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Clinical Effects of Theophylline-Based Therapy with Tracheal Collapse in Small-Breed Dogs

소형견의 기관 허탈에서 테오필린 기반치료에 대한 임상적 효과

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서울대학교 대학원
수의학과 임상수의학 전공
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이 논문을 수의학 석사 학위논문으로 제출함

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Abstract

Clinical Effects of Theophylline-Based Therapy with Tracheal Collapse in Small-Breed Dogs

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Tracheal collapse (TC) is characterized by a narrowed tracheal lumen due to deformation of the cartilage. It can cause respiratory symptoms, including “goose-honking” coughing, in small-breed dogs. Long-term treatment is necessary because this is a chronic and progressive disease. Nevertheless, there are patients who cannot tolerate long-term therapy because of poor response to or side-effects of the conventional medical management. Among patients visiting the Seoul National University Veterinary Medical Teaching Hospital from 2013 to 2017, 47 patients with TC who received theophylline-based therapy were included in the study. Fluoroscopic examination was performed to diagnose and grade TC. Theophylline was prescribed (7.5~30 mg/kg PO q12h) and theophylline serum concentrations

were measured. Coughing was assessed using a coughing scoring scale.

When assessing the grade of TC (from 0 to 4) by region in the present study, the mean grade in the cervical region was 1.64±1.62; in the thoracic inlet, it was 2.57±1.53; in the intra-thoracic region, it was 3.02±1.24; and in the carina, it was 3.53±1.02. The mean coughing score decreased after theophylline-based therapy {4.27±2.58 (range, 3~15)} compared to pre-treatment {9.69±4.39 (range, 3~18)}. The mean serum level of theophylline measured after 2~4 weeks of theophylline was 9.23±6.19 mcg/mL (range, 0.2~25.6 mcg/mL). Symptom improvement was also observed at concentrations below the minimum therapeutic serum concentration of 8~10 mcg/mL, suggested by Plumb's veterinary drug handbooks. As the intrathoracic TC grading increased, the final theophylline dosage also increased (*p*-value 0.019). The symptom-free period (SFP) with the therapy was 189.7±194.45 days (range, 0~720 days), and there was no statistically significant correlation between SFP and age, sex, or TC grade on fluoroscopy (*p*-value > 0.05).

Although theophylline has generally been used as a third-line treatment, it was used as the main treatment in this study and most patients showed improvements (n=46, 97.9%). Additionally, this study has clinical relevance in that the treatment can be expected to have a positive effect in patients who have poor therapeutic response to conventional drugs or those who are unable to tolerate long-term corticosteroid treatment.

Keywords : Tracheal collapse, Small-breed dogs, Fluoroscopy, Theophylline, Symptom-free period

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1. Introduction

Canine tracheal collapse (TC) is a chronic, primary disease of the respiratory tract. It is characterized by tracheobronchomalacia (TBM) with weakened and flattened C-shaped cartilage [1-5], which is accompanied by narrowing of the tracheal lumen and muscle prolapse of the dorsal trachea [4,6,7]. It mainly occurs in middle-aged to older, overweight, and small-breed dogs [4,5,8]. The most common symptoms in canine TC patients are harsh dry coughing, described as a goose-honking sound, difficulty breathing, and exercise intolerance [9-11]. Clinical signs, including coughing or cyanosis, may be exacerbated with excitement. X-ray, fluoroscopy, bronchoscopy, and computed tomography imaging can be used to diagnose TC and to grade it into 4 grades, depending on the degree of collapse in each region [4-7,10,12-14].

In routine care, weight loss, restriction of excessive exercise or excitement, replacement of the neck-collar, and avoidance of inhaled irritants may be recommended [15]. In emergency situations, oxygen should be provided, and medications, such as tranquilizers, opioids, and corticosteroids, are mainly administered by injection [12]. On the other hand, medical management, including corticosteroids, coughing suppressants, tranquilizers, and bronchodilators, can be used for chronic TC patients and lifelong medication may be necessary to relieve the symptoms [12,15]. Patients who are unresponsive to such medication finally require surgical or interventional treatment [10,11,15,16].

Theophylline (3-methylxanthine) is a bronchodilator typically used as an add-on therapy for chronic obstructive pulmonary disorder (COPD) or asthma

patients in whom the disease is not well controlled. It has been used for nearly 80 years in human medicine [17,18]. The mechanisms of action of theophylline remain unclear. However, inhibition of phosphodiesterase (PDE), adenosine receptor antagonism, and activation of histone deacetylase (HDAC), as well as some other mechanisms have been proposed to explain the actions of this agent [17]. Theophylline also has multiple effects on inflammatory cells and structural cells. First, it acts on inflammatory cells to reduce the numbers of eosinophils, reduce cytokine expression and traffic in T-lymphocytes, reduce chemical mediators in mast cells, decrease cytokine expression in macrophages, and reduce recruitment of neutrophils. It also acts on the structural cells to cause bronchodilation in airway smooth muscle and to reduce leakage through the endothelium, but the mechanisms by which it increases the strength of respiratory muscles remain unclear [17].

