

Clinical Evaluation of a Nutraceutical Diet as an Adjuvant to Pharmacological Treatment in Dogs Affected by Epiphora

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ABSTRACT

Epiphora is defined as tear overflow due to impaired tear drainage by way of the nasolacrimal duct. We evaluated a combined therapeutic approach for epiphora based on drug and a commercially available nutraceutical diet administration over a 30 days period in dogs poorly responsive or unresponsive to the only immune-suppressive treatment.

Forty-five client-owned household dogs of different breeds (19 females and 31 males) and aged 6.5 years were enrolled. Schirmer tear test-1, conjunctival inflammation, corneal keratinization and blepharitis were evaluated before and at the end of the evaluation.

Schirmer's test value significantly decreased from 22.96 ± 0.37 mm, at T0 to 18.86 ± 0.24 mm, at T30 (** $p < 0.001$), conjunctival inflammation significantly decreased from 1.30 ± 0.11 , at T0 to 0.14 ± 0.04 at T30 (** $p < 0.001$), corneal keratinization significantly decreased from a T0 value of 0.17 ± 0.05 to a T30 value of 0.07 ± 0.03 ($p < 0.05$) and blepharitis significantly decreased from 0.64 ± 0.1 , at T0 to 0.03 ± 0.02 at T30 (** $p < 0.001$).

This clinical evaluation represents the first evidence of the usefulness of a specific nutraceutical diet as a reliable tool to improve pharmacological treatment of epiphora.

INTRODUCTION

Epiphora is defined as tear overflow because of impaired tear drainage by way of the nasolacrimal duct.¹ It is a fairly common problem in some of the smaller breeds, such

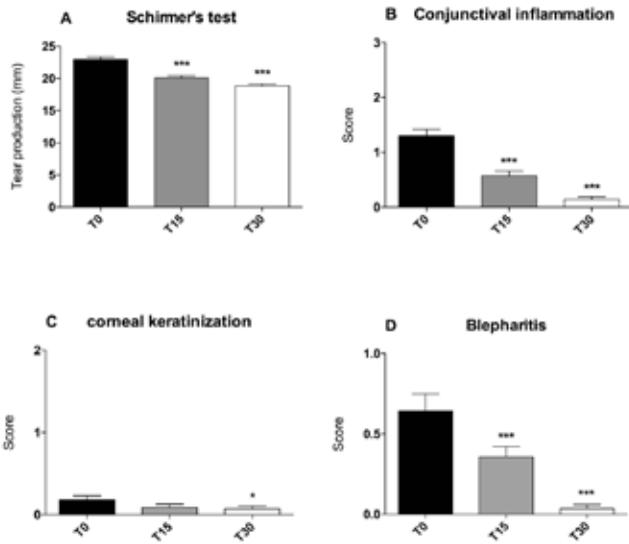
as Bichon Frisé, Maltese Terrier, Miniature and Toy Poodle, and Tibetan Spaniel, where it's particularly evident due to their pale coats, since tears stain them a rusty brown. The onset of this kind of condition is generally observed from 2 – 3 months of age onwards, and it is usually bilateral.² Predisposing features are:

- shallow orbit with a prominent globe
- close apposition of the eyelids to the globe, resulting in a shallow lacrimal lake that limits lacrimal drainage
- medial lower eyelid entropion
- misplacement of the lower punctum without medial lower eyelid entropion
- hair at the medial canthus, of both the eyelids and the lacrimal caruncle, tends to impinge on the ptf, thus keeping tears from flowing in the lacrimal duct.

We aimed to evaluate a combined therapeutic approach for epiphora based on the classical drug administration and the use of a commercially available nutraceutical diet in dogs where the only immune-suppressive treatment resulted poorly responsive or ineffective to control the ocular symptoms. The nutraceutical diet consisted in a mixed formula of fish meal and rice, as a single source of carbohydrates, and botanical extracts including Aloe vera, Astaxanthin (from *Hematococcus pluvialis*), bioflavonoids, Curcuma longa, Ribes nigrum, Vitis vinifera, and Omega3-Omega6 fatty acids ratio of 1:3.

MATERIALS AND METHODS

Figure 1. Schematic representation of clinical signs trend during the 30 days evaluation period (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)



Forty-five client-owned household dogs (19 females and 31 males) aged 6.5 (average) of different breeds were enrolled in this evaluation. Dogs were fed the nutraceutical diet for a 30-day period. Both eyes of each dog were photographed at each visit, and clinical signs according to the scores proposed by Moore et al.³ Conjunctival inflammation (0-3):

- 0 = normal conjunctiva
- 1 = mild hyperaemia without chemosis
- 2 = moderate hyperemia with mild chemosis
- 3 = intense hyperaemia with moderate to severe chemosis; Corneal keratinization (0-2): 0 = none, 1 = mild opacity, 2 = moderate opacity. Ophthalmic examinations included also slit-lamp biomicroscopy (Kowa Optimed Inc SL-14 Slit Lamp, Kowa Optimed, Europe Ltd, Berkshire, UK), fundoscopic examination (Heine Omega 180 Binocular Indirect Ophthalmoscope, HEINE Optotechnik, Herrsching, Germany), and fluorescein dye staining (fluorescein 0.5% collyre unidose TVM, Laboratoires TVM, Lempdes, France), and Schirmer tear test-1 (STT-1) (Dina Strip Schirmer-Plus

Dina-Hitex) on 90 eyes (two for each dog).⁴

The recommendations of the ARRIVE guidelines in animal research were consulted and considered.⁵

Statistical Analysis

Data were analysed using GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA). All data are presented as the means \pm standard error of the mean and were first checked for normality test using the D'Agostino-Pearson normality test. Differences in Schirmer's test, conjunctival inflammation, corneal keratinization, and blepharitis before and at the end of evaluation period were analyzed using a one-way analysis of variance (ANOVA) followed by Turkey multiple comparisons test. A $*p < 0.05$ was considered significant.

