A NEW EYE DROP FORMULATION USED IN THE MANAGEMENT OF CORNEAL ULCERS IN DOGS AND CATS

Iuliana IONAŞCU, Adina ARGĂSEALĂ, Seralp UZUN, Gina GÎRDAN, Alexis GÎRLOANŢĂ, Victoria CALENTARU

University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Marasti Blvd, District 1, Bucharest, Romania

Corresponding author email: driulianaionascu10@gmail.com

Abstract

Corneal ulcers in dogs and cats are very common. Regardless of etiology (melting or indolent corneal ulcers) and of the affected layers of the cornea (superficial or deep corneal ulcers), local treatment is performed using eye drops with antibiotic and corneal healing drugs (hyaluronic acid and acetylcysteine). Each eye should be instilled 5-8 times per day for 14-21 days. In Romania, the eye drops available on the market have only one active substance and the owner must apply the topical medication from several vials. To remove this drawback, a new healing eye drop formulation containing sodium hyaluronate, acetylcysteine and insulin (as a growth tissue factor) has been developed, reducing the number of daily administrations. This new formulation is well tolerated and the corneal healing is achieved by only 3-4 administrations per day.

Key words: cat, corneal ulcer, dog, eye drops.

INTRODUCTION

Corneal ulcers are very common encountered in veterinary practice. Depending on the number of affected corneal layers, they can be superficial or deep. Superficial corneal ulcers (Figure 1) are characterized by loss of corneal epithelium and exposure of corneal stroma without stromal loss (Gelatt et al., 2013; Eaton et al., 2017). Deep corneal ulcers involve stromal defect.

Clinically, the patients present with discomfort manifested as blepharospasm, conjunctival hyperemia, ephiphora, photophobia, corneal edema and possibly reflex uveitis (miosis and aqueous flare). A corneal ulcer is diagnosed based on these clinical signs and on the fluorescein uptake by the corneal stroma (Gelatt et al., 2013).

Corneal ulcers can have a wide variety of etiologies: trauma, entropion, ectopic cilia, trichiasis, distichiasis, quantitative or qualitative tear film abnormalities, foreign bodies, spontaneous chronic corneal epithelial defects (SCCED), microbial infection, facial nerve paralysys. Corneal sensitivity and aqueous tear production are lower in brachycephalic dogs.

Dogs with nasal folds are nearly five times more likely to be affected by corneal ulcers than those without (Packer et al., 2015; Bolzanni et al., 2020).

Figure 1. OD Two-years-old DSH with superficial corneal ulcer

Indolent ulcer or spontaneous chronic corneal epithelial defect (SCCED) is a chronic superficial corneal ulceration with no identifiable cause or complicating factor. It is diagnosed most often in middle-aged to older dogs, and the Boxer breed is overrepresented (Bentley, 2005; Eaton et al., 2017). It is bordered or partially covered with non-
adherent epithelium, and fails to heal within a normal time period (Ledbetter et al., 2006) (Figures 2 and 3).

![Figure 2. OS Seven-years-old French Bulldog with indolent corneal ulcer, bordered by a lip of non-adherent epithelium](image1)

A melting ulcer is characterized by rapid and progressive stromal loss and it is potentially globe threatening (Gelatt et al., 2013). Corneal ulcers’ standard treatment consists of topical antibiotics, corneal healing drugs and debridement in SCCED. Cases with deep corneal ulcer (Figure 4) may require surgery that may include application of a collagen bandage lens or amniotic membrane, third eyelid flap, keratectomy in SCCED, conjunctival grafts (Gelatt et al., 2013; Ionascu & Ion, 2013; Ion et al., 2016).

In Romania, the eye drops available on the market have only one active substance and the owner must apply the topical medication from several vials. Owner compliance is an important factor in the success rate of the treatment. Some owners find it difficult to administer eye drops 5-8 times daily, from 2-3 different bottles, especially if the patient is aggressive.

