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Use of autologous serum or Vizoovet to improve healing rates of spontaneous chronic corneal epithelial defects after diamond burr debridement in dogs

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Abstract

Purpose: To determine whether the use of autologous serum or Vizoovet® improved healing rates of spontaneous chronic corneal epithelial defects (SCCEDs) after diamond burr debridement (DBD) in dogs.

Study design: Two parallel group randomized prospective study with a historical control group.

Materials and methods: Canine patients having undergone DBD for treatment of SCCEDs were included. Data for the control group (ofloxacin only) were gathered from patient records. Patients were randomly assigned to treatment groups for post-procedural medical treatments of ofloxacin and autologous serum (group 1) or ofloxacin and Vizoovet®, an all-natural eyed drop containing propolis, aloe vera, and chamomile (group 2). Each dog was examined between 2 and 3 weeks until the cornea was fluorescein stain negative. Data points collected included age, sex, breed, type of medications used, retention of bandage contact lens (BCL), time to healing, and number of DBD performed.

Results: A total of 120 dogs, each contributing one eye to the study, underwent DBD for SCCEDs. Mean (± standard deviation) days until healed were 20.1 ± 11.1 days, 16.3 ± 4.5 days, and 16.0 ± 3.7 days for the control group, group 1, and group 2, respectively. There was a marginally significant difference in days until healed between groups ($p = .0515$). SCCEDs healed significantly faster in group 2 ($p = .03$) and marginally faster in group 1 ($p = .06$) compared with the control group. Days until healing between group 1 and 2 were not significantly different ($p = .76$).

Conclusions: As compared to the control group, use of Vizoovet® as adjunctive medical treatment resulted in shorter corneal healing time after DBD.

KEYWORDS

autologous serum, bandage contact lens, diamond burr debridement, dog, SCCED, Vizoovet®

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1 | INTRODUCTION

Spontaneous chronic corneal epithelial defects (SCCEDs) are chronic epithelial erosions that fail to heal through typical wound-healing processes.[1] Characteristic clinical findings include a superficial corneal ulcer with non-adherent surrounding epithelial edges in a middle-aged to older dog of many weeks duration with no obvious underlying etiology.[1,2] This condition is not fully understood, but various factors have been implicated including corneal epithelial basement membrane loss, formation of an acellular hyalinized zone in the anterior stroma, abnormal adhesion complexes, and abnormal plexus of substance P and calcitonin gene-related peptide nerve fibers.[1-5]

Treatment of SCCEDs typically involves a combination of surgical and medical therapies. Diamond burr debridement (DBD), with placement of a bandage contact lens (BCL), is the most recent surgical technique to be successfully utilized for SCCEDs cases. Gosling et al[6] reported a 70% success rate at 1 week and 92.5% success rate at approximately 2 weeks with 87.5% of patients requiring a single treatment. Dees et al[7] showed an overall mean healing time of 9.37 days and that BCL use and retention significantly influenced healing rates. Wu et al[8] reported resolution of SCCEDs in an average of 13.3 days and that the majority of patients (77.4%) only required a single treatment.

Studies have also evaluated post-DBD therapies and their abilities to improve healing rates.[7,9,10] Edelmann et al[9] evaluated adjunctive autologous platelet-rich plasma but found no improvement in healing rates as compared to artificial tear solution. Sebbag et al[10] looked at the use of a topical regenerative agent but found no statistically significant improvement in healing rates. Dees et al[7] evaluated the use of different topical antimicrobials and the use of hyperosmotic sodium chloride ointment; however, similar to the aforementioned studies, no significant difference in healing times was observed.

Autologous or homologous serum has been used for quite some time in the treatment of corneal disease, mainly keratomalacia.[11-16] The alpha-2 macroglobulin found within serum can be extremely helpful in slowing the collagenolytic process found with certain cases of bacterial keratitis. Other studies, however, have suggested that serum may promote corneal healing due to presence of epithelial growth factor and platelet-derived growth factor.[17,18]

Vizoovet® is an all-natural eye drop that contains three ingredients proposed to protect the ocular surface and provide anti-inflammatory activity including propolis (bee's wax), aloe vera, and chamomile. Two of these ingredients, propolis and aloe vera, have been shown to aid in repair of corneal injuries/ulcerations.[19-22]

The purpose of this study was to determine whether the use of autologous serum or Vizoovet® improved healing rates of SCCEDs after DBD in dogs.

