RESEARCH ARTICLE

Epidemiology of Canine Keratoconjunctivitis Sicca and the Efficacy of Cyclosporine and Tacrolimus in its Clinical Management and Tear Production: A Comparative Study

Apeksha S. Bhalodi[1*], Abhi S. Patel[2], Bhautik N. Saripadiya[3], Abhishek K. Patel[1], Arnold R. Mecvan[1], Ankush J. Mayani[1], Pinesh V. Parikh[1]

Abstract

Keratoconjunctivitis sicca (KCS) or dry eye is a significant cause of ocular morbidity in dogs. This study was aimed to determine the incidence of KCS and to compare the therapeutic efficacy of oil-based 2% cyclosporine and 0.03% tacrolimus ointment. Over a period of one-year, KCS was the most frequently diagnosed ophthalmic condition (24.70%, 41/166) among canine ocular affections. Incidence of KCS was the highest in dogs aged 1-5 years (65.85%), in females (58.54%), and in the Pug breed (43.90%). For the therapeutic trial, 26 client-owned dogs (52 eyes) were divided into two treatment groups: cyclosporine and tacrolimus and monitored for 60 days. The key clinical parameters, *viz.,* ocular discharge, conjunctival hyperaemia, corneal pigmentation and Schirmer tear test (STT) values were systematically scored. Both treatments significantly mitigated the inflammatory signs of ocular discharge and conjunctival hyperaemia ($p<0.05$). Treatment with tacrolimus successfully arrested the advancement of pigmentation, particularly in mild KCS cases, showing a statistically significant ($p<0.05$) advantage over 2% cyclosporine. 0.03% tacrolimus was also found to be significantly superior ($p<0.05$) to 2% cyclosporine in increasing STT values across all severity groups (mild, moderate, and severe) by day 60. In severe KCS cases, only tacrolimus produced a statistically significant increase in tear production. These findings underscores that while both agents address superficial inflammation, tacrolimus has a superior lacrimostimulant effect providing a superior therapeutic outcome by controlling the vision-threatening progression of corneal pigmentation for the management of canine KCS.

Key words: Canine, Cyclosporine, Keratoconjunctivitis sicca, Schirmer tear test, Tacrolimus, Tear production.

Ind J Vet Sci and Biotech (2026): 10.48165/ijvsbt.22.1.14

Introduction

Keratoconjunctivitis sicca (KCS) commonly known as dry eye, is a prevalent and often chronic ocular surface disease in dogs, characterized by inflammation of the cornea and conjunctiva resulting from an insufficient production of the aqueous component of the pre-corneal tear film (Williams, 2008). The tear film is a vital tripartite structure composed of lipid, aqueous, and mucin layers, which collectively serve to lubricate the ocular surface, provide essential nutrients to the avascular cornea, remove debris and offer antimicrobial protection (Dodi *et al.,* 2009). A deficiency in any of these components can compromise ocular health, leading to the clinical signs associated with KCS.

The etiology of KCS is multifactorial, but the most common form in dogs is immune-mediated, involving lymphocytic-plasmacytic infiltration and subsequent atrophy of the lacrimal glands (Giuliano and Moore, 2007; Dodi, 2015). Brachycephalic breeds such as Pugs and Shih Tzus are particularly predisposed, often due to anatomical factors like lagophthalmos which leads to increased tear evaporation (Williams, 2008). Clinically, KCS presents with signs ranging from conjunctival hyperaemia and mucoid to mucopurulent ocular discharge in acute stages, to corneal vascularization, pigmentation, ulceration and potential blindness in chronic cases (Berdoulay *et al.,* 2005). Diagnosis is based on clinical signs combined with quantitative tests like the Schirmer tear test (STT), which measures aqueous tear production and is the gold standard for diagnosing quantitative tear deficiency (Williams, 2005).