![Figure 4. OD Twelve-years-old Crossbred with deep corneal ulcer](image2)

To remove this drawback, a new healing eye drop formulation (ii-2018) containing sodium hyaluronate, acetylcysteine and insulin (as a growth tissue factor) has been developed, reducing the number of daily administrations. Insulin has been shown to improve corneal epithelial healing in vitro and in diabetic animal models (Nagano et al., 2003; Wang et al., 2017). However, clinical experience with topical insulin in patients with corneal wounds is minimal (Wang et al., 2017; Ghiasi et al., 2018).

The aim of this study is to test the clinical efficacy of the ii-2018, a new healing eye drop formulation.

**MATERIALS AND METHODS**

To determine the efficacy of this new eye-drop formulation (ii-2018), a total of 102 dogs and 35 cats diagnosed with superficial or deep ulcers were enrolled in this study. Prior to ophthalmic examination, affected eyes were topically anesthetized with oxybuprocaine hydrochloride 0.4% (Benoxi®, Unimed Pharma).

Dogs underwent ophthalmic examinations and 42 were diagnosed with indolent ulcer (SCCED) (Figures 5 and 6), 28 with deep corneal ulcers and 32 dogs with melting ulcer. All dogs with indolent ulcer underwent a sterile cotton-tipped swab debridement. The cotton-tipped swab was passed over the ulcer in multiple circular passes, removing the non-adherent epithelium.
Figure 5. OS Seven-years-old French Bulldog with indolent corneal ulcer, clinical aspect after debridement

Figure 6. OS Eight-years-old English Bulldog with indolent corneal ulcer, clinical aspect after debridement

A total of 35 cats were included in this study. They underwent complete ophthalmic examination and 8 cats were diagnosed with superficial corneal ulcer (Figure 7), 15 with deep corneal ulcer (Figure 8) and 12 cats with melting ulcer (Figure 9).

All patients received ii-2018 and a topical antibiotic (ofloxacin, Floxal, Bausch & Lomb Rochester, NY, SUA), 3 to 4 daily administrations until recovery (7-28 days). Deep and melting ulcers were treated systemically with doxycycline 10 mg/kg SID (Ronaxan 20 mg, Merial, France).

ii-2018 is presented in a 10 ml sterile bottle. The drops were prepared by a pharmacy by mixing insulin (Humulin R 100 UI/ml, Lilly S.A., Madrid, Spain) with 5% acetylcysteine and 0.2% sodium hyaluronate. The drops were refrigerated and used up to 1 month after preparation.

The corneal ulcers were considered healed when the cornea revealed a negative fluorescein test and there was no evidence of blepharospasm or ocular discharge.

Clinical follow-up included the evaluation of potential side effects as well, such as: local inflammation, pruritus, pain, excessive lacrimation.

Data were analyzed for breed, age, additional ocular disorders, duration of clinical signs.
before referral, number of days before healing was achieved, number of debridements, additional therapeutic interventions, complications. Patients were re-checked weekly (+/- 3 days) from the beginning of the treatment for a total of 4 weeks.

RESULTS AND DISCUSSIONS

The corneal ulcers had been treated by referring veterinarians for a median of 15 days (range: 1-40 days) prior to enrolment in this study. Medical treatment consisted of topical +/- systemical antibiotics, topical corticosteroids, artificial tear solutions with hyaluronic acid or dextanexenol.

Dog breeds included crossbreds (n = 28), Shih-Tzu (n = 21), French Bulldog (n = 20), Boxer (n = 10), English Bulldog (n = 9), Pug (n = 7), Caniche (n = 5), West Highland Terrier (n = 2).

The median age was 7 years, with a range between 9 months and 13 years.

From the total number of dog patients (n = 102), 42 dogs (41.17%) were diagnosed with indolent ulcers, 28 dogs (27.45%) with deep corneal ulcers and 32 dogs (31.37%) with melting ulcer.