2 | MATERIALS AND METHODS

Canine patients having undergone or undergoing DBD for treatment of SCCEDs were enrolled in this study. Informed owner consent was obtained from all owners prior to the use of patient data in this study. All patients were examined by a board-certified veterinary ophthalmologist (Dees), and examination included slit lamp biomicroscopy (Kowa SL-15; Kowa), indirect fundoscopy (Keeler Vantage; Keeler Instruments, Inc.), Schirmer tear test—1 (Schirmer tear test strips; Schering-Plough Animal Health Corp.), rebound tonometry (TonoVet®; Lumic International), and fluorescein staining (Fluress®, Fluorescein sodium 0.25%/Benoxinate hydrochloride 0.4%; Akorn).

Diagnosis of SCCEDs was based on characteristic clinical findings including a superficial corneal ulcer with non-adherent surrounding epithelium of more than 1-week duration and lack of evidence of a secondary ocular abnormality that could account for the ulceration.

After diagnosis confirmation, topical anesthesia was achieved using three applications (1 drop each application) of proparacaine hydrochloride 0.5% solution (Bausch & Lomb) 5 min apart. All procedures were performed by a single veterinary ophthalmologist (Dees). DBD was performed utilizing a battery-operated handheld diamond burr unit (Algerbrush, Alger Equipment Company) with a 3.5 mm burr tip in a medium grit. The removable burr tip was sterilized in a steam autoclave between each use. Patients were gently manually restrained. Sedation or general anesthesia was not required in any patient. The rotating burr tip was gently passed over the ulcer bed in a circular direction to remove non-adherent epithelium. Once stable epithelium was encountered, the burring process was stopped. Once the procedure was complete, a BCL (Bausch & Lomb; PureVision 2) was placed.

Patients were placed into three separate groups based on post-procedural medications used. For the control group, data were collected from historical patient records. Inclusion criteria included presence of a SCCED as diagnosed by a board-certified veterinary ophthalmologist having undergone DBD with placement of BCL and confirmed resolution of the corneal ulceration. Exclusion criteria included stromal ulceration, presence of suspected bacterial or fungal keratitis, keratomalacia, previous treatment for SCCED (diamond burr debridement, grid keratotomy, etc.), keratoconjunctivitis sicca, glaucoma, bandage contact lens loss prior to recheck examination,

lack of compliance for medication use, and patients lost to follow up. All patients in the control group received ofloxacin 0.3% (Falcon Pharmaceuticals) TID as the sole topical treatment.

For the treatment groups, data were collected in a prospective randomized manner (coin flip). Patients in group 1 received ofloxacin 0.3% TID and autologous serum TID to the affected eye. Patients in group 2 received ofloxacin 0.3% TID and Vizoovet® (Petnetwork) BID to the affected eye. Inclusion and exclusion criteria for the treatment groups were the same as for the control group. All patients were treated with carprofen (2.2 mg/kg, PO BID; Pfizer) and tramadol (2–4 mg/kg PO BID BID-TID; Amneal Pharmaceuticals), or gabapentin (5–10 mg/kg PO BID-TID; Amneal Pharmaceuticals). Patient owners and the attending ophthalmologist were not masked to treatment for each patient.

Each dog was examined between 2 and 3 weeks postprocedure until the cornea was fluorescein stain negative. If the cornea failed to heal at the recheck examination, a repeated DBD and placement of a new BCL was performed as described. Data points collected included age, sex, breed, type of medications used, retention of bandage contact lens (BCL), days until healed, and number of DBD performed.

Statistical analyses were performed using SAS 94. Kaplan-Meier survival curves with 95% confidence limits were constructed for days to healing. Log-rank tests were used to compare healing curves between groups. Negative binomial regression was used to compare the number of DBD procedures between groups. A significance threshold of $p \leq .05$ was used (Figure 1).

3 | RESULTS

A total of 120 individual dogs, each contributing one eye to the study, were included. The mean age of all dogs was 9.7 years (range = 5–14 years) with males ($n = 71$; 59%) outnumbering females ($n = 49$; 41%). All dogs were

