on corneal sensitivity.5,9,18,19

2 | MATERIALS AND METHODS

2.1 | Animals and laser procedure

Patients included in the study were part of previous prospective studies that evaluated control of intraocular pressure and vision following MP-TSCPC in dogs.10,11 Here, the medical records were screened for information pertaining to corneal sensitivity and aqueous tear production at baseline and post-operative visits. Eighteen dogs (n = 18 eyes) were recruited for the study, presented to Iowa State University’s Lloyd Veterinary Medical Center (ISU-LVMC, n = 13) or Long Island Veterinary Specialists (LIVS, n = 5) for management of glaucoma with the MicroPulse™ technology (Cyclo G6 Glaucoma Laser System, Iridex Corp). Details of each patient are described in Table 1. Micropulse transscleral cyclophotocoagulation (MP-TSCPC) was performed as previously described.10,11 Briefly, dogs were either sedated (n = 9) or anesthetized (n = 9), 2.5% hypromellose ophthalmic solution (Gonak, Akorn Inc) was instilled on the ocular surface for lubrication, the laser probe was positioned 1 mm posterior to the limbus, and a slow “sweeping motion” was used to treat the dorsal and ventral hemispheres while avoiding the 3 and 9 o’clock positions. The laser duty cycle was set to 31.3%, but the laser energy and treatment duration varied among patients (Table 1). The total number of procedures evaluated in this study is n = 24 as MP-TSCPC was repeated in 5 dogs (once in 4 dogs and twice in 1 dog) with 23-189 days between repeated treatments. None of the dogs had a temporary tarsorrhaphy placed at completion of surgery. Post-operative care varied among patients but generally included topical lubrication, topical anti-glaucoma, and oral anti-inflammatory medications.10,11

2.2 | Corneal esthesiometry and tear production

A Cochet-Bonnet aesthesiometer (Luneau Ophthalmologie) with a 0.12-mm diameter monofilament nylon and 0.0113 mm² surface was used to test the corneal sensitivity in each patient (pressure range 0.4-15.9 g/mm²). Starting at a filament length of 6 cm, the nylon fiber was held perpendicular to the ocular surface and advanced toward the central cornea until a slight bend in the fiber was noted. The filament was shortened in increments of 0.5 cm, and corneal tactile sensation (CTS) was recorded as the length (in cm) that elicited consistent blink reflex in at least 3 out of 5 attempts. Corneal sensitivity was measured before MP-TSCPC in all eyes (baseline), and in ≥2 post-operative visits at the following times: 0-7 days, 1 week, 1 week-1 month, 1 month, 1-3 months, 3 months, 6 months, and >6 months (“last visit”). Tear production was assessed with Schirmer tear test-1 (STT-1) by placing a standardized strip (Eye Care Product Manufacturing LLC) in the lateral lower conjunctival fornix for 1 minute. CTS and STT-1 were not available at all time points in each eye because some dogs were lost to follow-up, some eyes underwent a salvage procedure (enucleation, chemical ablation of ciliary body) due to uncontrolled glaucoma, or the data were not recorded by the clinician (retrospective evaluation).

2.3 | Data analysis

Normality of the data was assessed with the Shapiro-Wilk test. Data were normally distributed (P > .05), so parametric
3 | RESULTS

Clinical details of patients and CTS values at each visit are described in Table 1. Of note, MP-TSCPC was performed as the sole procedure in 22/24 occasions, or in combination with Ahmed gonio-implantation (n = 1; second occasion of case #11) or phacoemulsification (n = 1; case #15). Overall, corneal sensitivity decreased in 16/18 dogs (89%) and 22/24 laser procedures (92%), a reduction noted within a week in all patients. Mean ± SD CTS was 2.54 ± 0.90 cm at baseline (1.8 ± 0.9 cm in brachycephalic dogs, 2.8 ± 0.8 cm in non-brachycephalic dogs), 1.45 ± 0.88 cm at 0-7 days (day 1 in 7/11 measurements, days 3-6 in the others), 1.43 ± 0.85 cm at 1 week, 1.88 ± 1.06 cm at 1 week-1 month, 2.21 ± 1.16 cm at 1 month, 2.00 ± 1.27 cm at 1 month-3 months, 2.18 ± 1.15 cm at 3 months, 2.15 ± 1.06 cm at 6 months, and 1.80 ± 1.15 cm at the last visit. These changes correspond to an average decrease in corneal sensitivity of 10%-42% compared with baseline (up to 100% in 4 dogs), which was statistically significant at 1 week (P = .012) but not at other visits (P ≥ .089; Figure 1). Patient’s age was not associated with CTS at baseline (P = .203), and differences in CTS between younger (<8 years) and older (≥8 years) dogs were not detected at any visit (P ≥ .115). Similarly, glaucoma duration prior to MP-TSCPC (≤30 days or >30 days) did not significantly impact CTS at any visit (P ≥ .095; Figure 2A), nor did the laser power (≤2500 mW or >2500 mW; P ≥ .121) or total laser energy delivered to the eye (≤260 J or >260 J; P ≥ .347; Figure 2B). Brachycephalic dogs had significantly lower CTS than nonbrachycephalic dogs at baseline and all other visits (P ≤ .048) except for the last recheck exam (P = .208; Figure 2C).