For canine patients with TC, the commonly used first- and second-line drugs, such as prednisone, acepromazine, butorphanol, and codeine, have adverse effects in long-term use and result in poor treatment responses in some cases. Thus, the therapeutic response of TC patients in whom theophylline-based therapy was used as the main treatment, based on a coughing scale and the symptom-free period (SFP), was investigated. Furthermore, correlation of the SFP with various variables was also evaluated.

2. Materials and Methods

2.1. Study population

In the present study, all patients were retrospectively assessed, and their medical records were reviewed. Privately owned dogs who visited the Seoul National University Veterinary Medical Teaching Hospital (SNU-VMTH) from January 1, 2013, to December 31, 2017, were diagnosed with TC via fluoroscopic examination [7].

2.1.1. Inclusion criteria

Patients who met the following criteria were included in this study: 1) presence of respiratory symptoms, including coughing; 2) undergoing theophylline-based treatment; and 3) being managed at SNU-VMTH for > 3 months. If the patients had other concurrent diseases, they were included only if these diseases were stable.

2.1.2. Exclusion criteria

Dogs who underwent fluoroscopy preoperatively, but who had no symptoms, and dogs with other chronic conditions (e.g., unstable, clinically important, and severe disease) were excluded as these could markedly affect clinical signs. Patients in whom respiratory symptoms were suspected to be due to cardiac disease,

particularly pulmonary edema and marked lower respiratory problems, were excluded.

2.2. Radiographic and fluoroscopic evaluation

Patients were examined through X-ray imaging (EVA-HF525, Comed, Gyeonggi-do, Korea) and fluoroscopy (SPINEL 3G, GEMSS Medical, Gyeonggi-do, Korea). In addition, radiographic examination was performed to exclude severe lower respiratory diseases and pulmonary edema, or to evaluate cardiac patients. In fluoroscopy, views were obtained with the patient in lateral and ventro-dorsal recumbency, with a regular respiration phase and a forceful expiration phase. Besides being used to diagnose TC and indicate locations and gradings of TC in each area, fluoroscopy was also used to determine whether there was lung herniation, based on induced coughing in a humanoid position [7]. TC was evaluated in 4 regions (cervical, thoracic inlet, intrathoracic, and carinal regions) and was graded by measuring the decrease in luminal diameter: less than 25% (Grade 1), 25% to < 50% (Grade 2), 50% to 75% (Grade 3), and more than 75% (Grade 4) [4,6,7,11,16]. TC grade 0 represented the normal state. The mean TC grade at each region was determined as the sum of the product of the grade and the number of dogs with that grade in that region, for grades 0~4, divided by the total number of dogs.

2.3. Medical records

Patients' information from the medical records in an electronic charting

program (E-friends, pnV, Seoul, Korea): breed, sex, age, body weight, body condition score (BCS, 1~9), general condition, respiratory symptoms, concurrent disease, and survival status, was reviewed. The general condition of the patients was assessed using the canine Karnofsky score (CKS, 0~100) [21]. In CKS score 0, dogs are in a death status. Patients with a CKS score 100 participated normally in activities of daily life and no clinical signs even with small asymptomatic tumor [21].

Patient's medication history as well as improvements and side-effects after treatment were investigated in the course of treatment. In general, the side-effects of theophylline use include dyspnea, vomiting, diarrhea, nausea, tremor, anorexia, insomnia, aggravated cough, tachycardia, and excitement [17,18].

2.4. Theophylline-based therapy

Theophylline [a,b] (Theolan-B SR Cap. [a], Alvogenkorea Co., Ltd., Seoul, Korea or Etheophyl Cap. [b], Lindopharm, Hilden, Germany) was prescribed at a dosage of 7.5~30 mg/kg PO q12h, depending on the patient's status, with monitoring of theophylline serum concentrations. Theophylline serum concentrations were measured 2~4 weeks after starting medical treatment by a commercial laboratory (Neodin, Neodin BioVet Laboratory, Seoul, Korea); trough serum levels were determined before each subsequent dose. In addition, the adverse effects of theophylline were investigated.

When theophylline was used as the main treatment but yielded a poor response, prednisone and codeine was additionally prescribed according to the SNU-VMTH treatment protocol. Prednisone was used in the short-term to reduce

several side effects. It was prescribed at a dosage of 0.5~1 mg/kg PO q12h for 3~5 days and then tapered over a period of 3 weeks, while codeine was prescribed at a dosage of 1~2 mg/kg q12h orally until the symptoms improve for a few days. Additional drugs (such as bromhexine, acetyl cysteine, streptokinase, ambroxol, acepromazine, cetirizine, and tulobuterol patch) were used, depending on symptoms.

2.5. Assessment and scoring of coughing

Coughing was assessed at various time points, such as at diagnosis (pre-treatment), in the early stage of treatment (2~4 weeks after starting treatment), in the stable stage (2~6 months after starting treatment), using a new numerical scale for canines, based on the patients' medical records, analogous to the cough scoring used in humans [19,20]. In this study, the presence or absence of symptoms, and the intensity, duration, and interval of cough in our canine patients were evaluated.