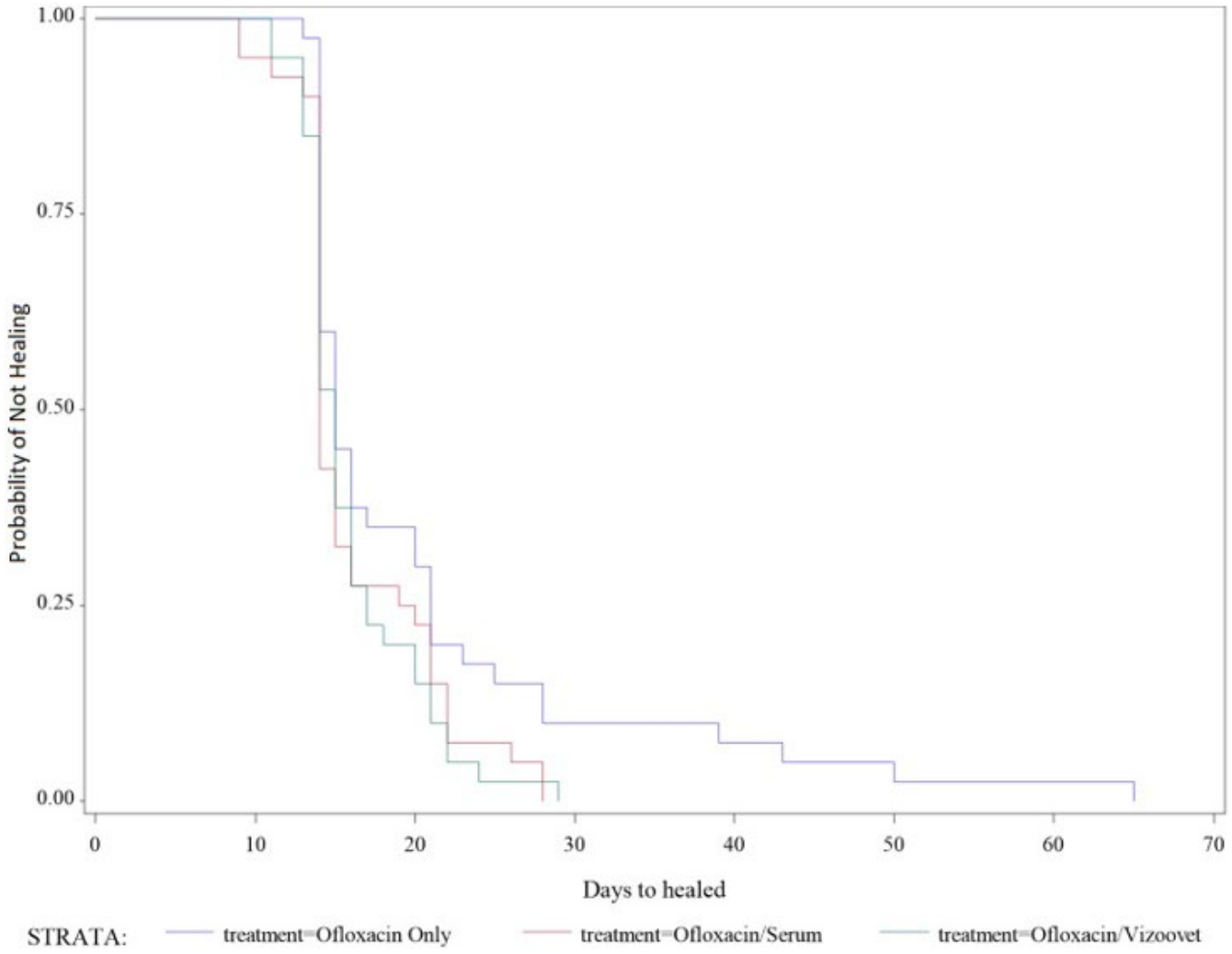

FIGURE 1 Kaplan-Meier survival curve for corneal healing

TABLE 1 Breed distribution

Breed	Number	Percentage of total
Boxer	31	25.8%
Mixed breed	22	18.3%
French Bulldog	9	7.5%
Golden Retriever	6	5.0%
Shih Tzu	6	5.0%
Labrador Retriever	6	5.0%
English Bulldog	4	3.3%
Chihuahua	4	3.3%
Weimaraner	3	2.5%
Dachshund	3	2.5%
Pembroke Welsh Corgi	2	1.7%
Standard Poodle	2	1.7%
American Cocker Spaniel	2	1.7%
Greyhound	2	1.7%
West Highland White Terrier	2	1.7%
American Bulldog	1	0.08%
Lhasa Apso	1	0.08%
Rat Terrier	1	0.08%
American Pit Bull	1	0.08%
Chinese Crested	1	0.08%
Jack Russell Terrier	1	0.08%
Miniature Poodle	1	0.08%
Havanese	1	0.08%
German Shorthair Pointer	1	0.08%
Boston Terrier	1	0.08%
Giant Schnauzer	1	0.08%
Great Dane	1	0.08%
English Springer Spaniel	1	0.08%
Yorkshire Terrier	1	0.08%
Brittany Spaniel	1	0.08%
Bull Terrier	1	0.08%

altered. Out of 120 eyes, right eyes ($n = 74$; 62%) outnumbered left eyes ($n = 46$; 38%). The most common breed represented was the Boxer ($n = 31$; 25.8%), followed by mixed breed ($n = 22$; 18.3%), French Bulldog ($n = 9$; 7.5%), Golden Retriever ($n = 6$; 5.0%), and Shih Tzu ($n = 6$; 5.0%) (Table 1).