RESULTS

Schirmer's test value significantly decreased from 22.96 ± 0.37 mm, at T0, to 20.09 ± 0.33 mm ($***p < 0.001$) at T15, to 18.86 ± 0.24 mm, at T30 ($***p < 0.001$). The same trend was observed for the clinical signs. More in details, conjunctival inflammation significantly decreased from 1.30 ± 0.11 , at T0, to 0.57 ± 0.08 ($***p < 0.001$), at T15, to 0.14 ± 0.04 at T30 ($***p < 0.001$). Corneal keratinization significantly decreased from a T0 value of 0.17 ± 0.05 to a T30 value of 0.07 ± 0.03 ($*p < 0.05$). As to blepharitis score, a significant decrease from 0.64 ± 0.1 , at T0, to 0.35 ± 0.06 ($***p < 0.001$), at T15,

Figure 2. Graphical representation of eyes improvement before (A, C, E) and after (B, D, F) 1 month of the nutraceutical diet supplementation



to 0.03 ± 0.02 at T30 ($***p < 0.001$) was observed.

DISCUSSION

To the best of our knowledge, this clinical evaluation represents first study that proposed the use of a specific nutraceutical diet as a reliable tool to improve pharmacological treatment of epiphora. The nutraceutical approach significantly decreased the eye's tear production, and clinically ameliorated the conjunctival inflammation status, the corneal keratinization and blepharitis in dogs poorly responsive or unresponsive to gold standard pharmacological therapy of epiphora.

The decreased STT-1 level in response to the nutraceutical diet was in agreement with what previously reported by Saito et al,

who compared mean tear production in dogs with and without epiphora.¹ Although we are unaware of the possible action mechanism exerted by botanicals present in the nutritional diet, we hypothesize a synergic action with raw materials in modulating functional and mechanical disorders, which are among the causes of epiphora.¹ According to literature reports, Aloe vera was observed to exert a positive effect on corneal epithelial cells speeding epithelization decreasing fibrosis in vitro.⁶ Moreover, it represents an alternative treatment of ocular surface of squamous dysplasia in humans.⁷

Several studies highlighted the effect of Astaxanthin from *Haematococcus pluvialis* and carotenoids in reducing retinal oxidative stress in different animal models.⁸⁻¹⁰ In particular, Astaxanthin and carotenoids can attenuate the apoptosis of retinal ganglion cells in rats affected by diabetic retinopathy, representing an alternative drug to treat this pathology, and can limit UVB damages.¹¹⁻¹³ Curcumin, the major curcuminoid contained in *Curcuma longa*, has been largely used for preventing or treating several disease including, ocular ones. Various studies investigate multiple positive effects of this active substance, such as anti-inflammatory, antioxidant and anti-angiogenic.^{14,15} Moreover, Curcumin seems to affect the expression of genes inhibiting the expression of oncogenes in tumor cells in human models.^{16,17} *Ribes nigrum* is a perennial shrub rich in anthocyanins, flavonols, phenolic acids, and polyunsaturated fatty acids.

A plethora of studies have been related the use of *Ribes nigrum* with the reduction of hypertension and other cardiovascular-associated illnesses and neurodegenerative and ocular diseases.^{18,19} *Vitis vinifera* is known worldwide for its medicinal values including ocular promotion. It contains polyphenols that can attenuate ocular inflammation in humans and animal models.^{20,21}

We also hypothesize that the inflammatory status that typically characterizes such conditions could be also fostered by the presence of toxic compounds, including

antibiotics, even more present and concentrated within pet and human food chain.²²⁻²⁹ In fact, pet food production mainly relies on poultry meal,³⁰ with a bone inclusion rate of 20-30%, and dragging all those compounds with a high affinity for calcium, in particular oxytetracycline,²⁴ which has been demonstrated to be cytotoxic, genotoxic, and pro-inflammatory in vitro.^{23,25,27}

It is quite puzzling how, although Food and Drug Administration³¹ and World Health Organization³² established maximum residue limits in foods, antibiotic residues in foods are present.³³ Unfortunately, this is due to the lack of detailed regulations concerning the antibiotic concentration in bones,³⁴ which are one of the source of pet and human, eg, wurstel and food. This might explain the onset of ocular manifestations in our cohort of dogs as well as their rapid disappearance after a simple diet supplementation. Moreover, the significant and rapid improvement of symptoms of dogs involved in this clinical evaluation after diet supplementation is in agreement with that observed by Mazzeranghi et al in cats affected by cutaneous adverse food reactions.²⁴

Although we are aware that this work would benefit of further in vitro evaluations including immunological profile and serum oxytetracycline evaluation to clearly correlate symptoms onset and disappearance, it introduces a serious warning concerning the presence of toxic compounds in pet and human food and their contribution to the etiopathogenesis of certain clinical conditions.

STATEMENT OF AUTHORSHIP

The authors hereby certify that all work contained in this article is original. The authors claim full responsibility for the contents of the article.

CONFLICT OF INTEREST

The authors confirm that they do not have any conflict of interest

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