Symptoms were evaluated by scoring the duration (grades 1~6: grade 1, less than 1 minute; grade 2, 1~5 minutes; grade 3, 5~10 minutes; grade 4, 10~20 minutes; grade 5, more than 20 minutes; grade 6, more than 1 hour), the interval (grades 1~8: grade 1, very rare, over 1 week; grade 2, when excited, less than 1 week; grade 3, more than 1 day; grade 4, every 8~12 hours; grade 5, every 6~8 hours; grade 6, every 4~6 hours; grade 7, every 2~4 hours; grade 8, every 2 hours or less), and the intensity (grades 1~4: grade 1, soft and weak; grade 2, mild; grade 3, moderate and uncomfortable; grade 4, severe and causing difficult to sleep). Furthermore, the scores for coughing duration, interval, and intensity were summed

and the total scores were evaluated (Table 1). The mean total coughing score was determined as the product of the duration score and number of dogs, plus the product of the interval score and the number of dogs, plus the product of the intensity score and the number of dogs, divided by the total number of dogs.

2.6. Symptom-free period analysis

The asymptomatic period from improvement to recurrence with theophylline-based therapy was investigated from medical records. In this case, SFP analysis was excluded if there was no recurrence history but survival was unknown. Patients who did not have recurrence records and those with known survival or death dates, but in whom the cough status in the interim period was unknown, were excluded. If symptoms were waxing and waning within a short period (30 days) SFP was set to 0 days. As a result, SFP was investigated in a total of 33 patients.

Additionally, the survival status of the patients up to February 18, 2019, was investigated by a telephone survey. The owners were asked about survival, the date of death, the cause of death, and the current cough status or cough status at the time of death. In cases where only the year and month, but not the exact day of death, were known, the 15th day of the month was set as the standard date.

2.7. Statistical analysis

Statistical analysis was performed using commercial software (R package,

ver. 3.1.1, The R Foundation for Statistical Computing, Vienna, Austria). Numerical data are presented as mean±standard deviation. The correlation of symptoms, serum theophylline concentrations, fluoroscopic images and SFP was analyzed. Logistic regression analysis was applied to categorical response variables, such as the presence or absence of side-effects and an increase or decrease in theophylline dosage, and the correlation of SFP with these variables was determined. On the other hand, linear regression models were used for continuous response variables, such as the period until symptoms improved. Furthermore, cumulative logistic regression analysis was performed for categorical variables, using a stepwise process, such as the degree of symptom improvement. *P*-values < 0.05 were considered significant.

3. Results

3.1. Study animals

In total, 488 dogs underwent fluoroscopy over a period of 5 years, of which 206 patients were diagnosed with TC. Finally, 47 dogs met the inclusion criteria. These dogs belonged to 10 breeds, with most being Maltese (n=14, 29.8%) or Shih-tzu (n=12, 25.5%) (Table 2). The mean age was 11.28±3.14 years (range, 1~15 years), the mean weight was 4.51±2.5 kg (range, 1.41~16 kg), and the mean BCS was 5.87±1.15 (range, 4~8) (Table 3). There were 21 females and 26 males (15 neutered females, 6 intact females, 22 castrated males, 4 intact males) (Table 3). The CKS ranged from 60 to 90 with a mean score of 78.09±8.25 (Table 4). In CKS score 60, dogs have at least one major disease with moderate lethargy, and mild anorexia. Patients with a CKS score 90 participated normally in activities of daily life and had minor and localized disease [21]. The study focused on dogs with cough or chronic cough (more than 2 months), and other clinical signs, such as dyspnea, nasal discharge, syncope, tachypnea, lethargy and cyanosis (Table 5) [9,10].

3.2. Tracheal collapse evaluation through fluoroscopic examination

The effect of the TC grade of each region, determined by fluoroscopy on symptoms and consequently on treatment was investigated. In the cervical region, TC grade 0 (n=21, 44.7%) was predominant and the mean TC grade in this region was 1.64±1.62 (range, 0~4). TC grades 3 (n=30, 63.8%) and 4 (n=34, 72.3%) were

the main grades found in the thoracic inlet and in the intrathoracic region. In the area of the carina, TC grade 4 (n=37, 78.7%) was the most common and TC grade 1 was not observed. The mean grade values were 2.57±1.53 (range, 0~4) in the thoracic inlet, 3.02±1.24 (range, 0~4) in the intrathoracic region, and 3.53±1.02 (range, 0~4) in the carina (Table 6).

3.3. Outcomes of TC patients on theophylline-based therapy

All 47 patients received theophylline-based therapy; the mean final dosage of theophylline in these patients was 16.01±4.34 mg/kg (range, 7.5~22 mg/kg) (Table 7). In the study, prednisone (n=17, 36.17%) and codeine (n=12, 25.53%) were additionally prescribed, and some patients (n=7, 14.89%) used all 3 drugs simultaneously. At pre-treatment, the mean cough score was 9.69±4.39 (range, 3~18) and the mean score in the early stage was 7.33±4.39 (range, 3~18), after 2~4 weeks' treatment. After 2~6 months' treatment, the mean score in the stable stage was 4.27±2.58 (range, 3~15) (Table 1).

