수의학석사학위논문

Clinical Features and Prognosis of Corneal Ulcers in Dogs with Chronic Kidney Disease

만성 신장 질환이 있는 개에서 발생한 각막 궤양의 양상 및 예후

2017년 2월

서울대학교 대학원

수의학과 임상수의학 전공

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Clinical Features and Prognosis of Corneal Ulcers in Dogs with Chronic Kidney Disease

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ABSTRACT

Delayed corneal healing could lead to complications such as corneal vascularization and uveitis in corneal ulcer. Insufficient stromal regeneration affected by complicated healing process could result in a weak corneal structure to maintain the globe. Healing of the cornea could be affected by the presence of systemic disease. In practice, chronic kidney disease (CKD) is known that one of the most common systemic diseases seen in corneal ulcer patients. This study was perforned to investigate the characteristics of

corneal ulcers in dogs with chronic kidney disease (CKD). Medical records of 34 dogs (38 eyes) that had been diagnosed with corneal ulcers and chronic kidney disease at Haemaru Referral Animal Hospital from April, 2011 to March, 2016 were investigated. A control group was randomly selected during the same time period (31 dogs, 37 eyes) which was included patients with corneal ulcers but no evidence of systemic disease. The mean healing time of superficial corneal ulcers in the CKD group was 21.0 ± 15.0 days, which was significantly longer than that was observed in the control group (11.0 ± 6.6 days, $p < 0.05$). The incidence rates of uveitis and keratoconjunctivitis sicca in the CKD group were significantly higher than in the control group ($p < 0.01$ and $p < 0.05$, respectively). The healing process of the corneal ulcers with CKD patients could be complicated by KCS and uveitis, therefore, prompt and aggressive treatment would be recommended when corneal ulcer was diagnosed in CKD patients.

Keywords: corneal ulcer, chronic kidney disease, uveitis, keratoconjunctivitis sicca, dog

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CONTENTS

INTRODUCTION

Corneal ulcers are caused by inadequate corneal epithelial protection or excessive corneal epithelial loss. Each component of the cornea heals at a different rate, and simple corneal ulcer should resolve within 7 days without progression into the stroma (Maggs, 2007). Delayed corneal healing could lead to complications such as corneal vascularization, uveitis and insufficient stromal regeneration and these conditions could result in a weak corneal structure to maintain the globe (Ledbetter and Gilger, 2013).

Healing of corneal ulcers could be delayed due to concurrent ophthalmic problems such as eyelid dysfunction, chronic irritation (e.g. distichiasis, eyelid tumors), and tear film deficiencies (e.g. keratoconjunctivitis sicca, meibomianitis). In these cases, concurrent problems should also be controlled if not, the ulcer could become complicated. Even though there was no any other ocular problems, healing of the cornea could also be affected by the presence of systemic disease. It is well known that hyperadrenocorticism and herpes virus infection delay the healing of corneal ulcers (Aroch *et al*., 2007; Cullen and Webb, 2013). Chronic kidney disease (CKD) is one of the more common systemic diseases seen in patients with corneal ulcers.

This study was performed to identify the clinical characteristics of corneal ulcers in patients with CKD and to demonstrate the correlation between CKD and healing time for corneal ulcers.

MATERIALS AND METHODS

1. Patient selection

Medical records of dogs that had been diagnosed with corneal ulcers and chronic kidney disease at Haemaru Referral Animal Hospital between April 1, 2011 and March 31, 2016 were investigated. The CKD patients were divided into 4 stages according to the International Renal Interest Society (IRIS) guidelines (Polzin, 2011). Stage 1 CKD patients were excluded from this study because they were not clinically symptomatic except inadequate urinary concentrating ability, abnormal renal imaging findings and proteinuria (Table 1). Medical records of the corneal ulcer patients with CKD IRIS stage 2, 3 and 4 were reviewed between the development of the ulcer and its ultimate healing or death.