[1]Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Anand-388001, Gujarat, India

[2]Department of Veterinary Biotechnology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Anand-388001, Gujarat, India

[3]Department of Veterinary Gynaecology & Obstetrics, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Anand-388001, Gujarat, India

Corresponding Author: Dr. Apeksha S. Bhalodi, M.V.Sc. Scholar, Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, KU, Anand-388001, Gujarat, India. e-mail: aspatel13599@gmail.com

How to cite this article: Bhalodi, A. S., Patel, A. S., Saripadiya, B. N., Patel, A. K., Mecvan, A. R., Mayani, A. J., & Parikh, P. V. (2026). Effect of Cyclosporine and Tacrolimus on Aqueous Tear Production in Canine Keratoconjunctivitis Sicca: A Comparative Study. Ind J Vet Sci and Biotech, 22(1), 72-76.

Source of support: Nil

Conflict of interest: None

Submitted 07/11/2025 **Accepted** 29/11/2025 **Published** 10/01/2026

The mainstays of modern KCS therapy are calcineurin inhibitors, namely cyclosporine A (CsA) and tacrolimus, aimed at modulating the T-cell response mitigating clinical signs and stimulating tear production, replacing tear film components and reducing inflammation. Both cyclosporine A (CsA) and tacrolimus are calcineurin inhibitors that suppress T-cell activation, thereby reducing the immune-mediated destruction of lacrimal tissue and stimulating tear production (Kaswan *et al.,* 1984; Kino *et al.,* 1987). While CsA has long been the standard of care, tacrolimus is reported to be significantly more potent and can be effective in cases refractory to cyclosporine (Berdoulay *et al.,* 2005). Given the high prevalence of KCS and its impact on canine welfare, this study was undertaken with the primary objectives to record the incidence of KCS in the clinical canine population, and conduct a comparative evaluation of the therapeutic efficacy of oil-based 2% cyclosporine and 0.03% tacrolimus ointment, in resolving the key clinical manifestations of KCS, *viz.,* ocular discharge, conjunctival hyperaemia and corneal pigmentation with a specific focus on their ability to stimulate aqueous tear production so as to provide clearer guidance for clinical practice.

Materials and Methods

The present study was conducted at the Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Anand, between August 2023 and July 2024. Canine patients of various breeds, age and sexes presenting with clinical signs suggestive of Keratoconjunctivitis sicca (KCS) were included. A detailed history for each dog was recorded, including the owner's chief complaint, duration of symptoms, vision status and any prior ocular diseases or treatments. Signalment data (age, breed, sex) were also recorded for incidence analysis. Over a period of one-year, among 6141 total canine cases presented, 166 canine had ocular affections, of which 41 dogs were diagnosed to have KCS.

Ophthalmic Examination

All dogs underwent a comprehensive ophthalmic examination on day 0 (presentation) and at follow-up intervals on days 15, 30, and 60. By gross examination the following parameters were scored (Hendrix *et al.,* 2011).

Ocular Discharge Score: 0 = No discharge; 1 = Slight discharge at the medial canthus; 2 = Discharge across the cornea or on eyelid margins. *Conjunctival Hyperaemia Score:* 0 = No hyperaemia; 1 = Mild hyperaemia; 2 = Moderate hyperaemia. *Corneal Pigmentation Area Score:* 0 = No pigmentation; 1 = Pigmentation over <25% of the cornea; 2 = 25-50%; 3 = 50-75%; 4 = >75%.

Neuro-Ophthalmic Examinations

Pupillary Light Reflex (PLR): Assessed using a focal light source and graded as strong (+++), moderate (++), mild (+), or absent (-) (Strubble, 1991).

Menace Reflex: Elicited by a threatening hand gesture and graded as positive, sluggish, or absent (Slatter, 2001).

Palpebral Reflex: Assessed by touching the medial and lateral canthi and graded as positive, sluggish, or negative (Slatter, 2001).

Diagnostic Test

Schirmer Tear Test (STT): Performed using standardized commercial strips (Visioaid, SAVA Vet, Gujarat, India) placed in the lateral third of the lower conjunctival fornix for 60 seconds. The results were interpreted as: Normal (≥15 mm/min), Mild KCS (11-14 mm/min), Moderate KCS (6-10 mm/min), and Severe KCS (≤5 mm/min) (Corr, 2015).

