TITLE: A prospective study of the prevalence of corneal surface disease in dogs receiving prophylactic topical lubrication under general anesthesia

AUTHORS: Charlotte Dawson, Rick F. Sanchez

JOURNAL TITLE: VETERINARY OPHTHALMOLOGY

PUBLISHER: Wiley

PUBLICATION DATE: March 2016

DOI: 10.1111/vop.12272

A PROSPECTIVE STUDY OF THE PREVALENCE OF CORNEAL SURFACE DISEASE IN DOGS RECEIVING PROPHYLACTIC TOPICAL LUBRICATION UNDER GENERAL ANESTHESIA.

Charlotte Dawson* BVetMed MRCVS and Rick F Sanchez* BSciBiol, DVM, DipECVO, FHEA, MRCVS

The Royal Veterinary College, Department of Clinical Science and Services, Hawkshead lane, North Mymms, Herts, AL9 7TA, United Kingdom

*Ophthalmology Service

Running title: Corneal surface disease and GA in dogs

Abstract:

Objective: To identify the prevalence of corneal ulceration in dogs receiving prophylactic gel lubrication under general anesthesia (GA).

Materials and Methods: An ophthalmic examination was performed before premedication and 24h after GA in 100 dogs (199 eyes) undergoing non-ophthalmic procedures. Individuals with known pre-existing ocular surface conditions were excluded. An ocular lubricating gel containing carmellose sodium was applied by the anesthetist at induction and every 2-4h until extubation. Logistic regression analysis was used to calculate risk factors for ulcerative disease, including signalment, length of GA, patient position, procedure performed, pre- and post-GA ophthalmic exam findings and admitting service. A Wilcoxon rank sum test compared pre- and post-GA Schirmer Tear Test-1 (STT-1) values.

Results: One dog (0.5% of total eyes) developed fluorescein stain uptake consistent with superficial corneal ulceration that resolved within 48h with supportive treatment. Twenty-five (18.6% of total eyes) developed a faint, patchy corneal uptake of stain in the axial cornea that was consistent with epithelial erosion. All erosions resolved with lubrication 24h later. The decrease in STT-1 readings at 24h post-GA was statistically significant from those pre-GA($P < 0.001$). No significant risk factors for corneal erosion/ulceration were identified.

Conclusions: The results of this study show that a basic protocol of prophylactic lubrication during GA was associated with a low prevalence of corneal ulceration but a higher prevalence of epithelial erosion. In addition, the study supports the need for post-GA corneal examination.

 Word count: 231

Introduction:

Corneal epithelial defects are a known consequence of the failure to apply topical lubrication during general anesthesia (GA) in human beings and dogs. [1-3] The prevalence of corneal epithelial defects in humans following GA is reported to be up to 10% in unprotected eyes and as little as 0.17% in eyes protected with lubricants or eyelid taping. [1,4] In addition, a study in humans found that for reasons not understood, older patients and those undergoing longer GA suffer a higher incidence of corneal ulceration.[5] There is one veterinary paper that provides guidelines for ocular lubrication in dogs, but it does not report the incidence of corneal lesions after GA.[6] A recent retrospective study in 14 dogs reported a prevalence of corneal ulceration of 1.9% relating to GA[7]. However, there are no similar, prospective studies with a larger group of animals in the veterinary literature. A prospective study that reported STT-1 readings in dogs pre- and post-GA did not mention the presence or absence of corneal surface disease.[8] A similar prospective study in dogs assessing tear production pre- and post-sedation with medetomidine or a medetomidine-butorphanol combination described a decrease in STT-1 readings that returned to near pre-sedation values within 15 minutes after reversal of sedation.[9] Recommendations were made for the use of topical lubrication in association with sedation but findings on corneal surface health post-sedation were not reported.[9]

The aim of the current prospective study was to investigate risk factors for corneal surface disease, such as length of anesthesia and patient positioning, in patients free from corneal ulcerative disease and under the protection of the widely available lubricating gel

carmellose sodium, applied immediately after GA induction and every 2-4h during anesthesia until extubation.