The control group was consisted of patients with corneal ulcers who had been randomly selected from the same hospital during the same time period. To minimize statistical interference of age and other systemic disease, patients in the control group were selected to be more than 10 years old with no evidence of kidney disease. The patients who had a history of hyperadrenocorticism or long-term steroid therapy were excluded because these conditions were reported to have a negative effect on corneal healing (Cullen and Webb, 2013; Ledbetter and Gilger, 2013).

Table 1. IRIS stages of CKD based on blood creatinine concentration (Polzin, 2011)

Stage	Blood creatinine (mg/dL)		Comments
	Dog	Cat	
1	< 1.4	< 1.6	Nonazotemic, Some other renal abnormality present.
2	1.4 – 2.0	1.6 – 2.8	Mils renal azotemia clinical signs usually mild or absent.
3	2.1 – 5.0	2.9 – 5.0	Moderate renal azotemia. Many extrarenal clinical signs may be present.
4	> 5.0	> 5.0	Increasing risk of systemic clinical signs and uremic crisis.

2. Data selection

Medical records including signalment, the date of diagnosis of the corneal ulcer and the date of healing, concurrent eye disease, blood urea nitrogen (BUN) concentration, plasma creatinine concentration, white blood cell count (WBC), type of corneal ulcer, surgical treatment, prognosis and concurrent systemic disease were analyzed. Within these patients, patients who lost the follow up of corneal ulcer or abandon the treatment were excluded. The analysis of the BUN (normal range 9-31 mg/dL), creatinine (normal range 0.5 - 1.5 mg/dL) were accomplished with chemical analyzer (IDEXX VetTest®, California, USA) and WBC (normal range 2.87 - 17.02 K/μL) was analyzed with Hematology analyzer (IDEXX ProCyte Dx®, California, USA). Corneal ulcers and status were evaluated via fluorescein staining (Haag-Streit AG, Koeniz, Switzerland) and slit lamp biomicroscopy (Topcon Corporation, Tokyo, Japan). Routine topical treatments were performed depending on the severity of the ulcer; these included antibiotics [Tobramycin (Ocuracin®, Samil Pharm.Co., Ansan, Korea), Ofloxacin (Ocuflox®, Samil Pharm.Co., Ansan, Korea), Ciprofloxacin (Cipex®, Samil Pharm.Co., Ansan, Korea), levofloxacin (Cravit®, Santen Pharmaceutical Co., Osaka, Japan)], hyaluronate (Lacure®, Allergan, Inc, Ansan, Korea), 1% EDTA (Ethylendiamine-tetraacetic acid disodium salt dehydrate, Sigma-Aldrich Co., St. Louis, USA) diluted in artificial tears, 4% acetylcysteine (Mucomyst®, Boryung Pharm, Ansan, Korea) diluted in artificial tears and autologous serum eye drops. The corneal ulcers were allocated to one of four categories: superficial (uncomplicated, simple or erosive, loss of less than one-third of the stroma), deep [stromal or exposing

descemet's membrane (descemetocele), complicated, loss of more than two-thirds of the stroma], melting and perforated (Kim *et al*., 2009). The criterion of the corneal healing was confirmed by the negative result of fluorescein stain test and unhealing criterion was including the positive result of fluorescein stain test or death before healing.

3. Statistical analyses

The age of the patients and the healing time for the ulcers were expressed as mean ± standard deviation (SD) for each group. Statistical analyses were performed using a commercial software program (SPSS 21.0, SPSS Inc.). The Kruskal-Wallis test was employed to compare the distribution of the type of corneal ulcer and the incidence of concurrent disease between the CKD and control groups. Correlation between corneal status and severity of uveitis was assessed using a Pearson's correlation coefficient. The effect of surgical intervention on healing of the ulcer was evaluated using Kendall's tau method. To compare the mean age of the patients, BUN, creatinine, WBC and the healing time for the ulcers, Student's *t*-test was used. *P* values of less than 0.05 were considered statistically significant.