Fluorescein Stain Test: A fluorescein-impregnated strip (Contacare ophthalmics, Gujarat, India) was moistened with sterile saline and applied to the bulbar conjunctiva. The cornea was examined with a cobalt blue light for stain retention, which would indicate an epithelial defect or ulceration.

Therapeutic Management and Grouping

A total of 26 dogs (52 eyes) were included in the therapeutic trial. The eyes were randomly allocated into two main treatment groups:

Group Cyclosporine (n=26 eyes): Treated with oil-based 2% Cyclosporine eye drops (prepared from Arpimune ME 100 mg capsules in corn oil) administered three times daily.

Group Tacrolimus (n=26 eyes): Treated with 0.03% Tacrolimus ointment (Tacrisight, Insight Eye Care Pvt. Ltd., Gujarat, India) administered twice daily.

Both groups also received 0.3% Carboxymethylcellulose eye drops (Oscinap, SAVA vet, Gujarat, India) and 0.5% Moxifloxacin eye drops (Moxifar, Vishal Pharma, Uttar Pradesh, India) as supportive therapy. For analysis, each treatment group was further stratified based on the initial STT value into Mild, Moderate, and Severe subgroups. The distribution was as follows: Mild (C) (n=10), Moderate (C) (n=8), Severe (C) (n=8), Mild (T) (n=8), Moderate (T) (n=11), and Severe (T) (n=7).

Statistical Analysis

The data were analysed using independent samples t-tests, one-way repeated measures ANOVA followed by Tukey's HSD test and two-way ANOVA. Statistical significance was set at $p<0.05$. All analyses were performed as described by Snedecor and Cochran (2014).

Results and Discussion

Incidence of KCS

During the study period, among the total of 6141 canine cases registered, 166 (2.70%) were presented with ophthalmic affections. Among these ocular conditions, KCS was the most prevalent, accounting for 24.70% (41/166) of cases. This was followed by cataracts (16.86%), corneal ulcers (16.26%), cherry eye (9.04%), corneal opacity (7.83%, and other conditions from

0.6 to 4.22 %, highlighting KCS as a primary cause of ocular morbidity in the studied population (Table 1).

Table 1: Total ocular affections and number of animals affected

Ocular affection	No. of dogs	Percent
KCS	41	24.70
Cataract	28	16.86
Corneal ulcer	27	16.26
Cherry eye	15	9.04
Corneal opacity	13	7.83
Conjunctivitis	7	4.22
Glaucoma	7	4.22
Eyelid growth	6	3.61
Proptosis	4	2.41
Retinal detachment	4	2.41
Progressive retinal atrophy (PRA)	3	1.81
Entropion	3	1.81
Pannus	3	1.81
Hyphema	2	1.20
Hypopion	1	0.60
Ectropion	1	0.60
Dermoid	1	0.60
Total	**166**	**100**

Age- and Sex-Wise Incidence

The incidence of KCS was highest in the 1-5 year age group (65.85%, 27/41), followed by dogs older than 5 years (26.83%, 11/41) and the least in dogs below 1 year of age (7.32%, 3/41). This finding aligned with previous reports suggesting that while KCS can affect dogs of any age, it is commonly diagnosed in young to middle-aged animals (Balicki *et al.,* 2008; Matheis *et al.,* 2012).

A higher incidence was observed in females (58.54%, 24/41) compared to males (41.46%, 17/41). This is consistent with literature suggesting a hormonal influence on lacrimal gland function, with lower androgen levels in females potentially predisposing them to immune-mediated inflammation (Dana and Hamarah, 2002; Bhavsar *et al.,* 2011).

Breed-Wise Incidence

Brachycephalic breeds were disproportionately affected. The Pug breed had the highest incidence (43.90%, n=18), followed by Shih Tzu and Lhasa Apso (12.20%, n=5 each), Labrador (9.75%, n=4), Pomeranian (7.31%, n=3) and others (Table 2). This strong predisposition is well-documented and attributed to anatomical factors such as exophthalmos and lagophthalmos, which increase the ocular surface area and lead to higher rates of tear evaporation (Renwick, 1996; Williams, 2008).