Materials and Methods:

This study was approved by the Royal Veterinary College Ethics Committee. An ophthalmic examination was performed in 100 dogs (199 eyes) by the same investigator (CD) under supervision of an ECVO Diplomate (RFS). This included Schirmer Tear Test -1 (STT-1), slit lamp biomicroscopy and fluorescein staining, and was performed before premedication for GA and 24h after GA. Individuals with known preexisting corneal ulceration, those on medical management for KCS, those with a history of ophthalmic disease and individuals with facial nerve paralysis were excluded from the study.

Anesthetic agents were used in different combinations for each patient depending on patient requirements. Premedication agents included acepromazine, medetomidine and opioid analgesia agents including methadone and buprenorphine. Induction agents included propofol and alfaxalone. Inhalational maintenance agents were either isofluorane or sevofluorane.

A total of 0.2mls, equal to half a vial of a sterile, preservative free ocular lubricant of carmellose sodium (Celluvisc® 1% Allergan, 0.4ml vial, USA) was applied topically onto the conjunctival sac and ocular surface of each eye of each patient by the attending anesthetist, immediately after induction. Anesthetists were masked to the study and continued as they normally would without the knowledge of this investigation. This was a

clinical study and there was a range of timings the lubricant was reapplied by the anesthetist because it depended on patient position, access to the head and stability of the GA. Patient signalment, ophthalmic history, length of GA, position on the operating table, procedure performed, admitting service and pre- as well as post-GA ophthalmic exam findings were recorded.

Corneal erosion was defined as superficial epithelial damage with no penetration into the basement membrane of the epithelium that was seen as an obvious, but patchy uptake of fluorescein staining. By contrast, corneal ulceration was defined as stromal exposure with an obvious, strong uptake of fluorescein stain[10].

Patients that developed corneal changes consistent with a corneal erosive lesion or corneal ulceration received supportive medical management in the form of topical ocular lubrication every 4h. The patient with corneal ulceration also had fusidic acid (Fucithalmic® gel, Dechra, UK) applied topically twice daily. All patients were examined once daily until the corneal lesion resolved.

Descriptive statistics, Wilcoxon Sum Rank Test for Schirmer Tear Test -1 values, and binomial logistic regression were performed. Statistical analysis utilized the statistical software SPSS version 20 (SPSS IBM, New York, USA).

Risk factors assessed were: age, breed, sex, pre-GA STT-1 readings, ophthalmic exam findings, post-GA STT-1 readings, GA time in minutes, position on operating table and

admitting service. These were entered into the binomial logistic regression. Patients in risk factors groups with a small sample size, were grouped and entered into the binomial logistic regression as follows:

- Breed groups: Brachycephalic and non-brachycephalic breeds
- Sex groups: Male/male neutered and female/female neutered
- Ophthalmic exam findings groups: No ocular abnormalities, and corneal and eyelid abnormalities, and other
- Admitting service groups: Neurology, and Orthopedics, and Soft Tissue services

Schirmer tear test-1 readings, GA time and age are continuous data, and thus were not subdivided and group-entered in the binomial logistic regression.

Results:

One hundred dogs (199 eyes) were prospectively recruited in the study. Median age was 64 months (range 3.5 to 384months). There were 66 males and 34 females. There were a variety of breeds with cross breed being the most commonly represented. Skull shapes included 20 brachycephalics, 15 dolichocephalics and 65 mesaticephalics.

The median GA time was 157.5min (range 15 to 465min) and the median pre- and post-GA STT-1 readings were 18mm/min (range 4 to 27mm/min) and 16mm/min (range 0 to 25mm/min), respectively. Pre-GA, there were 2 patients with STT-1 readings less than 10mm/min, 18 with readings of 11-15mm/min and 80 with more than 15mm/min. Post-GA, there were 14 patients with STT-1 readings less than 10mm/min, 21 with readings of

11-15mm/min and 65 with more than 15mm/min (Table 1). Fifty-eight of the 100 patients remained in the same group pre- and post-GA and from the results it was not possible to predict which individuals would have a lower post-STT-1 reading. None of the patients with STT-1 readings less than 10mm/min pre-GA had visible corneal pathology or other signs consistent with KCS.