The mean serum theophylline concentration at 2~4 weeks of this therapy was 9.23±6.19 mcg/mL (range, 0.2~25.6 mcg/mL). The effective serum concentrations were measured again when the drug dosage was changed based on symptoms and the mean second serum concentration was 11.67±4.46 mcg/mL (range, 2.8~20.1 mcg/mL). In the early treatment phase (2~4 weeks after starting treatment), cough intervals differed statistically significantly from the initial serum concentrations, based on the cumulative logistic regression model (coefficient -0.13, *p*-value 0.018), while cough duration and intensity had not changed statistically significantly.

In general, the side-effects of theophylline use include dyspnea, vomiting, diarrhea, nausea, tremor, anorexia, insomnia, aggravated cough, tachycardia, and excitement [17,18]. Fourteen patients (29.8%) experienced side-effects with theophylline treatment in this study. Most of these had diarrhea (10.6%), followed by dyspnea (6.4%), tremor (6.4%), and anorexia (6.4%) (Table 8). None of the patients developed nausea or tachycardia.

3.4. Correlations between TC grade through fluoroscopic examination and factors

First, the correlation between TC grade and cough improvement was assessed. The cough intensity in the early stage (2~4 weeks treatment) showed a statistically significant correlation with the intrathoracic region TC grade (coefficient 0.79, *p*-value 0.045). The association between the site-specific TC grade and theophylline dosage was also evaluated; the final dosage of theophylline was associated with the intrathoracic region TC grade (coefficient 1.74, *p*-value 0.019).

3.5. Prediction of SFP with theophylline-based therapy

The SFP in our TC patients was on average 189.7±194.4 days (range, 0~720 days) (Table 7). The correlation between sex, age, and fluoroscopic image features with SFP was investigated. The BCS was excluded from this evaluation because there were many missing values. There was no statistically significant correlation

of SFP with sex (coefficient -10.27, *p*-value 0.8828 in males) (Table 9). The SFP was evaluated based on age at diagnosis (Table 10). Under 14 years of age, the mean SFP obtained with the therapy was 219.81±202.00 day (range, 0~720 day) and for a mean age of 14 years or older, it was 54±52.99 day (range, 0~144 day). SFP was assessed by linear regression analysis, using a cut-off age of 14 years; the regression coefficient was -165.81 but the *p*-value was 0.057, although the sample size was small. Thus, SFP did not significantly correlate with sex, age, or fluoroscopic results. (Tables 9, 10). Although higher intrathoracic region TC grades showed a lower SFP, this did not reach statistical significance (*p*-value 0.294).

4. Discussion

While theophylline has been used as an add-on therapy to supplement the disadvantages of conventional first-line drugs [17], theophylline-based therapy was used as the main treatment approach in the present study and was found to be effective in patients with TC. Similar to previous studies, TC in the current study mostly occurred in middle-aged and older, obese, and small-breed dogs [4,5,8]. The theophylline serum concentrations required to achieve sufficient therapeutic response, without inducing adverse effects were monitored. Nonetheless, some patients had side effects after using theophylline, although these effects were ameliorated by reducing the drug dosage or by providing short-term supportive care. The patients' mean SFP was 189.7±194.4 days (range, 0~720 days) and their median survival time was 1,028.19±551.08 days (range, 127~2,048 days) (Table 7). Although, several factors that could be possible predictors of SFP were investigated, none were found to have significant prognostic value.

Cough can be caused by inflammation of the trachea but cough itself can also induce inflammation [10]. Therefore, to reduce inflammation, prednisone (0.5 mg/kg PO q12h, for 1~2 weeks and a 3 months' interval) or fluticasone (125~250 mcg puff q12h) inhalation steroids are applied in long-term therapy in conventional TC treatments [15,16,22]. Therapy with stanozolol, an anabolic androgenic steroid, has also been proposed for canine TC [23]. In addition, antitussive agents have been recommended, including hydrocodone (0.22 mg/kg PO q12h) and butorphanol (0.55 mg/kg PO q12h), to suppress cough [15]. Although bronchodilators (methylxanthines or beta-agonists) have also been used to relieve TC, there is

currently insufficient evidence of their advantages. Thus, as a follow-up treatment, it was common to add or withdraw theophylline while monitoring therapeutic responses [15].

The TC patients in the current study may have had concurrent disease in many cases, because they were middle-aged or older. Consequently, it was difficult to use conventional first-line inflammation-suppressing drugs, especially corticosteroids, repeatedly and for a long time in some patients (such as in patients with Cushing's disease, diabetes mellitus, gastric ulcers, pancreatitis, and elevated liver enzymes, etc.). Thus, theophylline was used as the primary treatment for TC patients in this study. Theophylline can also play a positive role in patients with insulin resistance and hyperglycemia. Fat tissues in obese individuals are characteristic of chronic low-grade inflammation. A previous study has shown that theophylline inhibits glucocorticoid- induced hyperglycemia, thereby lowering fasting blood glucose levels in patients and controlling IL-6 production by inhibiting glucocorticoid receptor activity [24]. In addition, one study of the inflammation-suppressing mechanism found that theophylline inhibits NF-κB activation by protecting IκBα, thereby inhibiting the production of proinflammatory cytokines [25]. As TC is a progressive disease, continuous management is essential. Thus, theophylline-based therapy has been used in patients who have had a poor response to long-term therapy with previous drugs, or for whom there are concerns about severe side-effects of conventional drugs.

