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

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JOURNAL TITLE: VETERINARY OPHTHALMOLOGY

PUBLISHER: Wiley

PUBLICATION DATE: March 2016

DOI: [10.1111/vop.12272](https://doi.org/10.1111/vop.12272)

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

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13 **Running title: Corneal surface disease and GA in dogs**

14 **Abstract:**

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

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

26 *Results:* One dog (0.5% of total eyes) developed fluorescein stain uptake consistent with
27 superficial corneal ulceration that resolved within 48h with supportive treatment. Twenty-
28 five (18.6% of total eyes) developed a faint, patchy corneal uptake of stain in the axial
29 cornea that was consistent with epithelial erosion. All erosions resolved with lubrication
30 24h later. The decrease in STT-1 readings at 24h post-GA was statistically significant
31 from those pre-GA($P < 0.001$). No significant risk factors for corneal erosion/ulceration
32 were identified.

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

38 **Introduction:**

39 Corneal epithelial defects are a known consequence of the failure to apply topical
40 lubrication during general anesthesia (GA) in human beings and dogs.¹⁻³ The prevalence
41 of corneal epithelial defects in humans following GA is reported to be up to 10% in
42 unprotected eyes and as little as 0.17% in eyes protected with lubricants or eyelid taping.
43^{1,4} In addition, a study in humans found that for reasons not understood, older patients and
44 those undergoing longer GA suffer a higher incidence of corneal ulceration.⁵ There is one
45 veterinary paper that provides guidelines for ocular lubrication in dogs, but it does not
46 report the incidence of corneal lesions after GA.⁶ A recent retrospective study in 14 dogs
47 reported a prevalence of corneal ulceration of 1.9% relating to GA⁷. However, there are
48 no similar, prospective studies with a larger group of animals in the veterinary literature.
49 A prospective study that reported STT-1 readings in dogs pre- and post-GA did not
50 mention the presence or absence of corneal surface disease.⁸ A similar prospective study
51 in dogs assessing tear production pre- and post-sedation with medetomidine or a
52 medetomidine-butorphanol combination described a decrease in STT-1 readings that
53 returned to near pre-sedation values within 15 minutes after reversal of sedation.⁹
54 Recommendations were made for the use of topical lubrication in association with
55 sedation but findings on corneal surface health post-sedation were not reported.⁹
56
57 The aim of the current prospective study was to investigate risk factors for corneal
58 surface disease, such as length of anesthesia and patient positioning, in patients free from
59 corneal ulcerative disease and under the protection of the widely available lubricating gel

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

62

63 **Materials and Methods:**

64 This study was approved by the Royal Veterinary College Ethics Committee. An
65 ophthalmic examination was performed in 100 dogs (199 eyes) by the same investigator
66 (CD) under supervision of an ECVO Diplomate (RFS). This included Schirmer Tear Test
67 -1 (STT-1), slit lamp biomicroscopy and fluorescein staining, and was performed before
68 premedication for GA and 24h after GA. Individuals with known preexisting corneal
69 ulceration, those on medical management for KCS, those with a history of ophthalmic
70 disease and individuals with facial nerve paralysis were excluded from the study.

71

72 Anesthetic agents were used in different combinations for each patient depending on
73 patient requirements. Premedication agents included acepromazine, medetomidine and
74 opioid analgesia agents including methadone and buprenorphine. Induction agents
75 included propofol and alfaxalone. Inhalational maintenance agents were either
76 isoflurane or sevoflurane.

77

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

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

88

89 Corneal erosion was defined as superficial epithelial damage with no penetration into the
90 basement membrane of the epithelium that was seen as an obvious, but patchy uptake of
91 fluorescein staining. By contrast, corneal ulceration was defined as stromal exposure with
92 an obvious, strong uptake of fluorescein stain¹⁰.

93

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

99

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

103

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

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

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

114

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

117

118 **Results:**

119 One hundred dogs (199 eyes) were prospectively recruited in the study. Median age was
120 64 months (range 3.5 to 384months). There were 66 males and 34 females. There were a
121 variety of breeds with cross breed being the most commonly represented. Skull shapes
122 included 20 brachycephalics, 15 dolichocephalics and 65 mesaticephalics.

123

124 The median GA time was 157.5min (range 15 to 465min) and the median pre- and post-
125 GA STT-1 readings were 18mm/min (range 4 to 27mm/min) and 16mm/min (range 0 to
126 25mm/min), respectively. Pre-GA, there were 2 patients with STT-1 readings less than
127 10mm/min, 18 with readings of 11-15mm/min and 80 with more than 15mm/min. Post-
128 GA, there were 14 patients with STT-1 readings less than 10mm/min, 21 with readings of

129 11-15mm/min and 65 with more than 15mm/min (Table 1). Fifty-eight of the 100 patients
130 remained in the same group pre- and post-GA and from the results it was not possible
131 to predict which individuals would have a lower post-STT-1 reading. None of the
132 patients with STT-1 readings less than 10mm/min pre-GA had visible corneal pathology
133 or other signs consistent with KCS.

134

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

143

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

152 position did not allow more regular access to their eyes, and they were put into a separate
153 lubrication group (L-C). In total, 39.2% of 199 eyes were lubricated once during a GA
154 <2h (L-A group), 53.3% of 199 eyes were lubricated every 2 hours (L-B group) and 7.5%
155 of 199 eyes were lubricated every 2-4 hours (L-C group).

156

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

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

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

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

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

182 There were a large variety of surgical procedures for which the animals in this study
183 underwent GA (Table 2). Although risk factors, such as duration of GA, were entered
184 into the binominal logistic regression along with all the other risk factors, surgical
185 procedures were grouped based on the service that admitted the patient. This resulted in
186 58 admissions by the Neurology service, 23 by the Orthopedic service and 19 by the Soft
187 Tissue service. The shortest GA time was for cerebrospinal fluid collection at 15 minutes
188 and the longest GA time was for a fracture fixation at 465 minutes. Neither the length of
189 GA nor the service admitted were a risk factor for corneal erosion or ulceration.

190

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

195

196 **Discussion:**

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

200

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

207

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

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

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

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

247

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

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

261 **Conclusions:**

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

264 ophthalmic examination post-GA, that includes both STT-1 and fluorescein staining, and
265 it is possible the application of ocular lubrication also may be required more frequently
266 than every 2h. Further studies in the frequency and types of ocular lubricants are required
267 to establish best practice protocols for maintaining ocular surface health in veterinary
268 patients under GA.
269

270 **Table 1:** STT-1 readings pre- and post-GA. The median pre- and post-GA STT-1
271 readings were 18 mm/min (range 4–27 mm/min) and 16 mm/min (range 0–25 mm/min),
272 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

273 STT-1 readings were significantly lower post-GA ($P < 0.001$).
274

275

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

277 There were 57 surgeries with the patient in sternal recumbency, 35 surgeries with the patient in dorsal recumbency, and
 278 8 surgeries with the patient in lateral recumbency. There were 39 patients with general anesthesia time that was less
 279 than 2 h and 61 patients with GA time that was 2 h or more than 2 h.

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

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

283 Continuous data were not grouped.

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