RESULTS

After reviewed 814 medical records of CKD dogs, the CKD group was 34 patients (38 eyes) who were diagnosed as corneal ulcer with above IRIS CKD stage 2. The control group consisted of 31 dogs (37 eyes). The mean ages of the patients in the CKD and control groups were 13.5 ± 2.5 and 12.6 ± 1.8 years old, respectively, and there was no significant difference between the groups ($p > 0.05$). The predominant breed in both groups was Shih-tzu (Table 2).

Table 2. Breed predisposition of corneal ulcer patients

	CKD group (n=34)	**Control group (n=31)**
Shih-tzu	12	18
Yorkshire terrier	6	-
Maltese	5	4
Pekingese	3	1
Mixed breed	3	2
Miniature schnauzer	2	1
Pomeranian	1	1
Cocker spaniel	1	1
Poodle	1	-
Miniature pinscher	-	1
Chow chow	-	1
Dachshund	-	1

1. Concurrent ophthalmic diseases

The concurrent ophthalmic diseases in order of prevalence were uveitis, keratoconjunctivitis sicca (KCS), and glaucoma in both groups (Figure 1). However, the incidence of uveitis and KCS was significantly higher than in the CKD group than in the control group ($p < 0.01$ and $p < 0.05$, respectively). Correlation of corneal status with severity of uveitis was statistically significant in CKD group ($r^2 = 0.08$, $p < 0.05$).

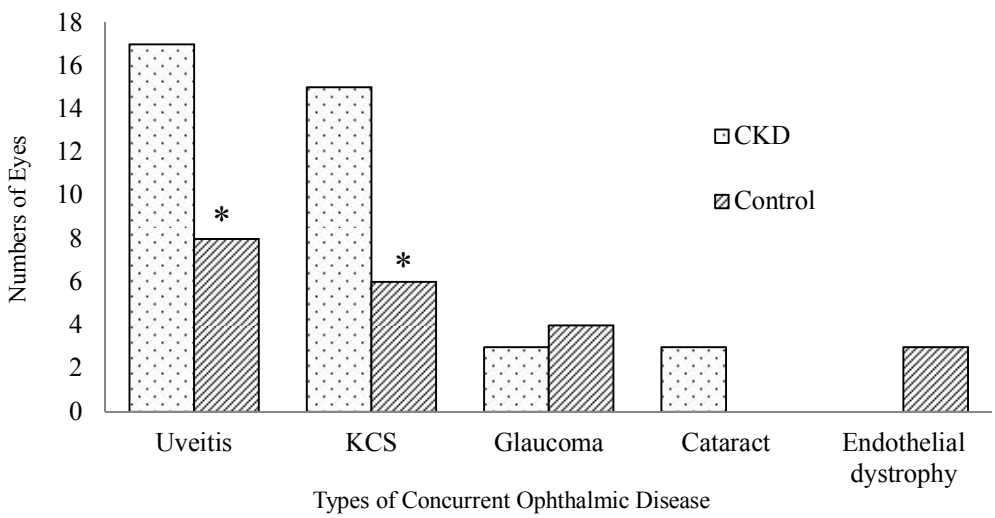

Figure 1. Concurrent ophthalmic diseases in each group.

*Significantly different compared to CKD group.