Theophylline has been administered in human patients with asthma and COPD [26]. However, a human study has suggested that the use of methylxanthines should be avoided during COPD exacerbations because of the greater adverse

effects and few benefits [18,27]. Recently, some studies have shown that combination therapy involving low doses of theophylline and inhaled corticosteroids is effective in COPD patients, resulting in few side effects [28,29]. A non-bronchodilator effect of theophylline, involving modulation of steroid insensitivity, was found to play an important role in this effect [30]. However, in the present study, none of the patients showed such severe side-effects as to result in discontinuation of theophylline treatment.

Theophylline serum concentrations are known to be associated with improvement of symptoms and side effects [26]. Several factors affect the clearance of the drug, which determines the serum concentration [17]. Serum concentrations (0.2~25.6 mcg/mL) of theophylline obtained at a dosage of 7.5~30 mg/kg PO q12h for 2~4 weeks, were varied. Theophylline has a narrow therapeutic index of serum concentrations (10~20 mcg/mL) in humans and can easily cause side effects over the range [18,31,32]. However, dogs are less sensitive to high serum concentrations (above 20 mcg/mL) [31]. One study reported adverse effects at serum concentrations of 37~60 mcg/mL in dogs receiving theophylline [33]. A serum level of at least 8~10 mcg/mL is recommended for therapeutic serum levels of theophylline in dogs [34]. In this study, an improvement of symptoms was observed even at theophylline serum concentrations lower than 8 mcg/mL (n=15; 32.0%).

The SFP refers to the period in which the patient is asymptomatic and is used in several fields [35-39]. This study aimed to identify early predictors of the SFP, but significant correlations between SFP and several evaluated factors, including sex, age, and fluoroscopic image features were not found (Table 9). Therefore, the results of fluoroscopy are only used for a diagnostic examination and cannot be

used to predict the SFP. A study in humans examined whether laboratory results and clinical parameters were related to the SFP of hereditary angioedema, but also found no significant associations [38]. However, the relationship may differ depending on the disease and factors investigated. Consequently, additional research will be needed to investigate factors predicting SFP.

The study had some limitations, including a small sample number and missing values, such as for BCS. By increasing the evaluation period and the size of the patient population, these limitations could be addressed and statistical significance could be clarified. Another limitation was the difficulty of controlling the living environment of the individual patients. Since this was not a study of experimental animals, but rather a retrospective study of client-owned patients, the exposure to environmental factors, such as humidity, ventilation, irritants, and environmental pollutants may vary from patient to patient. For instance, a study of chronic cough in canines identified environmental tobacco smoke and wood smoke as significant environmental factors related to chronic cough in canines [9].

5. Conclusion

In conclusion, no previous study has evaluated canine TC patients who received theophylline-based therapy as a first-line treatment, rather than as an add-on therapy. In this study, the final theophylline dosage was affected by the TC grade of the intrathoracic region. However, SFP had no statistically significant correlation with sex, age, and TC grading based on fluoroscopy. The findings of this study indicate that this may be a useful approach for the treatment of many TC patients, resulting in improvement of symptoms.

Table 1. Protocol for cough scoring scale by several variables with tracheal collapse in the present study

Variables of cough	Score	Clinical characterization	No. of dogs (Total 47 dogs)		
			Pre-treatment	2~4 weeks treatment	2~6 months treatment
Duration	1	Less than a minute	34	37	46
	2	1~5 minutes	2	1	1
	3	5~10 minutes	1	2	0
	4	10~20 minutes	0	1	0
	5	Over 20 minutes	1	1	0
	6	Over an hour	5	2	0
	NA	No record	4	3	0
Interval	1	Very rare (in weeks)	1	9	29
	2	Only excitement (in days)	11	10	8
	3	Over 24 hours	3	10	6
	4	Every 8~12 hours	2	1	0
	5	Every 6~8 hours	1	0	1

	6	Every 4~6 hours	5	1	0
	7	Every 2~4 hours	2	3	1
	8	Every 1~2 hours	14	8	2
	NA	No record	8	5	0
Intensity	1	Soft and weak	5	17	38
	2	Mild	14	14	6
	3	Moderate, uncomfortable	8	3	2
	4	Severe and hard to sleep	19	10	1
	NA	No record	1	3	0
Total score (Mean±SD*, range†)			9.69±4.39, 3~18	7.33±4.39, 3~18	4.27±2.58, 3~15

NA, not applicable or not available.

*{(Duration score × the number of dogs) + (Interval score × the number of dogs) + (Intensity score × the number of dogs)}/the total number of dogs.

†Total score range : 3 (good)~18 (bad).