3.1 | Neurotrophic corneal ulcers

The average CTS was lower in ulcerated vs. nonulcerated eyes at all visits (Figure 2D); differences approached significance at baseline (P = .060) and reached statistical significance at 0-7 days (P = .036), 1 week (P = .010), 3 months (P = .007), and 6 months (P = .012). In total, superficial corneal ulcers developed in 6/18 dogs (33.3%) including 4 eyes of brachycephalic dogs (#2, 3, 5, 13) and 2 eyes of nonbrachycephalic dogs (#15, 16). Brachycephalic dogs were significantly more likely to develop a corneal ulcer post-operatively compared with nonbrachycephalic dogs (P = .003). These neurotrophic ulcers were noted 8.2 ± 6.0 days (3-20 days) following MP-TSCPC, and resolved within 26.7 ± 13.7 days (16-53 days). The appearance of the corneal ulcers at a single visit is shown in Figure 3 (cases # 5, 15, 16) while the clinical pictures of case # 2 at sequential visits are shown in Figure 4. Photographs of case #3 can be found in a previous publication by Sebbag et al.10

3.2 | Recovery of corneal sensitivity

Out of 24 laser procedures, CTS did not decrease in n = 2 eyes (both nonbrachycephalic dogs), CTS decreased and never returned to baseline in n = 9 eyes (5 brachycephalic, 4 non-brachycephalic), and CTS decreased but returned to baseline...
in n = 13 eyes (1 brachycephalic, 12 nonbrachycephalic) with a mean ± SD (range) of 54 ± 61 days (8–180 days). This represents 50% of dogs (8/16) that did not recover full corneal sensitivity following MP-TSCPC, even months after the procedure. The probability for CTS to fully recover after MP-TSCPC was significantly lower in brachycephalic dogs compared with nonbrachycephalic dogs (P = .015), but was not affected by repeated procedures (P = .615).

FIGURE 2 Mean + standard deviation CTS (in cm) at baseline and subsequent recheck visits following MP-TSCPC in 18 dogs, depicting data from different glaucoma durations prior to laser therapy (A), different laser energy received per eye (B), different skull conformation (C), and absence/presence of post-operative corneal ulceration (D). An asterisk (*) indicates statistical difference between both groups at the specific visit.

FIGURE 3 Clinical pictures of neurotrophic corneal ulcers in dogs treated with MP-TSCPC. (A) Case #5—the ulcer developed 20 d post-operatively (CTS = 1.0 cm) and healed within 16 d. (B) Case #15—the ulcer developed 8 d post-operatively (CTS = 2.0 cm) and healed within 17 d. (C) Case #16—the ulcer developed 6 d post-operatively (CTS = 0 cm) and healed within 28 d.
Aqueous tear production was normal in all patients before the procedure, with STT-1 values ranging from 15-27 mm/min (20.9 ± 4.6 mm/min). Following MP-TSCPC, STT-1 values decreased below 15 mm/min in 8/18 dogs (44%) within 5-270 days (73.5 ± 100.6 days); in these patients, STT-1 decreased rapidly then gradually increased over time (Figure 5), although STT-1 values were not significantly different compared with baseline (P = .233). Clinical signs consistent with keratoconjunctivitis sicca (KCS) were noted in 2/18 dogs (11%). In case #12, KCS developed 6 weeks following MP-TSCPC (4 mm/min) and responded rapidly to twice-daily 1% cyclosporine (17 mm/min by 3 weeks). In case #15, KCS developed 9 months post-operatively (6 mm/min) and responded slowly to twice-daily 0.2% cyclosporine (8 mm/min by 1 month and >10 mm/min by 5 months). Of note, corneal hypoesthesia did not systematically result in aqueous deficiency in all cases; out of 14 dogs with corneal hypoesthesia and available post-operative STT-1 measurements, only 7/14 (50%) dogs had STT-1 values <15 mm/min at follow-up visit(s).

