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Clinical Evaluation of Traditional Chinese Medicines for the Treatment of Canine Keratoconjunctivitis Sicca: A Comparison with Cyclosporine A

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Abstract: Keratoconjunctivitis Sicca (KCS) is a term used to describe a condition of decreased tear production. Another commonly used term to describe this disease is "dry eye". Cyclosporine A (CsA) is an efficient treatment for KCS. However, a significant number of canine KCS patients do not respond to CsA treatment. The aim of this study was to evaluate the efficacy of Traditional Chinese Medicines (TCM) in alleviating the clinical signs of KCS in dogs and to compare the efficacy with that of CsA ointment. This study included 19 dogs with KCS previously untreated with CsA. Dogs were randomly assigned to a treatment group and medicated daily for 8 weeks. After that time, the schirmer tear test result was 19.3±1.7 mm min^{-1} in the TCM group and 21.2±1.2 mm min^{-1} in the CsA group. The improvement in the clinical signs of inflammation in eyes treated with the TCM was equal to that in eyes treated with CsA ($p = 0.58$). In conclusion, the results of this study showed that the TCM is safe to use and the efficacy was equal to that of CsA. In addition, the method of oral administration was simpler and the treatment was less expensive than CsA ointment for the control of KCS in dogs.

Key words: Cyclosporine A, dry eye, keratoconjunctivitis sicca, traditional Chinese medicines, group

INTRODUCTION

Keratoconjunctivitis Sicca (KCS) is a Latin medical term used to describe a condition of decreased tear production. The term technically means inflammation of the cornea and conjunctiva from drying. When the watery part of tears is not produced in adequate amounts, the eye becomes chronically inflamed and scarring and pigmentation of the cornea may lead to a decrease in vision. Another commonly used term to describe this disease is "dry eye". KCS can be defined as a progressive inflammatory condition of the cornea and conjunctiva caused by a lack of tears and a deficiency of the pre-corneal tear film that is commonly encountered in small animal practice (Aguirre *et al*., 1971; Heijn, 1993; Kaswan *et al*., 1998; Moore *et al*., 2001). Tears play an important role in maintaining the health and normal functions of the cornea and conjunctiva; they provide essential nutrients to the cornea, help remove foreign matter and waste products and contain immunoglobulins, lysozymes and other components of the ocular defense mechanism. Therefore, it is not surprising that tear deficiency is a major cause of corneal and conjunctival inflammation. The disease is prevalent in dogs with a diagnosis of KCS made in 1-1.5% of all the dogs visiting veterinary teaching hospitals in North America (Kaswan and Salisbury, 1990).

In both humans and dogs, the most common form of dry eye is a quantitative deficiency in the middle, aqueous layer of the tear film. This deficiency can cause a large range of clinical signs, depending on the severity and duration of the disease. Acute cases may present with severe pain and corneal ulceration which may rapidly progress to corneal perforation and iris prolapse (Moore *et al*., 2001). Chronic cases present with classic signs of keratitis (including infiltration of inflammatory cells, vascularization, pigmentation and thickening) and conjunctivitis (including congestion, pigmentation and thickening) (Matheis *et al*., 2012). Mucoid to mucopurulent discharge is present and secondary bacterial infection is a common complication (Matheis *et al*., 2012).

There are numerous causes of KCS in dogs. Histopathological studies of lacrimal tissue of affected dogs show that lymphocytic-plasmacytic infiltration is associated with acinar atrophy, suggesting an immunemediated basis for the disease in this species (Fullard *et al*., 1995). The disease may also be associated

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Table 1: Ingredients of the Traditional Chinese Medicines (TCM) used in this study

Ingredients	Dosage (twice a day) (g/kg body weight)
Rehmannia	1.50
Codonopsis pilosulae radix	1.50
Chuanxiong	0.60
Radix astragali	0.30
Angelica	0.90
Chrysanthemum	0.90
Radix paeoniae	0.90

with systemic canine autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and pemphigus. In humans, it is also suspected that autoimmune inflammation of the lacrimal glands, mediated by T cells, similarly plays an important role in the disease pathogenesis (Pflugfelder *et al*., 1999).