The ophthalmic examination findings in dogs pre-GA were as follows: cataracts (n= 2), corneal scarring (n= 2), distichiasis (n= 14), distichiasis and entropion (n=1), ectropion (n=2), endothelial disease (n=1), entropion (n=2), eyelid mass (n=2), corneal crystalline deposit (n=2), medial canthal entropion (n=10), medial canthal trichiasis (n=1), persistent pupillary membranes (n=1) or none (n= 60). These findings remained unchanged post-GA with the exception of the addition of corneal ulceration and/or erosion in affected cases. For statistical purposes these findings were grouped as: none (60 dogs), eyelid or corneal abnormalities (37 dogs) and other (3 dogs).

The length of GA was split into two groups: GA less than 2 hours (<2h) and GA longer or equal to 2 hours (≥2h). Thirty-nine anesthetics lasted <2h and 61 anesthetics lasted ≥2h. In the <2h group lubrication was applied only once at the beginning of the anesthetic event. These patients formed the lubrication group, L-A. In the ≥2h group, lubrication was applied at the beginning of the anesthetic event, and it was repeated if body and drape position allowed access to the eyes. Repeat lubrication was possible every 2h in 53/61 patients, which formed the lubrication group L-B. The remaining 8/61 of the patients had lubrication every 2-4h because their body and drape

position did not allow more regular access to their eyes, and they were put into a separate lubrication group (L-C). In total, 39.2% of 199 eyes were lubricated once during a GA <2h (L-A group), 53.3% of 199 eyes were lubricated every 2 hours (L-B group) and 7.5% of 199 eyes were lubricated every 2-4 hours (L-C group).

Corneal surface disease was observed in 38 of the total 199 (19.1%) eyes. One eye (0.5% of total eyes) developed fluorescein stain uptake consistent with superficial corneal ulceration. Thirty-seven eyes (18.6 % of total eyes) developed a faint, patchy corneal uptake of fluorescein stain in the axial cornea that was consistent with epithelial erosion.

The incidence of corneal surface disease was compared between the different lubrication groups. Of those eyes lubricated once during a GA <2h (L-A group), 15 developed corneal erosions and one developed a corneal ulcer. Of those eyes lubricated every 2 hours (L-B group) 19 developed a corneal erosion. Of those eyes lubricated every 2-4 hours (L-C group) three developed a corneal erosion. No eyes in the L-B or L-C groups developed a corneal ulcer. Thus, the incidence of corneal surface disease between the three groups was similar: 20.5% in the L-A group, 17.9% in the L-B group and 20.0% in the L-C group.

Of the 26 dogs that developed corneal surface disease, seven were brachycephalic breeds that included: two French Bulldogs, one English Bulldog, one Pug, one Cavalier King Charles Spaniel, one Lhaso Apso and one Chihuahua. None of these brachycephalic patients had low STT-1 pre-GA readings, except for one French Bulldog.

The single corneal ulcer diagnosed in this study developed in a miniature Schnauzer dog

that was lubricated once (L-A group) and was in sternal recumbency under GA during a total time of 72 minutes. This patient had been diagnosed pre-GA with a single distichia that pointed away from the surface of the eye. The ulcer resolved within 48h with supportive treatment every 4h with the same topical ocular lubricant used during the GA and twice daily fusidic acid. This patient was examined once daily until the corneal lesion resolved. The epithelial erosions diagnosed in 25 dogs resolved within 24h with supportive treatment administered every 4h with the same topical ocular lubricant used during the GA.

There were a large variety of surgical procedures for which the animals in this study underwent GA (Table 2). Although risk factors, such as duration of GA, were entered into the binominal logistic regression along with all the other risk factors, surgical procedures were grouped based on the service that admitted the patient. This resulted in 58 admissions by the Neurology service, 23 by the Orthopedic service and 19 by the Soft Tissue service. The shortest GA time was for cerebrospinal fluid collection at 15 minutes and the longest GA time was for a fracture fixation at 465 minutes. Neither the length of GA nor the service admitted were a risk factor for corneal erosion or ulceration.

The binomial logistic regression analysis demonstrated that none of the risk factors studied had a significant association with corneal erosion or ulceration (Table 3). The Wilcoxon rank sum test demonstrated a significant ($P < 0.001$) decrease in STT-1 readings 24h post-GA versus pre-GA measurements (Table 1).