FIGURE 4 Clinical pictures of a neurotrophic corneal ulcer (Case #2) that developed 3 d following MP-TSCPC, depicting the progression at 25 d (A; CTS = 0 cm), 35 d (B; CTS = 1 cm), and 46 d (C; CTS = 1.5 cm) post-operatively.

FIGURE 5 Mean ± standard deviation Schirmer tear test-1 values (in mm/min) in 8 dogs that developed aqueous tear deficiency (<15 mm/min) at subsequent recheck visit(s) following MP-TSCPC.

DISCUSSION

The present study showed that MP-TSCPC decreased corneal sensitivity in 16/18 (89%) dogs affected with glaucoma, a reduction that was rapid (≤7 days) and pronounced (10%-42% on average, up to 100%). Dogs undergoing CW-TSCPC experience a similar loss of corneal sensation (by 27.4% on average), noted on the first day after laser treatment and persistent throughout the 14-day monitoring period.9 Corneal denervation from MP-TSCPC resulted in two serious adverse effects in our canine patients: aqueous tear deficiency and neurotrophic corneal ulcers. Reduced tear production (STT-1 < 15 mm/min) and clinical signs consistent with KCS developed in 8/18 dogs (44%) and 2/18 dogs (11%), respectively. STT-1 provides an estimate of the total tear production (basal, reflex, and residual). Corneal nerves influence all components of tear secretion,20 although reduction in corneal sensitivity likely affects reflex tearing the most. Corneal sensitivity was positively correlated to reflex tearing in various species, though it only explained 7.1% of the variation in tear production.21 Of note, decreased tear production was not observed in healthy canine eyes undergoing CW-TSCPC, although follow-up was limited to 2 weeks as the eyes were harvested for histologic evaluation of corneal nerves.9 Together, these findings underscore the importance to monitor STT-1 long-term, use frequent lubrication and consider prophylactic lacrimostimulants post-operatively.

Further, 6/18 dogs (33%) developed a corneal ulcer after MP-TSCPC, a complication that was recently described in two human patients.17 This prevalence of post-operative corneal ulceration is unacceptably high, but somewhat lower than traditional diode laser. Using CW-TSCPC, Weigt and colleagues reported corneal ulcerations in 9/15 glaucomatous dogs (60%), a complication that required
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1 week to 3 months to heal. In our patients, the ulcers healed within 2 weeks-2 months (average 26.7 days) but often resulted in pronounced corneal scarring (examples in Figures 3B and 4C). Poor wound healing is likely explained by the poor recovery of corneal sensitivity following nerve injury. Indeed, when corneal sensitivity decreased following MP-TSCPC (22/24 procedures), CTS returned to baseline values (average 54 days) in merely 13/22 occasions (59%) while CTS never fully recovered in 9/22 occasions (41%). Brachycephalic dogs had lower corneal sensitivity, lower likelihood to regain baseline CTS, and higher chance to develop a corneal ulcer compared with nonbrachycephalic dogs. However, other risk factors evaluated herein (age, laser power, total energy delivered, glaucoma duration) were not found to be significant. Although corneal sensitivity decreases with age in humans, beginning in the periphery and progressing centrally, we did not detect an effect of age on CTS values at baseline or subsequent visits. This may be due to low sample size or lack of testing peripheral corneal sensitivity in our canine patients.