Table 2. Breeds and numbers of patients with tracheal collapse in the present study

Breeds	No. of dogs (%)
Maltese	14 (29.8)
Shih-tzu	12 (25.5)
Yorkshire Terrier	7 (14.9)
Pomeranian	4 (8.5)
Chihuahua	2 (4.3)
Japanese Chin	2 (4.3)
Miniature Pinscher	2 (4.3)
Poodle	2 (4.3)
Cocker Spaniel	1 (2.1)
Mixed breed	1 (2.1)
Total	47 (100)

Table 3. Characteristics of patients with tracheal collapse in the present study

Signalments	Value
Age (Mean±SD years, range)	11.28±3.14, 1~15
BW (Mean±SD kg, range)	4.51±2.5, 1.41~16
BCS (Mean±SD, range)	5.87±1.15, 4~8
Sex	
Female (n, %)	6, 12.8
Spayed female (n, %)	15, 32.0
Male (n, %)	4, 8.5
Castrated male (n, %)	22, 46.8

BW, body weight; BCS, body condition score.

Table 4. Karnofsky score of dogs with tracheal collapse in the present study

Canine karnofsky score*	No. of dogs (%)
0	0
10	0
20	0
30	0
40	0
50	0
60	6 (12.8)
70	3 (6.4)
80	32 (68.1)
90	6 (12.8)
100	0
Total	47 (100)

*Valladao M, et al., 2010.

Table 5. Clinical signs in 47 dogs with tracheal collapse in the present study

Clinical signs	No. of dogs (%)
Cough	47 (100)
Chronic cough*	30 (63.8)
Dyspnea	5 (10.6)
Nasal discharge	3 (6.4)
Syncope	2 (4.3)
Tachypnea	2 (4.3)
Lethargy	1 (2.1)
Cyanosis	1 (2.1)

*Cough over 2 months.

Table 6. Grades of tracheal collapse and lung herniation as fluoroscopic examination in the 47 dogs in the present study

Region	Grade*	No. of dogs (%)	Mean grade of each region† (Mean±SD)
Cervical	0	21 (44.7)	1.64±1.62
	1	1 (2.1)	
	2	7 (14.9)	
	3	10 (21.3)	
	4	8 (17.0)	
Thoracic inlet	0	9 (19.1)	2.57±1.53
	1	3 (6.4)	
	2	5 (10.6)	
	3	12 (25.5)	
	4	18 (38.3)	
Intrathoracic	0	4 (8.5)	3.02±1.24
	1	1 (2.1)	
	2	8 (17.0)	
	3	11 (23.4)	
	4	23 (48.9)	
Carina	0	2 (4.3)	3.53±1.02
	1	0 (0)	
	2	6 (12.8)	

	3	2 (4.3)
	4	37 (78.7)
Lung herniation	Presence	31 (66.0)
	Absence	4 (8.5)
	No record	12 (25.5)

* TC grade 0 represented the normal state.

†{(0×the number of dogs with grade 0 in that region)+(1×the number of dogs with grade 1 in that region)+(2×the number of dogs with grade 2 in that region)+(3×the number of dogs with grade 3 in that region)+(4×the number of dogs with grade 4 in that region)}/the total number of dogs.

Table 7. Patients' several values including characteristics, imaging results, theophylline dosage, cough score and SFP in the present study

Case of No.	Breed	Sex	Age at Dx (years)	Survival (day)	BW (kg)	BCS (1~9)	Imaging exam (TC grade of sites and etc.)					Final dosage of theophylline (mg/kg)	Cough score and SFP			
							Cervical	Thoracic inlet	Intra-thoracic	Carina	Lung hernia-tion		The time at Dx	Tx After 2~4 weeks	Tx After 2~6 months	SFP (day)
1	Shih-tzu	FS	14	475	5.05	6	3	3	3	4	O	15	10	15	15	0
2	Maltese	IM	14	288	3.45	-	0	3	3	4	O	20	18	6	6	0
3	Maltese	MC	12	1,416	3.00	-	3	3	4	4	O	20	12	12	12	0
4	Miniature Pinscher	IF	13	-	4.20	6	0	0	2	2	O	17	6	5	3	0
5	Shih-tzu	IF	12	-	4.37	4	0	4	0	0	O	15	12	15	12	0
6	Pomeranian	FS	8	-	3.39	5	0	4	4	4	O	17	-	3	3	30
7	Shih-tzu	MC	9	1,806	4.61	5	0	0	4	4	O	20	7	5	3	30
8	Maltese	FS	11	503	2.05	-	2	3	2	4	O	15	9	-	4	40
9	Shih-tzu	FS	13	371	5.70	6.5	0	2	3	4	O	17	9	5	5	60
10	Shih-tzu	MC	15	1,567	5.76	5	0	0	0	4	O	10	9	13	3	60
11	Mongrel	IM	14	-	12.30	7	0	4	4	4	O	20	8	13	3	60
12	Miniature Pinscher	MC	14	-	5.60	7	1	1	1	2	X	10	4	7	5	60
13	Maltese	MC	5	1,324	5.96	5	4	4	4	4	X	15	4	5	5	90
14	Yorkshire Terrier	MC	11	1,287	4.30	6	4	4	4	4	-	20	9	-	3	90