The mean (± standard deviation) days until healed for all patients in the study were 17.5 days (range = 9–65 days). The mean days until healed were 20.1 ± 11.1 days (range = 13–65 days), 16.3 ± 4.5 days (range = 9–28 days), and 16.0 ± 3.7 days (range = 11–29 days) for the control group, group 1, and group 2, respectively. The median days until healed were 15 days (95% CI, 14–17 days), 14 days (95% CI, 14–15 days), and 15 days (95% CI, 14–16 days) for the control group, group 1, and group 2, respectively. Seventy-five percent of eyes were healed by 21 days (95% CI, 16–28 days) in the control group, 19.5 days (95% CI, 15–22 days) in group 1, and in 17 days (95% CI, 15–21 days) in group 2. There was a marginally significant difference in healing between groups ($p = .0515$). SCCEDs healed significantly faster in group 2 ($p = .03$) and marginally faster in group 1 ($p = .06$) compared with the control group. The speed of healing between groups 1 and 2 was not significantly different ($p = .76$).

The mean number of DBD procedures required for corneal healing for all patients was 1.2. The mean number of DBD procedures was 1.5 ± 0.8 (range = 1–4), 1.2 ± 0.4 (range = 1–2), and 1.1 ± 0.3 (range = 1–2) in the control group, group 1, and group 2, respectively. The median number of DBD procedures was 1 for all groups with 27/40 eyes (67.5%) in the control group, 34/40 eyes (85.0%) in group 1, and 37/40 eyes (92.5%) in group 2 healing after one procedure. The number of DBD procedures to achieve clinical resolution of the SCCED was not significantly different between groups ($p = .24$).

4 | DISCUSSION

Diamond burr debridement has emerged as a very successful treatment for SCCEDs in dogs.[6-8] In this study, the mean time to ulcer healing was 17.5 days for all patients with the majority (range = 67.5–92.5%) showing clinical resolution after one DBD procedure. This compares favorably with the results of Gosling et al and Wu et al.[6,8] The overall mean healing time reported by Dees et al,[7] however, was less than reported here (9.37 days vs. 17.5 days). The stark difference may be attributed to the fact that in the Dees et al study, and patients were evaluated on a weekly basis versus every 2 weeks as in this study. This could have allowed capture of healing data at an earlier stage and thus providing a more accurate time to healing estimation. We chose a re-evaluation time point of between 2 and 3 weeks due to COVID-19-related clinical issues with limited appointment slots and because, based on previous reports, average healing time for SCCEDs after DBD is approximately 2 weeks. This is considered a limitation of the study, and future research should attempt to recheck patients on a weekly basis for the most accurate time estimations.

Although the DBD procedure is considered quite successful for SCCEDs, researchers continuously work to improve healing times in these cases with adjunctive medical therapies. Autologous platelet-rich plasma, topical regenerative agents, varying antimicrobials, and topical hyperosmotic sodium chloride ointment failed to improve time to healing after DBD.[7,9,10] In this study, we evaluated

autologous serum and an all-natural eye drop Vizoovet®. Previous studies have shown that serum may promote corneal healing due to presence of epithelial growth factor and platelet-derived growth factor.[17,18] Others have suggested that the constituents in Vizoovet®, namely propolis and aloe vera, have been shown to aid in repair of corneal injuries/ulcerations.[19-22] We found that eyes healed faster with the use of both autologous serum and vizoovet; however, only the latter was statistically significant. Also, the percentage of patients that healed after one DBD was improved in both treatment groups, but again the results were not significantly different. The lack of statistical significance could be due to patient numbers and a larger study could potentially show improved results. It is also possible that there truly is no difference, with respect to autologous serum, as another similar study has shown.[9]

The physiology behind the improvement in healing is unknown. The epithelial growth factor and platelet-derived growth factor in serum and the propolis/aloe vera combination in Vizoovet® may actually promote corneal re-epithelialization in these cases. One could argue, however, that the simple act of applying additional drops to the eye could provide additional lubrication hence promoting a faster epithelialization process.[23] In this study, we did not use simple wetting drops topically in the control group, which would be considered another limitation. Future studies evaluating either autologous serum or Vizoovet®, should use topical wetting drops in the control eyes in order to truly elucidate the effect of the drops being tested.

In conclusion, use of Vizoovet® with topical antimicrobial after DBD for SCCEDs statistically improved corneal healing times, as compared to the use of topical antimicrobial alone, and should be considered an effective adjunctive treatment for these cases. As compared to autologous serum, Vizoovet® did not show a statistically faster corneal healing time.

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