Table 2: Breed-wise incidence of KCS in dogs

Breed	No. of dogs	Percent
Pug	18	43.90
Shih Tzu	5	12.20
Lhasa Apso	5	12.20
Labrador	4	9.75
Pomeranian	3	7.31
German Shepherd	2	4.88
Rottweiler	2	4.88
Dachshund	1	2.44
Cocker Spaniel	1	2.44
Total	**41**	**100**

Etiological Factors and Vision Status

Out of the 52 eyes included in the therapeutic study, the cause of KCS was idiopathic (unknown) in the majority of cases (38.46%). Iatrogenic causes, such as corrected third eyelid gland prolapse ("cherry eye"), accounted for 19.23% of cases, reinforcing the importance of preserving the gland of the nictitating membrane during surgery. Other factors included lagophthalmos (11.54%), prior use of systemic sulfonamides (9.62%), cataract (9.62%), topical atropine (7.69%) and ectropion (3.84%) (Table 3). On presentation, 50% (26) of the affected eyes had complete vision, 34.62% (18) had partial vision, and 15.38% (8) were blind, underscoring the potential for KCS to cause severe vision loss if not managed effectively (Berdoulay *et al.,* 2005).

Table 3: Causative factors of KCS in dogs

Causative factors	No. of eyes	Percent
Unknown	20	38.46
Corrected third eyelid gland prolapse	10	19.23
Lagophthalmos	6	11.54
Prior treatment with systemic antibiotics	5	9.62
Cataract	5	9.62
Prior treatment with topical atropine	4	7.69
Ectropion	2	3.84
Total	**52**	**100**

Therapeutic Efficacy on Clinical Signs of KCS

Resolution of Ocular Discharge: Both cyclosporine and tacrolimus were highly effective at reducing ocular discharge. As shown in Table 4, both treatment groups demonstrated a statistically significant decrease in discharge scores over the 60-days trial ($p<0.05$). In mild cases, tacrolimus appeared to have a slightly faster onset of action, with significant improvement noted by day 15, compared to day 30 for cyclosporine. This improvement is a direct result of the drugs' anti-inflammatory and lacrimostimulant effects, which help normalize the tear film and reduce the compensatory overproduction of mucin (Bounous *et al.,* 1995; Best *et al.,* 2014).

Reduction of Conjunctival Hyperaemia: The anti-inflammatory properties of both drugs were evident in their ability to reduce conjunctival hyperaemia (Table 4). In mild and moderate cases, both treatments led to significant improvement. A notable difference was observed in the severe KCS group, where tacrolimus achieved a significant reduction in hyperaemia by day 30, whereas the cyclosporine group only showed significant improvement at the 60-days

endpoint. This suggests that the greater potency of tacrolimus may be clinically advantageous for controlling severe inflammation more rapidly (Izci *et al.,* 2002).

Management of Corneal Pigmentation: The most significant difference between the two therapies was in their effect on corneal pigmentation (Table 4). Across all severity levels, eyes treated with cyclosporine showed a continued, non-significant increase in the area of pigmentation over 60 days. In contrast, eyes treated with tacrolimus showed a trend towards stabilization and even slight reduction of pigmentation after an initial period. This difference reached statistical significance ($p<0.05$) in the mild KCS group at day 60. This finding is clinically paramount, as progressive pigmentation is a direct path to vision loss. The superior performance of tacrolimus in this area may be attributed to its greater potency reportedly 100 times that of cyclosporine allowing for more effective control of the chronic inflammatory processes that drive melanocyte migration onto the cornea (Thomson *et al.,* 1995; John, 2017).

Therapeutic Efficacy on Aqueous Tear Production

The primary measure of therapeutic efficacy for stimulating tear production was the Schirmer tear test (STT) (Table 5). Both treatment protocols successfully increased tear production over the 60-days study period, but tacrolimus demonstrated a significantly more potent effect, particularly in severe cases. In the *Mild KCS* groups, both cyclosporine and tacrolimus produced a significant increase in STT values from day 15 onwards. In the *Moderate KCS* groups, both drugs led to a significant increase from day 30 onwards. In the *Severe KCS* group, tacrolimus produced a significant increase in STT values from day 30 onwards. In stark contrast, the cyclosporine group showed no statistically significant increase in tear production even by day 60.