We also noted that post-operative CTS was not affected by the laser energy settings (mW) or total energy delivered to dogs (J/eye). Nerve damage could theoretically be reduced with lower energy settings and decreased exposure time from the standard diode laser, but such speculations may not be true with MicroPulse™ since the technology allows tissues to “cool off” between laser pulses. It is interesting to note, however, that corneal sensitivity and tear production are not affected when using a different diode laser (670-nm) that delivers a much lower energy (430 mW) compared with MP-TSCPC. With chronicity, glaucoma leads to globe stretching (buphthalmos) and scleral thinning that can damage nerves and result in corneal hypoesthesia, a finding confirmed in dogs undergoing evisceration surgery for end-stage eyes. In our study, there was no significant effect of glaucoma duration on pre- or post-operative corneal sensitivity, although the cutoff for “long-term” glaucoma was merely set to 30 days in order to obtain sufficient eyes in each group. None of the eyes treated with MP-TSCPC were grossly buphthalmic at baseline, although caliper or ultrasonographic measurements were not obtained. Importantly, we suspect that corneal hypoesthesia and related complications (aqueous deficiency, neurotrophic ulcers) would be more prevalent and severe in dogs that are diabetic or dogs that undergo ocular surgery concurrently to MP-TSCPC. None of our patients had diabetes mellitus—a condition known to cause corneal hypoesthesia due to peripheral neuropathy—and only n = 2 of our patients underwent another concurrent surgery. In humans, uneventful phacoemulsification can markedly reduce the subbasal nerve plexus density and require 4 to 8 months to restore normal corneal sensitivity.

The exact mechanism of corneal denervation from TSCPC is unknown. Wallerian degeneration of corneal nerves was demonstrated in rabbits undergoing cryoablation of the ciliary body, and the same is likely true for diode laser. In fact, the neuronal damage could be direct (ie, laser targeting the nerve) but also indirect from excessive heat. Thermal injury explains why corneal denervation is noted with TSCPC despite avoidance of the 3 and 9 o’clock positions (where the long ciliary nerves are located), and why neurotrophic ulcers can develop when diode laser is not targeting the sclera, as exemplified by pars plana laser retinopexy or trans-pupillary laser retinopexy (L. Sebbag and JS. Sapienza personal experience, unpublished data). Another hypothesis is the inadvertent injury to the perilimbal nerve plexus if the laser probe is placed too anteriorly toward the cornea. Last, corneal denervation may be partially caused, or exacerbated, by the frequent peri-operative use of topical medications, either related to the preservative benzalkonium chloride or the drug itself (ie, timolol, dorzolamide, latanoprost).

Regardless of the exact etiopathogenesis, corneal denervation increases the risk of developing serious ocular surface complications, as noted in our canine patients. Indeed, neuronal deficit plays a major role in development of ocular surface disease as corneal denervation leads to one or several of the following risk factors: (a) Reduced tear production due to disruption of the afferent pathway of lacrimation, resulting in reduced corneo-conjunctival lubrication but also reduced tear clearance, with consequent accumulation of toxic agents and pro-inflammatory cytokines on the ocular surface; (b) Loss of trophic neuro-peptides secreted by corneal nerves, slowing down the centripetal migration of new epithelial cells and causing older, pre-exfoliating cells to remain in the center of the cornea; and (c) Diminished blink frequency and protective blink reflex.

In the present study, a combination of these factors likely resulted in corneal epithelial defects following MP-TSCPC. The lesions had characteristics of neurotrophic ulcers: Most dogs were not overly painful, the corneal sensitivity was reduced, defects were located in the axial cornea, and epithelial edges were loose with sub-epithelial seepage of fluorescein dye. Patients may be quite comfortable given the reduced/abolished corneal sensitivity, but the ocular surface disease is significant and can rapidly progress to stromal melting or corneal perforation. Clinically, neurotrophic keratopathy can be characterized in humans as mild (epithelial changes without epithelial defect), moderate (epithelial defect without stromal defect), or severe (stromal involvement). In our canine patients, n = 2 and n = 3 ulcers would be characterized as moderate and severe, respectively, although we failed to record subtle epithelial changes (mild grade) in a consistent manner. Hence, the prevalence of neurotrophic keratopathy following MP-TSCPC is likely underestimated in the present study. Once a neurotrophic ulcer develops, re-epithelialization time is often prolonged (up to 53 days in our cases) as the environment is not conducive to normal wound healing. In
particular, supportive corneal nerves take months to years to regenerate following injury, as demonstrated in rabbits undergoing a 180-degree limbal incision or human patients undergoing corneal cross-linking, corneal transplantation, and laser-assisted in situ keratomileusis.