Further, indication of the immune-mediated inflammatory etiology of the disease comes from the studies in dogs and human demonstrating that topical Cyclosporine A (CsA) is an efficient treatment for KCS. This immunosuppressive therapy results in a significant increase in tear production and improvement in the clinical signs of inflammation in dogs (Sansom *et al*., 1995) and for the past 15 years veterinarians have been using CsA ointment (Optimmune; Schering-Plough) or solution for the treatment of canine KCS. Successful trials in humans have recently led to the approval of a CsA ophthalmic emulsion (Restasis; Allergan) for the treatment of human patients (Stevenson *et al*., 2000).

However, a significant number of canine KCS patients do not respond to CsA treatment and patent and supply issues affect availability in some markets (Berdoulay *et al*., 2005). In this study, a Traditional Chinese Medicines (TCM) (Table 1) showed significant activity in animal models of dry eye diseases in particular in dogs. The aim of the present study was to test the therapeutic effect for KCS to confirm the efficacy of the TCM in alleviating the clinical signs of KCS in dogs and compare it with the veterinary form of CsA (Optimmune).

MATERIALS AND METHODS

Animals: The 19 canine KCS patients previously untreated with any medicines were included in the study. This study was approved by the institutional review board of our university. The dog owners read an information sheet and signed an informed consent form prior to participation. Dogs of either gender or age were enrolled in the study following diagnosis of uni or bilateral KCS. KCS was diagnosed when the Schirmer Tear Test (STT) reading was <15 mm min^{-1}. The exclusion criteria were any ophthalmic (including adnexal) disease or clinical signs attributable to disease states that might affect tear production (e.g., endocrine disease such as hypothyroidism) or concurrent medications that might affect tear production (e.g., systemic sulfonamides).

Treatments: The test material was the TCM which included rehmannia, codonopsis pilosulae radix, chuanxiong, radix astragali, angelica, chrysanthemum, radix paeoniae and poria. They were all herbal medicine and were stored at room temperature; the conditions of use are shown in Table 1. All drugs were administered orally. The stability of the formulation was guaranteed for the duration of the study if the required storage conditions were observed.

Optimmune (Schering-Plough), the commercial ophthalmic ointment approved for veterinary use containing 0.2% CsA was used as the comparative product. In cases of dry eye, topical treatment with antibiotic solution was not permitted. Secretions were cleaned from the lids 15 min prior to drug administration. When several medications were administered, the order of treatment was as follows: artificial tears followed by the KCS medication. Owners were instructed to wait 15 min between medications.

Dogs that met the inclusion criteria were randomly assigned to either the CsA or the TCM group. Both treatments were administered twice daily for 8 weeks in both eyes. In cases of unilateral disease, only the data of the affected eye were analyzed in this study.

Schirmer Tear Test (STT): A single batch of standard STT strips (Color Bar Schirmer tear test strip; Eagle Vision Corp.; Memphis, TN) was used on all animals to avoid any inconsistencies in absorbency (Hartley *et al*., 2006). All measurements were undertaken by the same individual and under similar conditions (e.g., temperature, humidity). STT samples were taken from all dogs between 10:00 a.m. and 12:00 p.m. Each STT strip was placed in the lateral third of the lower conjunctival sac for a period of 60 sec. All tests were performed indoors at a similar temperature and humidity. To minimize the stress caused to the animals and to simplify the statistical analysis both eyes were tested for each animal.

Evaluation of clinical efficacy: Upon enrollment and at weeks 2, 4, 6 and 8, all dogs underwent complete physical and ophthalmic examinations including slit-lamp biomicroscopy, the STT and indirect ophthalmoscopy. The STT was performed using commercial tear test strips from the same batch (Color Bar Schirmer tear test strip;

Eagle Vision Corp.; Memphis, TN). A complete medical history was recorded at each visit and all examinations of a given animal were conducted by the same practitioner.

Statistical analysis: This study was based on descriptive statistics and all analyses were conducted using Statistical Analysis Software (SAS; v. 8.1.3; SAS Institute Inc., Cary, NC, USA). Results were considered statistically significant if $p<0.05$.