At the 60-days endpoint, a statistically significant difference ($p<0.05$) was observed between the two treatment protocols across all three severity groups, with tacrolimus consistently resulting in higher STT values (Table 4). The superior efficacy of tacrolimus was most pronounced in severe cases of KCS, where cyclosporine failed to produce a significant response in tear production. This confirms the superior lacrimostimulant effect of tacrolimus, especially in severe cases where lacrimal gland function is profoundly compromised, a finding consistent with previous studies (Hendrix *et al.,* 2011; Radziejewski and Balicki, 2016).

Table 4: Mean ± SE scores of ocular discharge, conjunctival hyperaemia and corneal pigmentation area in KCS affected dogs following cyclosporine (C) and tacrolimus (T) treatment

Criteria	Group	Day 0	Day 15	Day 30	Day 60
Ocular discharge score	Mild (C)	0.7 ± 0.21^{a}	0.6 ± 0.16^{ab}	0.1 ± 0.10^{bc}	0.0 ± 0.0^{c}
	Mild (T)	1.0 ± 0.19^{a}	0.25 ± 0.16^{b}	0.13 ± 0.13^{b}	0.0 ± 0.0^{b}
	Moderate (C)	1.37 ± 0.18^{a}	1.0 ± 0.27^{ab}	0.75 ± 0.31^{b}	0.63 ± 0.26^{b}
	Moderate (T)	1.45 ± 0.16^{a}	1.18 ± 0.18^{ab}	0.91 ± 0.16^{bc}	0.55 ± 0.21^{c}
	Severe (C)	1.88 ± 0.13^{a}	1.5 ± 0.19^{ab}	1.13 ± 0.30^{b}	1 ± 0.33^{b}
	Severe (T)	1.86 ± 0.14^{a}	1.57 ± 0.20^{ab}	1.14 ± 0.26^{bc}	0.57 ± 0.20^{c}
Conjunctival hyperaemia score	Mild (C)	0.9 ± 0.23^{a}	0.3 ± 0.15^{b}	0.2 ± 0.13^{b}	0.0 ± 0.0^{b}
	Mild (T)	0.75 ± 0.16^{a}	0.25 ± 0.16^{b}	0.0 ± 0.0^{b}	0.0 ± 0.0^{b}
	Moderate (C)	1.25 ± 0.25^{a}	1.0 ± 0.27^{a}	0.37 ± 0.18^{b}	0.12 ± 0.13^{b}
	Moderate (T)	1.36 ± 0.20^{a}	1.18 ± 0.26^{a}	0.54 ± 0.21^{b}	0.27 ± 0.14^{b}
	Severe (C)	1.62 ± 0.18^{a}	1.37 ± 0.18^{a}	1.25 ± 0.16^{ab}	0.5 ± 0.19^{c}
	Severe (T)	1.71 ± 0.18^{a}	1.42 ± 0.20^{a}	0.85 ± 0.14^{b}	0.28 ± 0.18^{c}
Corneal pigmentation area score	Mild (C)	1.8 ± 0.20	1.9 ± 0.23	2.1 ± 0.35	2.2 ± 0.33*
	Mild (T)	1.0 ± 0.27	1.38 ± 0.38	0.88 ± 0.23	0.88 ± 0.23*
	Moderate (C)	2.13 ± 0.40	2.38 ± 0.38	2.63 ± 0.32	2.88 ± 0.35
	Moderate (T)	1.8 ± 0.45	2.45 ± 0.37	2.00 ± 0.27	1.91 ± 0.48
	Severe (C)	2.88 ± 0.44	3.25 ± 0.25	3.38 ± 0.26	3.50 ± 0.19
	Severe (T)	2.71 ± 0.52	3.00 ± 0.38	2.71 ± 0.42	2.57 ± 0.30

Values with different superscripts (a, b, c) within a row represent significant differences ($p<0.05$) within groups. An asterisk (*) indicates a significant difference ($P<0.05$) between treatment groups at day 60.