Discussion:

Hospitalized patients, particularly those in intensive care,[11] are at risk of decreased tear production due to the effect of any number of medications[9,12-14] and GA.[6,8,15,16] Decreased tear production is a known risk factor for corneal ulceration and erosion. [3,17,18]

The present study demonstrated that 0.5% of eyes developed a superficial corneal ulcer and that 18.6% of eyes developed a corneal erosion in patients during GA while under the protection of a routine, prophylactic, topical lubrication gel protocol. It also highlighted the importance of performing a post-GA corneal examination with fluorescein staining in all patients to detect possible corneal surface ulcerative disease, and to perform post-GA STT-1 to detect possible decreased tear production.

Risk factors for corneal ulcerative disease in association with GA identified in human studies include lengthy surgical procedures, lateral positioning, head or neck surgery, and increased patient age. [19-21] The current study considered similar risk factors and found that none were associated with an increase in surface ocular disease. A higher rate of corneal injuries is reported in human patients when student nurse anesthetists are involved. [21] The level of experience of the anesthetist was not recorded in the current study, which took place in a teaching hospital, but it would be an interesting risk factor to analyze in future studies. Studies in humans report that the incidence of corneal injury under GA may be significantly reduced with the implementation of a perioperative ocular care program. [21] The animals in the current prospective study were prophylactically treated with a simple ocular care program designed for dogs during general anesthesia and surgical procedures currently performed in many veterinary hospitals.

Due to the clinical nature of the study lubrication was not applied at close regular intervals in all cases. As a result, and in order to draw conclusions that were as meaningful as possible, the study population was split into the three lubrication groups described in the materials and methods section. Comparisons between these lubrication groups revealed that corneal ulceration occurred in only one patient, from the L-A group, and none of the other lubrication groups; whereas corneal abrasion occurred with equal frequency from each of the lubrication groups.

The prevalence of 1% dogs with corneal ulceration post-GA in the current prospective study is comparable to the prevalence of 1.9% in the only other veterinary study published to date, which was retrospective and found that lengthy procedures or spinal surgery increased the risk of corneal ulceration.[7] The current study identified none of the risk factors assessed, including length of anesthesia, to be associated with corneal ulcerative disease. However, comparisons between Park's study, which had a patient population of 14 animals, and the present study are difficult, as the current study represents a much larger patient population (100 dogs and 199 eyes) and is prospective rather than retrospective.[7] Moreover, the Park study did not report if there were pre-existing ocular diseases. Analysis of the data through binomial logistic regression in the current study concluded that a statistical difference could not be found when separately entering breed or services. This can be caused when analyzed groups have small numbers. To account for this, the authors grouped the patients as described in the Materials and Methods section (Table 3), which demonstrated that there were still no statistical differences when grouped this way.

General anesthesia and sedation protocols have been shown to reduce STT-1 readings significantly.[8-9] The current study, showed STT-1 readings were significantly lower 24h post-GA when compared to pre-GA readings in agreement with these findings. Although STT-1 readings have been reported to return to pre-GA values at 24h post operatively,[8] they remained lower in this current study.

The post-GA ophthalmic examination was performed 24h after GA and it is possible that some cases of corneal surface disease might have already resolved, or that a superficial corneal ulceration was detected as erosion by that time. The timing of the ophthalmic examination postoperatively was planned at 24h post-GA due to practicalities. The anesthetists were masked to the study and this would have been immediately compromised if an ophthalmic examination was performed around the recovery period of the patient, which was overseen by a member of the anesthesia team for 2 or more hours postoperatively.

The patients that were excluded from the study, such as long-term, non-responsive KCS cases and cases with known history of corneal ulcerative disease or eyelid disease, might have had a high risk of developing corneal ulcerative disease under GA. Further studies are required to determine if this is true and if they would require more extensive prophylactic ocular protection during GA.

Conclusions:

Corneal erosion and ulceration developed in patients undergoing GA despite the use of a topical ocular lubricant. The results of this study show it is important to perform an

ophthalmic examination post-GA, that includes both STT-1 and fluorescein staining, and it is possible the application of ocular lubrication also may be required more frequently than every 2h. Further studies in the frequency and types of ocular lubricants are required to establish best practice protocols for maintaining ocular surface health in veterinary patients under GA.