Table 7. continued

15	Maltese	MC	10	127	2.37	4	3	3	4	4	X	15	11	5	3	113
16	Poodle	IF	10	1,185	1.70	-	2	2	2	2	-	-	13	6	3	120
17	Yorkshire Terrier	IF	13	915	2.80	6	4	4	4	4	O	22	13	13	3	120
18	Cocker Spaniel	MC	14	-	16.00	8	0	1	2	4	O	20	5	3	3	144
19	Chihuahua	MC	10	1,454	3.47	6	4	4	4	4	O	7.5	-	5	5	150
20	Maltese	MC	8	1,334	2.67	-	0	0	2	4	O	20	6	6	3	150
21	Maltese	MC	13	740	2.75	6	2	2	4	4	O	20	18	4	3	180
22	Yorkshire Terrier	FS	3	-	3.00	7	4	4	4	4	O	20	5	5	5	180
23	Maltese	FS	13	-	4.92	-	0	4	4	4	X	20	18	14	4	210
24	Shih-tzu	IM	13	1,005	6.03	6	3	4	4	4	O	20	6	3	3	223
25	Maltese	FS	11	529	2.50	4	2	4	4	4	O	20	9	5	3	270
26	Pomeranian	FS	10	1,524	3.84	7	2	2	2	2	O	-	4	-	4	270
27	Maltese	MC	13	-	2.82	-	4	4	4	4	O	10	-	5	4	360
28	Yorkshire Terrier	MC	10	-	5.04	7	3	3	3	3	-	20	-	3	3	390
29	Poodle	FS	13	1,530	4.10	-	2	2	4	4	-	20	12	3	3	510
30	Shih-tzu	MC	13	-	4.03	5	0	4	3	4	O	8	18	18	3	510
31	Shih-tzu	IF	11	1,109	3.80	-	0	1	3	4	O	20	-	5	3	510
32	Pomeranian	FS	3	669	1.87	5	3	3	3	4	O	10	4	4	3	609

Table 7. continued

33	Maltese	MC	1	-	3.13	4	0	0	0	3	O	10	-	7	4	720
34	Maltese	FS	12	1,826	4.35	-	3	3	3	4	O	20	11	11	8	-
35	Shih-tzu	MC	13	-	6.35	6	2	4	4	4	O	20	8	8	3	-
36	Chihuahua	FS	12	1,201	2.05	6	4	4	4	4	O	10	13	7	3	-
37	Japanese Chin	FS	13	975	5.50	6	3	3	2	2	O	15	6	8	5	-
38	Shih-tzu	MC	12	-	6.70	8	3	3	4	4	O	10	3	3	3	-
39	Japanese Chin	FS	10	1,217	6.46	-	0	0	2	4	O	15	13	6	3	-
40	Yorkshire Terrier	MC	8	2,048	4.30	-	4	4	4	4	O	20	-	3	3	-
41	Yorkshire Terrier	IF	13	192	3.80	-	3	3	3	0	X	15	9	3	3	-
42	Yorkshire Terrier	MC	14	457	4.60	-	0	4	3	4	O	12	13	3	3	-
43	Shih-tzu	MC	14	335	8.64	8	0	3	3	2	X	15	18	18	6	-
44	Pomeranian	IM	13	1,289	3.36	5	0	4	4	4	O	15	-	-	3	-
45	Shih-tzu	FS	11	-	4.78	6	0	0	4	4	O	20	11	11	3	-
46	Maltese	MC	15	1,887	2.89	-	0	0	4	4	O	10	9	9	5	-
47	Maltese	MC	13	317	1.41	-	0	0	0	4	X	10	5	-	3	-
Mean± SD (range)			11.28± 3.14 (1~15)	1,028.19± 551.08 (127~ 2,048)	4.51± 2.58 (1.41~ 16)	5.87± 1.15 (4~8)	1.64± 1.62 (0~4)	2.57± 1.53 (0~4)	3.02± 1.24 (0~4)	3.53± 1.02 (0~4)		16.01± 4.34 (7.5~22)	9.69 ± 4.39 (3~18)	7.33 ± 4.39 (3~18)	4.27 ± 2.58 (3~15)	189.7± 194.45 (0~720)

BW, body weight; BCS, body condition score; TC, tracheal collapse; SFP, symptom-free period; Dx, diagnosis; Tx, treatment; FS, spayed female; IF, intact female; MC, castrated male; IM, intact male; O, lung herniation; X, no lung herniation; -, Some data were not available due to medical loss.

Table 8. Side-effects of theophylline-based therapy in the present study

Side-effects	No. of dogs (%)
Diarrhea	5 (10.6)
Dyspnea	3 (6.4)
Tremor	3 (6.4)
Anorexia	3 (6.4)
Vomiting	2 (4.3)
Cough	2 (4.3)
Excitement	1 (2.1)
Nausea	0 (0)
Tachycardia	0 (0)
Insomnia	0 (0)
Total	14*(29.8)

*Some subjects had more than one side-effect.