Table 5: Mean ± SE values (mm/min) of Schirmer tear test (STT) in KCS affected dogs following cyclosporine (C) and tacrolimus (T) treatment

Group	Day 0	Day 15	Day 30	Day 60
Mild (C)	12.7 ± 0.33^{a}	13.9 ± 0.23^{b}	15.2 ± 0.36^{c}	16.4 ± 0.31^{d}*
Mild (T)	12.5 ± 0.42^{a}	14.37 ± 0.38^{b}	16.5 ± 0.42^{c}	18.37 ± 0.46^{d}*
Moderate (C)	7.75 ± 0.56^{a}	8.0 ± 0.57^{a}	10.25 ± 0.73^{b}	12.37 ± 1.0^{b}*
Moderate (T)	8.18 ± 9.27^{a}	8.81 ± 0.55^{a}	12.0 ± 0.45^{b}	14.54 ± 0.49^{c}*
Severe (C)	3.62 ± 0.32^{a}	3.75 ± 0.37^{a}	3.76 ± 0.31^{a}	3.85 ± 0.42^{a}*
Severe (T)	3.71 ± 0.29^{a}	3.85 ± 0.34^{a}	5.14 ± 0.26^{b}	5.85 ± 0.40^{c}*

Values with different superscripts (a, b, c, d) within a row differ significantly ($p<0.05$). An asterisk (*) indicates a significant difference ($p<0.05$) between treatment groups at day 60.

Conclusions

The current study revealed that Keratoconjunctivitis sicca (KCS) is the most frequently diagnosed ophthalmic condition in the canine population of Anand region, with a higher prevalence in female dogs, those aged 1-5 years, and particularly in the Pug breed. Both 2% cyclosporine and 0.03% tacrolimus effectively reduced ocular discharge, conjunctival redness, and stimulated aqueous tear production in dogs with mild to moderate KCS, but tacrolimus showed superior control over corneal pigmentation - a key factor in vision loss. By better preventing pigmentation and addressing both inflammatory and chronic signs, and stimulating aqueous tear production, as measured by the Schirmer tear test, across all severities of KCS and in particular sever cases, 0.03% tacrolimus emerges as a more effective long-term therapy of choice for managing canine KCS.

Acknowledgement

We are grateful to the authorities of Kamdhenu University, and Principal, College of Veterinary Science, Anand for the facilities provided for this study.

References

Balicki, I., Radziejewski, K., & Silmanowicz, P. (2008). Studies on keratoconjunctivitis sicca incidence in crossbred dogs. *Polish Journal of Veterinary Sciences*, *11*(4), 353-358.

Berdoulay, A., English, R.V., & Nadelstein, B. (2005). Effect of topical 0.02% tacrolimus aqueous suspension on tear production in dogs with keratoconjunctivitis sicca. *Veterinary Ophthalmology*, *8*(4), 225-232.

Best, L.J., Hendrix, D.V., & Ward, D.A. (2014). Diagnosis & treatment of keratoconjunctivitis sicca in dogs. *Today's Veterinary Practice*, *4,* 16-22.

Bhavsar, A.S., Bhavsar, S.G., & Jain, S.M. (2011). A review on recent advances in dry eye: Pathogenesis and management. *Oman Journal of Ophthalmology*, *4*(2), 50-56.

Bounous, D.I., Carmichael, K.P., Kaswan, R.L., Hirsh, S., & Stiles, J. (1995). Effects of ophthalmic cyclosporine on lacrimal gland pathology and function in dogs with keratoconjunctivitis sicca, Veterinary and Comparative Ophthalmology, *5*(1), 5-12

Corr, A. (2015). Canine Keratoconjunctivitis Sicca (KCS). Canine dry eye. Metropolitan Veterinary Associates & Emergency Services, Newsletter, *4*(1), 2

Dana, M.R., & Hamrah, P. (2002). Role of immunity and inflammation in corneal and ocular surface disease associated with dry eye. *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3: Basic Science and Clinical Relevance Part A and B*, p. 729-738.