2. Clinical features of corneal healing

The CKD group contained of 17 eyes with superficial ulcers (45%), 8 eyes with stromal ulcers (21%), 6 eyes with melting ulcers (16%), and 7 eyes with perforated ulcers (18%). The control group contained 20 eyes with superficial ulcers (52.6%), 16 eyes with stromal ulcers (43.2%), and 2 eyes with perforated ulcers (5.4%). The type of corneal ulcer did not differ significantly different between the two groups ($p > 0.05$). In the CKD group, 11 out of 17 eyes (64.7%) with superficial ulcers healed, whereas all eyes with superficial ulcers in the control group healed. The mean healing time for superficial ulcers in the CKD group was 21.0 ± 15.0 days, which was significantly longer than the mean healing time for the same type of ulcer in the control group (11.0 ± 6.6 days, $p < 0.05$). Only two eyes (25%) with stromal ulcers in the CKD group healed and the mean healing time was 38 days, while 14 eyes (87.5%) with the same type of ulcer in the control group healed over an average of 17.1 ± 10.4 days. No eyes with melting ulcers healed and only one eye with a perforated ulcer (50%) healed in CKD group; the perforated ulcer took 92 days to heal. In control group, there were no eyes with melting ulcers. Only one of the eyes with a perforated ulcer (50%) in the control group healed, after 64 days (Table 3). Stromal, melting, and perforated ulcers in CKD and control groups could not be statistically compared because the numbers of healed eyes were too small to determine statistical significance.

Table 3. Healing ratio and healing time of corneal ulcer in CKD and control group

Type of ulcer	CKD		Control	
	Healing ratio (%)	**Mean healing time (days)**	**Healing ratio (%)**	**Mean healing time (days)**
Superficial	11/17 (64.7)	21.0 ± 15.0*	20/20 (100.0)	11.0 ± 6.6
Stromal	2/8 (25.0)	38.0 ± 0.0	14/16 (87.5)	17.1 ± 10.4
Melting	0/6 (0.0)	-	-	-
Perforated	1/7 (14.3)	92.0 ± 0.0	1/2 (50.0)	64.0 ± 0.0

* mean ± SD

3. Correlations with BUN, creatinine and WBC

BUN, creatinine and WBC were reviewed in the CKD group (Table 4). Healing versus nonhealing eyes correlation with BUN, creatinine and WBC could not be analyzed in the stromal, melting and perforated ulcers due to small numbers of eyes. Therefore, these correlations were investigated only in the superficial ulcer with CKD group (Table 5). According to the results, BUN, creatinine and WBC did not significantly affect the superficial ulcer prognosis in the CKD group.

Table 4. The mean values of BUN, creatinine and WBC in the CKD group

Type of ulcer	BUN* (eyes/total)	Creatinine* (eyes/total)	WBC** (eyes/total)
Superficial	71.4 ± 38.8 (16/17)	2.5 ± 2.2 (16/17)	15.6 ± 12.7 (12/17)
Deep	96.6 ± 74.6 (8/8)	2.8 ± 2.0 (8/8)	21.8 ± 9.7 (7/8)
Melting	116.3 ± 99.2 (6/6)	3.3 ± 2.4 (6/6)	21.6 ± 6.3 (6/6)
Perforated	72.3 ± 59.4 (7/7)	2.0 ± 1.6 (7/7)	21.0 ± 8.5 (7/7)

* mg/dL, ** K/μL

Table 5. The healing *vs* nonhealing mean value of BUN, creatinine and WBC in the superficial ulcers in CKD group

		N (eyes)	Mean ± SD
BUN (mg/dL)	healing	10	60.90 ± 28.63
	nonhealing	6	89.00 ± 49.40
Creatinine(mg/dL)	healing	10	1.85 ± 0.58
	nonhealing	6	3.67 ± 3.38
WBC (K/μL)	healing	8	18.61 ± 14.38
	nonhealing	4	9.52 ± 5.62

4. Correlations with surgical intervention

Surgical intervention was performed in 11 eyes in the CKD group. This included temporary tarsorrhaphy, conjunctival graft, and direct corneal suture. However, surgical intervention did not significantly affect corneal healing time in the CKD group (Table 6, $p > 0.05$).