Table 1: STT-1 readings pre- and post-GA. The median pre- and post-GA STT-1 readings were 18 mm/min (range 4–27 mm/min) and 16 mm/min (range 0–25 mm/min), respectively

STT-1 reading pre-GA (mm/min)	Number of dogs	STT-1 readings post-GA (mm/min)	Number of dogs	Number of dogs remaining in the same group
<10	2	<10	14	2
11–15	18	11–15	21	5
>15	80	>15	65	51

STT-1 readings were significantly lower post-GA ($P < 0.001$).

Table 2: Showing the procedures and length of GA time for each

Procedure	Number of Patients	Position on operating table	Length of GA (min)	Age range of patients (months)
Anal sacculectomy	2	Sternal (*n* = 2)	155–175	106–134
Arthroscopy	6	Dorsal (*n* = 5) lateral (*n* = 1)	130–315	9–84
Staphylectomy	6	Sternal (*n* = 6)	25–100	27–112
Carpal valgus	2	Dorsal (*n* = 2)	140–180	6–14
Castration	1	Dorsal (*n* = 1)	185	14
Cruciate stabilization	7	Dorsal (*n* = 7)	125–320	11–76
Cerebrospinal fluid collection	1	Lateral (*n* = 1)	15	10
Electromyography	1	Lateral (*n* = 1)	130	35
Exploratory laparotomy and gastropexy	1	Dorsal (*n* = 1)	120	29
Explore interdigital swelling	1	Dorsal (*n* = 1)	180	10
Fracture	3	Lateral (*n* = 2) Dorsal (*n* = 1)	220–465	3.5–23
Hemilaminectomy	22	Sternal (*n* = 22)	120–370	35–150
Intravenous urogram	1	Sternal (*n* = 1)	20	16
Mass removal	1	Sternal (*n* = 1)	135	180
MRI	20	Sternal (*n* = 17) Dorsal (*n* = 3)	20–175	4–348
MRI and cerebrospinal fluid collection	9	Sternal (*n* = 7) Dorsal (*n* = 2)	45–155	13–115
Patella surgery	2	Dorsal (*n* = 2)	185–215	13–40
Perineal hernia repair	2	Dorsal (*n* = 2)	250–255	72–140
Portosystemic shunt ligation	1	Dorsal (*n* = 1)	260	5.5
Portovenogram and liver biopsies	1	Dorsal (*n* = 1)	160	42
Radiographs and cerebrospinal fluid collection	2	Dorsal (*n* = 1) Lateral (*n* = 1)	75–80	9–17
Sacroiliac luxation fixation	1	Dorsal (*n* = 1)	80	132
Tail amputation	1	Sternal (*n* = 1)	215	35
Total ear canal ablation and bulla osteotomy	1	Lateral (*n* = 1)	120	26
Tendon surgery	1	Dorsal (*n* = 1)	230	31
Lateralization of arytenoid	1	Lateral (*n* = 1)	145	122
Ventral distraction-stabilization of intervertebral disk extrusion	3	Dorsal (*n* = 3)	180–450	84–132

There were 57 surgeries with the patient in sternal recumbency, 35 surgeries with the patient in dorsal recumbency, and 8 surgeries with the patient in lateral recumbency. There were 39 patients with general anesthesia time that was less than 2 h and 61 patients with GA time that was 2 h or more than 2 h.

Table 3: Showing the P values for the risk factors included in the binomial logistical regression analysis, n = number of dogs

Risk factor	Grouping	*P* value (*P* < 0.005 was considered significant)
Age		0.93
Skull shape	Brachycephalic (*n* = 20); nonbrachycephalic (*n* = 80)	0.98
Sex	Males (*n* = 66); females (*n* = 34)	0.027
Pre-GA STT-1 value		0.594
Ophthalmic examination findings	No ophthalmic abnormalities (*n* = 60); eyelid/corneal findings (*n* = 37); other (*n* = 3)	0.932
Post-GA STT-1 value		0.985
GA time (mins)		0.703
Position on operating table	Sternal (*n* = 57); dorsal (*n* = 35); lateral (*n* = 8)	0.414
Admitting service	Neurology (*n* = 58); orthopedic (*n* = 23); soft tissue surgery (*n* = 19)	0.597

Continuous data were not grouped.