RESULTS

Distributions of age in the groups: The 19 dogs had an average age of 39.9±7.4 months with a range from 25-59 months. The ages in the groups and the distributions of normal eye states in the study groups are shown in Table 2.

Study population: The 19 dogs were enrolled into the study of which 10 dogs were randomly assigned to treatment with the TCM and 9 to treatment with CsA. Of the 19 dogs that completed the study, all were diagnosed with bilateral disease. Therefore, the total number of eyes evaluated in this study was 38, of which 18 were treated with CsA and 20 were treated with the TCM. The dogs were all neutered and 73.7% of the subjects in the study population were female (Table 2).

Increase in tear production: At baseline (before treatment), the mean STT values in the TCM and the CsA groups were 7.31±1.3 mm min^{-1} (n = 20) (Fig. 1) and 6.5±1.1 mm min^{-1} (n = 18) (Fig. 2), respectively (p = 0.173).

Table 2: Distributions of age and neutering duration in the dry eye cases

Gender	No.	Age at which KCS occurred (months)	STT (mm)
Male	1	25	8.1
	2	46	7.3
	3	44	7.8
	4	37	6.1
	5	39	9.1
Female	1	30	6.7
	2	32	6.8
	3	37	6.6
	4	43	4.1
	5	43	6.7
	6	45	7.4
	7	36	5.6
	8	36	7.7
	9	43	7.1
	10	48	9.0
	11	36	8.1
	12	41	5.6
	13	59	5.9
	14	39	6.1

Statistically significant improvements from baseline were observed within both groups ($p<0.001$) at all follow-up visits. In the TCM group, mean STT values of 11.7±2.1, 16.4±2.1, 18.5±1.8 and 19.3±1.7 mm min^{-1} were observed at weeks 2, 4, 6 and 8 (Fig. 1), respectively compared to 13.1±1.8, 17.7±2.7, 19.8±1.4 and 21.2±1.2 mm min^{-1} in the CsA group (Fig. 2). Though at every recheck the improvement in STT in the TCM group was lower than that in the CsA group, the difference did not reach statistical significance (p = 0.58) (Fig. 3).

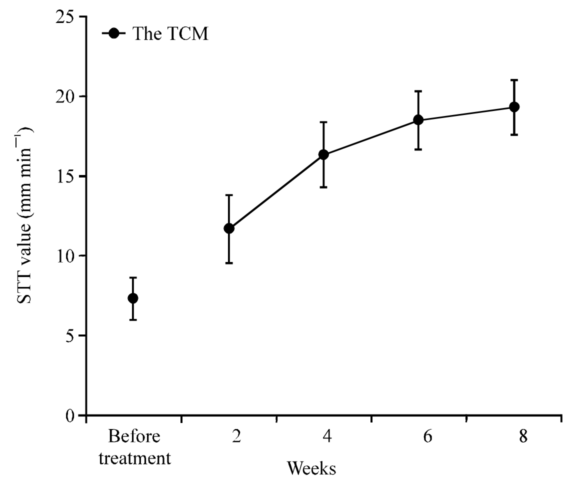

Fig. 1: Effect of the TCM powders (•) on tear production in dogs with KCS. The baseline STT in the TCM group was 7.31±1.3 mm min^{-1} (n = 20). Statistically significant improvements were seen after TCM treatment of 2, 4, 6 and 8 weeks

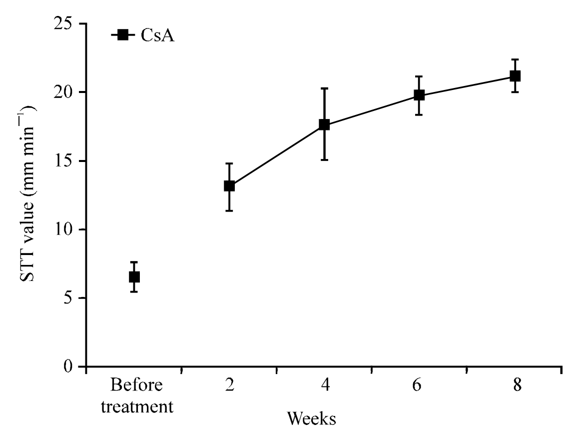

Fig. 2: Effect of CsA ointment (•) on tear production in dogs with KCS. The baseline STT in the CsA group was 6.5±1.1 mm min^{-1} (n = 18). Statistically significant improvements were seen after CsA treatment of 2, 4, 6 and 8 weeks