Table 6. The healing *vs* nonhealing ratio of surgical interventions in CKD group

		Eyes (%)
Surgical intervention	Healing	3 (40.7%)
	Nonhealing	8 (59.3%)
Non-surgical intervention	Healing	11 (27.3)
	Nonhealing	16 (72.7%)

DISCUSSION

In practice, many clinicians have noted that corneal ulcers in dogs with CKD are often complicated or do not get healed and have considered that the presence of KCS can be one of the reasons as it is in humans. In this study, retrospective evaluation was performed to identify characteristic differences between corneal ulcers in dogs with CKD and healthy dogs. The incidence of corneal ulcers in dogs with CKD in this study was 4.2% (34 dogs of 814 CKD dogs). Similar to a previous study that reported that brachycephalic breeds were prone to corneal ulcers, Shih-tzu was the predominant breed with corneal ulcers in both the control and CKD groups in this study (Kim *et al.*, 2009).

The most common concurrent ocular disease was uveitis (44.7% in the CKD group, 21.6% in the control group). The correlation between type of corneal ulcer and severity of uveitis was statistically significant ($r^2 = 0.08$, $p < 0.05$). The incidence of uveitis was significantly higher in the CKD group than in the control group ($p < 0.01$). Uveitis might be followed by the development of a corneal ulcer, and it might affect negatively healing of the ulcer.

KCS was the second most common concurrent ocular disorder in both groups and was thought to be the main cause of the corneal ulcers. The incidence rate of KCS was significantly higher in the CKD group (36.8%) than in the control group (16.2%, $p < 0.05$). The mechanism behind the development of KCS in CKD has been described in humans as squamous metaplasia of conjunctival epithelium and transformation of

secretory conjunctival epithelium into non-secretory keratinized epithelium. This, in addition to dehydration caused by a decreased ability to concentrate urine and anorexia, leads to KCS (Porter and Crombie, 1973). It has not yet been proven that this metaplasia occurs in the dog conjunctival epithelium as well, and further study is required.

Many articles in human medicine refer to the relationship between CKD and ocular disease. One human study evaluating corneal and conjunctival calcification in CKD patients reported that calcification and reduced tear production were the reasons for the red eye seen in these patients (Porter and Crombie, 1973). Another study investigating ocular surface disorders reported that CKD patients showed significantly abnormal tear film production (Ozdemir *et al*., 2004). A report on ocular changes in children with CKD revealed that dry eye syndromes were more common among these children (Akinci *et al*., 2009). Despite the fact that a number of these studies exist in humans, there have been few studies evaluating the relationship between ocular changes and CKD in dogs.

In this study, all dogs in the CKD group with nonhealing ulcers had elevated WBC counts. Although elevated WBC had not been statistically significant, it should be considered that the cornea could be affected by systemic condition. Chronic kidney disease leads to metabolic changes that result in acute or chronic systemic inflammatory changes in the organs. A previous study showed that inflammatory biomarkers including C-reactive protein (CRP) and interleukin-6 were significantly elevated in CKD patients. Oxidative stress biomarkers including plasma protein

carbonyl groups, plasma free F_2-isoprostane, and plasma protein reduced thiols were also significantly elevated in these patients (Oberg *et al*., 2004). Another study shows the mechanism of aldosterone-induced systemic inflammation of CKD patients (Gilbert and Brown, 2010). Elevated aldosterone level of CKD patients stimulates the activation of the mineralocorticoid receptor in adipocytes and increasing oxidative stress than contributes to insulin resistance. Furthermore, metabolic acidosis status and malnutrition-inflammation complex syndrome could affect the homeostasis of CKD patients (Kalantar-Zadeh *et al*., 2004). Unfortunately, the inflammation markers or oxidative stress markers could not be collected in this study. But these markers might be the prognostic factor of corneal ulcer as a systemic disease. Although the elevated WBC counts was not significant in this study, the correlation between inflammation and corneal ulcer healing process in CKD patients would be necessary to be reevaluated with early markers and more cases.

Severity of corneal ulcers did not differ significantly between the two groups ($p > 0.05$). However, eyes with superficial ulcers in the CKD group took significantly longer to heal than those in the control group ($p < 0.05$). Healing times of stromal ulcers, melting ulcers, and perforated ulcers could not be compared statistically because there numbers were too small.