References:

1. Cucchiara RF, Black S. Corneal abrasion during anesthesia and surgery. *Anesthesiology*. 1988; 69: 978–979.

2. Snow JC, Kripke BJ, Norton ML *et al.* Corneal injuries during general anesthesia. *Anesthesia and Analgesia*. 1975; 54: 465–467.

3. Startup FG. Corneal ulceration in the dog. *Journal of Small Animal Practice*. 1984; 25: 737–752.

4. Grover VK, Kumar KV, Sharma S *et al.* Comparison of methods of eye protection under general anaesthesia. *Canadian Journal of Anesthesia.* 1998; 45: 575–577.

5. Roth S, Thisted RA, Erickson JP *et al*. Eye injuries after nonocular surgery: a study of 60,965 anesthetics from 1988 to 1992. *Anesthesiology*. 1996; 85: 1020-1027.

6. Vestre WA, Brightman AH, Helper LC *et al*. Decreased tear production associated with general anesthesia in the dog. *Journal of The American Veterinary Medical Association*. 1979; 174: 1006–1007.

7. Park YW, Son WG, Jeong MB *et al*. Evaluation of risk factors for development of corneal ulcer after nonocular surgery in dogs: 14 cases (2009-2011). *Journal of the American Veterinary Medical Association*. 2013; 242: 1554-1548.

8. Herring IP, Pickett JP, Champagne ES *et al.* Evaluation of aqueous tear production in dogs following general anesthesia. *Journal of the American Animal Hospital*

Association. 2000; 36: 427–430.

9. Sanchez RF, Mellor D, Mould J. Effects of medetomidine and medetomidine-butorphanol combination on Schirmer tear test 1 readings in dogs. *Veterinary Ophthalmology.* 2006; 9: 33–37.

10. Featherstone HJ and Heinrich CL Ophthalmic examination and diagnostics (part 1). In:*Veterinary Ophthalmology*. Fifth edition (eds. Gelatt KN, Gilger BC, Kern TJ) John Wiley & Sons, Inc; Ames, Iowa, 2013; 1: 580-581.

11. Chandler JA, van der Woerdt A, Prittie JE et al. Preliminary evaluation of tear production in dogs hospitalized in an intensive care unit. *Journal of Veterinary Emergency and Critical Care.* 2013; 23: 274-279.

12. Ghaffari M, Madani S, Trbolova A *et al.* Effects of intramuscular chlorpromazine alone and chlorpromazine–morphine combination on Schirmer tear test results in clinically normal dogs. *Comparative Clinical Pathology.* 2011; 20: 413–415.

13. Biricik HS, Ceylan C, Sakar M. Effects of pethidine and fentanyl on tear production in dogs. *Veterinary Record.* 2004; 155: 564–565.

14. Dodam JR, Branson KR, Martin DD. Effects of intramuscular sedative and opioid combinations on tear production in dogs. *Veterinary Ophthalmology.* 1998; 1: 57–59.

15. Shepard M, Accola P, Lopez L. Effect of duration and type of anesthetic on tear production in dogs. *American Journal of Veterinary Research.* 2011; 72: 608-612.

16. Gaynor JS, Dunlop CI, Wagner AE *et al.* Complications and mortality associated with anesthesia in dogs and cats. *Journal of The American Animal Hospital Association.* 1999; 35: 13–17.

17. Kim JY, Won H, Jeong SW. A retrospective study of ulcerative keratitis in 32 dogs. *The International Journal of Applied Research in Veterinary Medicine.* 2009; 7: 27–31.

18. Sanchez RF, Innocent G, Mould J *et al.* Canine keratoconjunctivitis sicca: disease trends in a review of 229 cases. *Journal of Small Animal Practice.* 2007; 48: 211–217.

19. Yu HD, Chou AH, Yang MW *et al.* An Analysis of Perioperative Eye Injuries After Nonocular Surgery. *Acta Anaesthesiologica Taiwanica.* 2010; 48: 122–129.

20. Orlin SE, Kurata FK, Krupin TT *et al.* Ocular lubricants and corneal injury during anesthesia. *Anesthesia and Analgesia.* 1989; 69: 384–385.

21. Martin DPD, Weingarten TNT, Gunn PWP, *et al.* Performance improvement system and postoperative corneal injuries: incidence and risk factors. *Anesthesiology.* 2009; 111: 320–326.