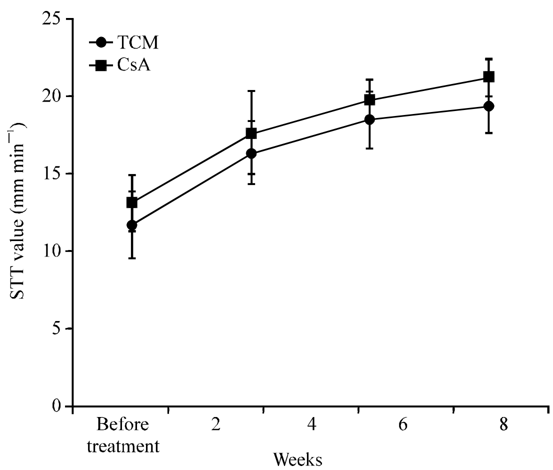

Fig. 3: Effects of the TCM powders (•) and CsA ointment (•) on tear production in dogs with KCS. No statistical significance (p = 0.58) was seen between the TCM and CsA groups

DISCUSSION

Diagnosis of KCS in the dog is based on STT values and clinical signs. The study by Hartley *et al.* (2006) showed that tear production variations with time of day, although present are not large in magnitude and therefore the clinical diagnosis of KCS does not need to control for the time of day. In our study, the fixed time of 10:00 a.m. to 12:00 p.m. was selected for the measurement of STT to reduce interference.

Variations in STT values with age and gender have been studied previously with some studies demonstrating no statistically significant effects and others significant effects on STT measurements (Hartley *et al*., 2006). Some studies demonstrated that neutered animals of either gender were more likely to be tear deficient within a population of ophthalmology cases (Kaswan *et al*., 1998). KCS has been reported to affect more females than males (Sansom *et al*., 1985; Barnett and Sansom, 1987). Other studies, however have shown similar incidences of KCS in males and females (Aguirre *et al*., 1971; Kaswan *et al*., 1985; Kern, 1989). In humans, a similar decline in tear production with age has been documented (Moss *et al*., 2004). For this reason, this study selected dogs younger than 6 years of age for dry eye investigations to avoid the interference of age and gender.

If factors of gender and breed that cause KCS could be ignored, the influence of hormones on canine KCS is thought to be a potential key factor. In further study, the correlation between neutering and the incidence/severity of KCS was analyzed. It remains to be established whether ocular surface dysfunction is related to estrogen/androgen imbalance. There are no studies in the veterinary literature that have investigated the correlation between KCS and neutering in dogs. Our experiments elucidated the mechanisms by which hormones regulate particular biomarkers expressed in the tissues of eyes affected with KCS. The findings of the study may allow us to understand the complex etiology of canine KCS and develop new strategies for the prevention of this disease in dogs. According to our further investigation, lasting for one year to date, the neutered dogs had a higher incidence rate (our results showed that the incidence of KCS in the neutered dogs was 9.5%) than normal dogs (the incidence in normal dogs is approximately 1-4%). The results demonstrated that the TCM was highly effective in alleviating the clinical signs of KCS in dog's with reduced tear secretion. In particular, a significant increase in tear secretion as well as a significant decrease in the clinical signs of inflammation were observed at the first recheck after 2 weeks of treatment. The effect of TCM was similar to that of CsA group. No statistical significance in the clinical signs of conjunctival and corneal inflammation was seen after 8 weeks of treatment (p = 0.58).

CONCLUSION

In the present study, the clinical efficacy of 0.2% cyclosporine ophthalmic ointment in controlling the clinical signs of KCS in dogs was similar to that previously described (Sansom *et al*., 1995). However, unlike previous observations, the response to CsA was independent of the initial KCS severity. Our results showed that the TCM is safe to use and the efficacy is equal to that of CsA. In addition, the method of oral administration is simple and the treatment is less expensive than CsA ointment for the control of KCS in dogs.

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