After 1 week of treatment, 16.66% (7/42) of cases with indolent corneal ulcers healed (Figures 10, 11 and 12).

After 2 weeks of treatment, 64.28% (27/42) of cases with indolent corneal ulcer (Figure 13), 28.57% (8/28) of cases with deep ulcer and 31.25% (10/32) of cases with melting ulcer had healed.

At the third recheck examination, 88.09% (37/42) of cases with indolent corneal ulcer, 67.85% (19/28) of cases with deep ulcer and 78.12% (25/32) of cases with melting ulcer had healed.

After 4 weeks of treatment, 92.85% (39/42) of cases with indolent corneal ulcer (Figures 16 and 17), 100% (28/28) of cases with deep ulcer
(Figures 14, 15 and 18) and 93.75% (30/32) of cases with melting ulcer had healed.

Figure 14. OD Seven-years-old Shih Tzu with deep corneal ulcer at the beginning of the treatment

Figure 15. Previous case, seven-years-old Shih Tzu healed at 28 days of treatment

Cases with indolent corneal ulcer had corneal vascularization in 40% of cases at the time of the second examination (Figure 16).

Figure 16. OS Eight-years-old English Bulldog with indolent corneal ulcer, clinical aspect 14 days after the beginning of the treatment (fluorescein test is positive and cornea has neovascularization)

A second debridement was performed in 35.71% (15/42) of cases, based on presence of redundant epithelial tissue at the ulcer’s margins. Ulcer healed at 28 days of treatment with superficial corneal scar (Figure 17).

Figure 17. Previous case eight-years-old English Bulldog with indolent corneal ulcer healed at 28 days of treatment with superficial scarring (same case from Figure 6)

Figure 18. OD Twelve-years-old Crossbred with deep corneal ulcer healed at 28 days of treatment (same case from Figure 4). Corneal opacity and mild neovascularization

Systemic antibiotic, doxycycline 10 mg/kg SID (Ronaxan, Merial, France) were prescribed in all brachycephalic cases and in cases where a large corneal area had been debrided. The 3 cases with indolent ulcer that failed to heal after 4 weeks of therapy were treated with Softshield® bandage collagen lens and a third eyelid flap. After 21 days, at sutures’ removal, 100% (3/3) of lesions were healed. The reason for ii-2018 failure in this cases might be the age of the patients (10, 12 and 13 years old), the associated treatment with systemical corticosteroids (for lymphoma and optic neuritis).

Two melting ulcers had a bad outcome after 3, respectively 7 days of treatment and underwent surgical treatment with Softshield® and third...
eyelid flap as well. After 21 days, at sutures’ removal, 100% (2/2) of lesions were healed. Both cases were represented by brachycephalics. In one case, the owner could not administer the eye drops.

Cat breeds represented in this study included Domestic Shorthair (n = 20), British Shorthair (n = 8), Persian (n = 5) and Sphinx (n = 2). The median age was 6 years, with a range between 7 months and 11 years. From the total number of cat patients (n = 35), 8 cats (22.86%) were diagnosed with superficial ulcers, 15 cats (42.86%) with deep corneal ulcers and 12 cats (34.28%) with melting ulcer. All superficial corneal ulcers healed in the first week (3/8) and after 14 days of treatment (8/8) (Figure 19).

Four out of fifteen (26.66%) cats with deep corneal ulcer were healed after 14 days of treatment, 11/15 (73.33%) after 21 days, and all cases were healed after 28 days (Figures 20 and 21). One cat with melting ulcer healed after 14 days. At the third recheck examination, 4/12 (33.33%) with melting ulcer had healed. A total of seven additional cases were resolved at 28 days, bringing the total number of resolved cases to 11/12 (91.66%).

The complications encountered in this case series were corneal scarring, pigmentation, vascularization, corneal sequestrum, opacification and specific vascularization in cases with concurrent keratoconjunctivitis sicca.