Usually, surgical intervention such as the creation of a conjunctival flap results in shorter healing times (Kim *et al*., 2009), but in this study there was no significant effect. This result might be influenced by the high mortality rate the patients requiring surgical intervention. Healing time could not be properly evaluated in 12 dogs (15 eyes)

because they died of CKD complications within one month of the diagnosis of a corneal ulcer.

While investigating this study, there were considerable factors that could be affecting the prognosis. First factor was creatinine level. Although it was not significantly related to prognosis in this study ($p > 0.05$), if the early biomarker of renal function like symmetric dimethylarginine (SDMA) were used, it could be affect the results. A recent study was reported that plasma (or serum) concentration of SDMA reflects GFR in cats and dogs, may be more sensitive than blood creatinine for early detection of CKD, and may be less affected by loss of lean body mass than blood creatinine (Nabity *et al*., 2015). The second factor was WBC which was revealed as not significant factor in this study. But incidence rate of uveitis in the CKD group was significant, so that the systemic inflammatory conditions might be evaluated in the late stage of CKD group, especially concurrent with uveitis. The early inflammatory marker, like CRP concentration would be included in the further study. The last factor should be considered was hydration status of CKD patients. Dehydration could lead the temporal KCS status, serial estimations of lacrimal secretion before and after hydration, and after healing process (Miller PE, 2008).

There were lots of variations that affect corneal healing process in CKD patients. Although there were many limitations in this study, concurrent uveitis and KCS were more common in CKD patient and delayed healing time was proved. Understandings of the mechanism between CKD patients and delayed corneal healing would be necessary to treat corneal ulcer.

CONCLUSIONS

In this study, the incidence rates of uveitis and keratoconjunctivitis sicca in the CKD group were significantly higher than in the control group and the healing process of the corneal ulcers with CKD patients were delayed significantly, therefore, early, aggressive treatment would be recommended.

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국 문 초 록

만성 신장 질환이 있는 개에서 발생한 각막 궤양의 양상 및 예후

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만성 신장 질환 (chronic kidney disease, CKD)은 임상에서 각막궤양이 호발하는 흔한 전신질환 중 하나이다. 각막궤양 치유가 지연되는 경우 각막의 혈관화, 포도막염의 병발과 같은 합병증이 발생하게 된다. 궤양의 치유가 정상적으로 이루어 지지 않게 되면 기질층의 두께가 충분히 확보되지 못할 수 있으며 이런 경우 안구의 구조적 약화를 불러 일으킬

수 있다. 본 연구는 CKD 환자에서 각막 궤양이 발생한 경우 그 궤양의 특성을 조사하기 위해 설계되었다. 2011년 4월1일부터 2016년 3월 31일 사이 해마루 동물병원에 내원하여 만성 신장 질환으로 진단 받은 환자 중 각막 궤양이 발생한 개 (34개체, 38안)를 대상으로 조사가 이루어 졌으며, 대조군은 같은 기간에 내원한 각막 궤양 환자 중 전신 질환을 갖고 있지 않은 개 (31개체, 37안)를 대상으로 무작위 추출되었다. CKD 군에서의 포도막염과 건성 각결막염의 발생률은 대조군에 비해 유의적으로 높았다 (p<0.01, p<0.05). CKD 군에서 표층 각막 궤양군의 평균 치유기간은 21.0±15.0일이었으며, 이것은 대조군 (11.0 ± 6.6일, p<0.05)보다 유의적으로 길었다. 본 연구 조사에서는 CKD 환자에서 각막 궤양이 발생한 경우 KCS 및 포도막염이 유의적으로 많이 발생하며 치료기간이 길어짐을 확인하였다. 그러므로 CKD 환자에서 각막궤양이 발생한 경우 초기에 적극적인 치료가 이루어 지는 것이 권장 된다.

주요어: 각막 궤양, 만성 신장 질환, 포도막염, 건성 각결막염, 개

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