Dodi, P.L., Zanotti, C., Rossi, S., & Aloe, L. (2009). Tear level of nerve growth factor in normal dogs. *Acta Ophthalmologica*, *87*(244), 327.

Dodi P. L. (2015). Immune-mediated keratoconjunctivitis sicca in dogs: current perspectives on management. *Veterinary Medicine*, *6*, 341-347.

Giuliano, E.A., & Moore, C.P. (2007). Diseases and surgery of the lacrimal secretory system. *Veterinary Ophthalmology*, *4,* 633-661.

Hendrix, D.V., Adkins, E.A., Ward, D.A., Stuffle, J., & Skorobohach, B. (2011). An investigation comparing the efficacy of topical ocular application of tacrolimus and cyclosporine in dogs. *Veterinary Medicine International*, *2011,* 487592

Izci, C., Celik, I., Alkan, F., Ogurtan, Z., Ceylan, C., Sur, E., & Ozkan, Y. (2002). Histologic characteristics and local cellular immunity of the gland of the third eyelid after topical ophthalmic administration of 2% cyclosporine for treatment of dogs with keratoconjunctivitis sicca. *American Journal of Veterinary Research*, *63*(5), 688-694.

John, C. (2017). Early detection, pathophysiology and management of keratoconjunctivitis sicca in canine. *M.V.Sc. Thesis*. Deemed university, Indian Veterinary Research Institute, Izatnagar, Bareilly, UP, India

Kaswan, R.L., Martin, C.L., & Chapman Jr, W.L. (1984). Keratoconjunctivitis sicca: histopathologic study of nictitating membrane and lacrimal glands from 28 dogs. *American Journal of Veterinary Research*, *45*(1), 112-118.

Kino, T., Hatanaka, H., Miyata, S., Inamura, N., Nishiyama, M., Yajima, T., Goto, T., Okuhara, M., Kohsaka, M., & Aoki, H. (1987). FK-506, a novel immunosuppressant isolated from a Streptomyces. II. Immunosuppressive effect of FK-506 *in vitro*. *The Journal of Antibiotics*, *40*(9), 1256-1265.

Matheis, F.L., Walser-Reinhardt, L., & Spiess, B.M. (2012). Canine neurogenic kerato-conjunctivitis sicca: 11 cases (2006-2010). *Veterinary Ophthalmology, 15*(4), 288-290.

Radziejewski, K., & Balicki, I. (2016). Comparative clinical evaluation of tacrolimus and cyclosporine eye drops for the treatment of canine keratoconjunctivitis sicca. *Acta Veterinaria Hungarica, 64*(3), 313-329.

Renwick, P. (1996). Diagnosis and treatment of corneal disorders in dogs. *In Practice*, *18*(7), 315-328.

Slatter, D. H. (2001). Basic diagnostic tests. In: Slatter, D. H. (ed). *Fundamentals of Veterinary Ophthalmology*. 3rd edn., Saunders, Saint Louis, Missouri, USA, pp. 85-123.

Snedecor, G.W., & Cochran, W.G. (2014). *Statistical Methods*. 8th edn., The Iowa State University Press, Ames, Iowa, USA.

Strubble, D.T. (1991). Ophthalmic examination and Diagnostic procedures. In: Gelatt, K. N (ed). *Veterinary Ophthalmology*. 3rd edn., Lippincott, William and Wilkins, Baltimore, Maryland, USA, pp. 427-430.

Thomson, A.W., Bonham, C.A., & Zeevi, A. (1995). Mode of action of tacrolimus (FK506): molecular and cellular mechanisms. *Therapeutic Drug Monitoring*, *17*(6), 584-591.

Williams, D.L. (2005). Analysis of tear uptake by the Schirmer tear test strip in the canine eye. *Veterinary Ophthalmology*, *8*(5), 325-330.

Williams, D.L. (2008). Immunopathogenesis of keratoconjunctivitis sicca in the dog. *Veterinary Clinics of North America: Small Animal Practice*, *38*(2), 251-268.