Table 9. Mean symptom-free period after theophylline-based therapy according to sex and fluoroscopic characteristics in 33 dogs in the present study

Factors	Variables for SFP prediction	SFP prediction with factors using linear regression analysis		
		Coefficient	95% CI*	*p*-value†
Sex	Male	-10.27	-151.08 to 130.55	0.8828
	Female	(Reference)		
Fluoroscopic imaging	TC grade of cervical	12.71	-47.04 to 72.46	0.664
	TC grade of thoracic inlet	7.00	-63.68 to 77.69	0.839
	TC grade of intrathoracic	-52.46	-153.58 to 48.65	0.294
	TC grade of carina	61.79	-55.25 to 178.84	0.286
	Lung herniation	51.21	-181.18 to 283.59	0.653

*Confidence interval

†Statistically significant difference: *p*-value <0.05 (Therefore, all of the factors had no statistical significance with SFP).

Table 10. Mean symptom-free period after theophylline-based therapy according to age in 33 dogs in the present study

Age (years)	Mean SFP to age (Mean±SD day, range, n*)		SFP prediction with age using linear regression analysis		
	< Age	Age≤	Coefficient	95% CI†	*p*-value‡
10	258.43±284.78, 30~720, n=7	171.15±165.08, 0~510, n=26	-87.27	-255.84 to 81.29	0.2991
11	237.67±223.79, 30~720, n=12	162.24±175.43, 0~510, n=21	-75.43	-218.59 to 67.74	0.2909
12	235.13±214.00, 30~720, n=16	146.88±169.34, 0~510, n=17	-88.24	-224.81 to 48.33	0.1972
13	209±214.91, 0~720, n=18	166.47±171.11, 0~510, n=15	-42.53	-182.53 to 97.46	0.54
14	219.81±202.00, 0~720, n=27	54±52.99, 0~144, n=6	-165.81	-337.22 to 5.59	0.05747

*Number of dogs

†Confidence interval

‡Statistically significant difference: *p*-value <0.05 (Therefore, age had no statistical significance with SFP).

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국문 초록

소형견의 기관 허탈에서
테오필린 기반치료에 대한 임상적 효과

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개의 기관 허탈은 연골의 변형으로 인해 발생하며, 이로 인하여 기관 직경이 좁아지게 된다. 그 결과 다양한 증상이 발생할 수 있다. 만성적이며 진행성인 호흡기 질병이기 때문에 장기간의 치료가 필수적이다. 치료 과정에서 기존 약물에 대한 치료반응이 떨어지거나 부작용이 우려되어 해당 약물을 장기간 복용할 수 없는 환자들이 존재한다. 본 연구는 2013년 1월부터 2017년 12월까지 서울대학교 동물병원에 방문한 환자 중에서 본원에서 3개월 이상 테오필린 기반 치료를 받은 47마리의 기관 허탈 환자를 대상으로 하였다. 기관 투시검사를 활용하여 기관 허탈 여부를 조사하고, 허탈의 단계를 평가하였다. 환자들은 증상에 따라 테오필린을 7.5~30 mg/kg으로 일일 2회 복용하였으며, 2~4주간 복용 이후 혈청 내 최저 테오필린 농도를 측정하였다. 주요 임상증상인 기침은 평

가 기준 프로토콜을 따라서 평가되었다.

부위별 기관 허탈 등급을 0~4등급으로 평가할 때 본 연구 결과에서 경부기관은 평균 1.64±1.62등급, 흉곽 입구는 평균 2.57±1.53등급, 흉곽 내 영역은 평균 3.02±1.24등급, 기관 분지부는 평균 3.53±1.02등급으로 나타났다. 평균 기침 점수는 치료 이전 {9.69±4.39(범위, 3~18)}과 비교하여 치료 이후 안정화 단계 {4.27±2.58(범위, 3~15)}에서 감소하였다. 2~4주간 테오필린 복용 이후 측정된 평균 테오필린 혈청 농도는 9.23±6.19 mcg/mL(범위, 0.2~25.6 mcg/mL)였으며, Plumb's veterinary Drug Handbooks에서 제시한 최소 치료 혈청 농도 8~10 mcg/mL 보다 낮은 농도에서도 증상 개선이 확인되었다. 또한 흉곽 내 영역의 기관 허탈 단계와 테오필린 최종 투여 용량이 통계적으로 유의적인 관계를 보였다(*p*-value 0.019). 치료 후 무증상 기간의 경우, 평균 189일(범위, 0~720일)로 관찰되었고, 무증상 기간을 예측할 수 있는 인자를 찾기 위하여 연령, 성별, 기관 허탈 단계를 분석하였지만 통계적 유의성이 없었다(*p*-value 0.05 이상).

과거 테오필린은 일반적으로 후순위의 치료법으로 사용되어 왔다. 하지만, 본 연구에서 테오필린을 기관 허탈 치료의 기반약물로 적용하였을 때, 대부분의 환자에서 개선을 보였다(47례 중 46례, 97.9%). 또한 기존 1, 2차 약물에 대해 치료반응이 떨어지는 환자나 장기간 corticosteroids 약물을 처방하기 어려운 소형견 환자에서 테오필린 치료가 유의적인 치료반응을 기대할 수 있다는 점에서 본 연구는 임상적

의의를 갖는다.

주요어 : 기관 허탈; 소형견; 기관 투시검사; 테오필린; 무증상 기간

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