In dogs, 18/28 deep ulcers healed with corneal scarring and 25/32 melting ulcers developed post-healing corneal opacity, persistent vascularization (Figure 18) and pigmentation. In cats, 6/15 with deep ulcer developed corneal scarring, and 9/12 of melting ulcers healed with corneal opacity. Two cases of melting ulcer developed corneal sequestrum 3 weeks, respectively 2 months after healing (Figure 22).
This eye drop formulation was developed based on the existing studies in the literature. Acetylcysteine has mucolytic and anticollegenolytic documented properties and had been used to treat keratoconjunctivitis sicca, alkali-burned corneas in rabbits and corneal mucous plaques. 3% acetylcysteine is effective in decreasing the healing time of corneal wounds in dogs (Aldavood et al., 2003).

The effect of topical insulin on corneal lesions has been documented in rodent models. In diabetic rats, topical insulin improves corneal sensation and promotes wound healing after corneal abrasions (Zagon et al., 2007; Wang et al., 2017).

Insulin-like growth factor-1 (IGF-1) has been shown to be an important modulator of corneal wound healing. In some studies, IGF-1 was shown to act synergistically with substance-P to promote corneal epithelium wound healing (Nagano et al., 2003; Nishida & Yanai, 2009; Wang et al., 2017). Shanley et al. (2004) suggest a mechanism by which insulin may influence corneal wound healing in vitro (Shanley et al., 2004) and exposure of corneal epithelium to insulin facilitated closure of in vitro small wounds through enhanced cell migration instead of proliferation.

Hyaluronic acid is commonly used as part of the treatment in superficial ulcers. Gronkiewicz et al. (2017) found that the viscoelastic properties of hyaluronic acid containing-solutions is also a factor which may be contributing to corneal wound healing. Hyaluronic acid promotes tear film stability, (Nakamura et al., 2004; Hirai et al., 2005). Healthy precorneal tear film contains growth factors that play an important role in corneal epithelial wound healing (Klenker et al., 2007; Gronkiewicz et al., 2017). A more recent study demonstrates that a cross-linked, modified HA hydrogel provides further benefit by accelerating time to corneal wound closure compared to a non-cross-linked HA solution (Williams et al., 2017).

The disadvantages of surgical treatment of deep and melting ulcers, include the need for general anesthesia, increased postoperative opacity secondary to corneal scarring and increased costs for the owner. Treatment with ii-2018 is inexpensive, and produces rapid and complete healing in the majority of treated cases. We must emphasize here the need for careful selection of the patients. If the corneal defect is very deep, down to the Descemet membrane, if the melting ulcer is very aggressive, or if the indolent ulcer does not heal in an acceptable time period, surgical treatment is advised. Careful monitoring for deterioration of corneal ulcers is warranted when prescribing ii-2018. Except for mild ocular discomfort manifested with blepharospasm and pruritus (29/137) and mild inflammation of the conjunctiva (1/137), the patients did not show other local or systemic side effects.

The pruritus, the attempt to rub the eye, might be due to the acetylcysteine. The discomfort manifested for less than 10 minutes after administration of ii-2018. The owner compliance is very good, as it is no longer necessary to administer treatment from multiple bottles. This case series is limited by the heterogeneity of the cases and lack of a comparative control group.

This study did not seek to compare ii-2018 with other treatment option, but to simply determine if it’s safe and effective. Further studies are necessary to compare this new eye drop formulation with other therapies.
CONCLUSIONS

The results of this study suggest that the use of this new eye-drop formulation (ii-2018) may be a safe and effective treatment for corneal ulcers in dogs and cats. This new formulation is well tolerated and the corneal healing is achieved by only 3–4 administrations per day. Local treatment using a single bottle instead of three is easy for the owner. Further studies are necessary to determine the clinical efficacy in extended trials.

REFERENCES