Guidelines for managing neurotrophic keratopathy in humans were recently summarized in a review article by Dua and colleagues. A variety of therapies can be used to promote healing of neurotrophic ulcers. Corneal debridement removes thickened epithelium and permits the more peripheral, healthier epithelium to continue its migration over the defect. A bandage contact lens protects the sick epithelium from the shearing forces of the eyelids. A tarsorrhaphy provides multiple benefits and is considered a cornerstone in the management of neurotrophic keratopathy: The procedure protects the cornea from the environment, reduces friction caused by eyelid movement, and conserves tear fluid on the ocular surface. Amniotic membrane eye drops and blood products such as autologous serum and platelet-rich plasma can be used topically to provide key elements for nerve regeneration and corneal wound healing (eg, nerve growth factor, substance P, epidermal growth factor, fibronectin). Of note, an ophthalmic solution containing recombinant nerve growth factor (Oxervate™ eye drops) has shown great promise in several clinical trials of neurotrophic keratopathy, and was recently approved by the FDA (August 2018); however, this medication is currently cost-prohibitive for the veterinary community. As a last resort, a novel surgical procedure called corneal neurtization can be used to reinnervate the cornea with donor sensory nerves from elsewhere in the body—the surgery is technically challenging but rapidly improves corneal sensation and ocular surface health.

In dogs, every effort should be made to prevent a neurotrophic ulcer to develop, as healing time is long (weeks-months) and significant corneal scarring can occur (Figures 3,4), even with appropriate therapy. Before surgery, clinicians should identify patients with high-risk factors (eg, brachycephalic dogs, diabetes mellitus) and, if possible, consider a procedure other than TSCPC for glaucoma management. During surgery, a constant drip of refrigerated saline can be used over the cornea to reduce thermal injury from the diode laser (S Kirschner, personal communication). After surgery, corneal protection can be achieved with a bandage contact lens and temporary tarsorrhaphy, and the following medications should be considered: frequent lubrication with preservative-free hyaluronic acid (or blood product), topical cyclosporine (improves lacrimation and corneo-conjunctival sensitivity), oral fish oil supplements (inhibit pro-inflammatory mediators and increase corneal nerve density), and oral tetracyclines (anti-inflammation and neuroprotection). The aforementioned prophylactic measures are solely based on evidence-based practice in humans and the authors' personal experience in dogs, and therefore require additional studies to confirm their usefulness. For instance, a tarsorrhaphy has theoretical advantages but may not be as beneficial to patients when used prophylactically rather than therapeutically. In a study by Blocker et al, 3 out of the 7 dogs that developed corneal ulceration post-evisceration had a temporary tarsorrhaphy placed at time of surgery.

Because of the retrospective nature of the study, not all variables were available for each patient at each visit. Similarly, the peri-operative management was not standardized among patients. The variability in pre- and post-operative medications (ie, type and frequency of anti-glaucoma medications) could have influenced corneal sensitivity, as well as the anesthesia or sedation utilized for MP-TSCPC (especially for the CTS measurements obtained on day 1 post-operatively), although evaluation of these effects was beyond the scope of our study. Importantly, information on corneal sensitivity and aqueous tear production was only available in the treated eye in most cases; future prospective studies should assess the contralateral (untreated) eye to provide paired comparison and thereby reduce variability related to diurnal variation, environmental conditions (eg, ambient humidity), and other factors (eg, general anesthesia). Another limitation is inherent to the Cochet-Bonnet esthesiometer, a diagnostic test that is subjective and highly variable. Even when striving to achieve 4% bend in the nylon thread when contacting the cornea, there are large variations in the pressure applied, so it is nearly impossible to standardize the amount of pressure applied. Hence, corneal sensitivity was described in the present study as the “corneal tactile sensation” and recorded as the filament length (in cm) rather than the pressure (g/mm²) required to elicit a blink response. Newer tools such as graded hyperosmotic solutions are being developed and could be useful to the veterinary community in the future.

In conclusion, corneal hypoesthesia is a common complication of MP-TSCPC in dogs, and can lead to serious adverse effects such as aqueous tear deficiency and neurotrophic corneal ulcers. Brachycephalic dogs represent a population at higher risk. Patients undergoing MP-TSCPC should receive frequent lubrication and close monitoring of ocular surface health for months following the procedure.

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