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A retrospective study of theophylline-based therapy with tracheal collapse in small-breed dogs: 47 cases (2013–2017)

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ABSTRACT

Theophylline acts as a bronchodilator and has an anti-inflammatory effect. In addition, theophylline can be applied in patients where there are concerns regarding the side-effects of corticosteroids. This retrospective case series evaluated theophylline-based therapy in tracheal collapse (TC) canine patients. Forty-seven dogs with TC that received theophylline-based therapy during 2013–2017 were investigated. A fluoroscopic examination was performed to diagnose and grade TC. Theophylline was prescribed (7.5–30 mg/kg PO q12h) and the theophylline serum concentrations were measured. Coughing was assessed using a coughing scoring scale. The mean coughing score decreased after the theophylline-based therapy compared with that observed before treatment. Clinical improvements were observed in 46/47 patients (97.9%). As the intrathoracic TC grading increased, the final theophylline dosage also increased (p value 0.019). The symptom-free period (SFP) with therapy was 189.7 ± 194.45 days (range, 0–720 days) and there was no statistically significant correlation between the SFP and age, sex, or TC grade on fluoroscopy. 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. Dogs have a wider therapeutic index of serum concentrations than humans, and any undesirable effects were easily overcome. With further research, this therapy may prove to be a useful approach, but its safety for long-term use in the treatment of canine TC patients needs to be established.

Keywords: Trachea collapse; small breed dogs; fluoroscopy; theophylline; symptom-free period

INTRODUCTION

Canine tracheal collapse (TC) is a chronic, primary disease of the respiratory tract. The disease is characterized by tracheobronchomalacia 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 [2,6,7]. TC occurs mainly in middle-aged to older, overweight, and small-breed dogs [2,4,8]. The most common symptoms in canine TC patients are

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

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harsh dry coughing, which is described as a goose-honking sound, difficulty breathing, and exercise intolerance [9-11]. The 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 classified it into four grades, depending on the degree of collapse in each region [2,4,6,7,9,12-14].

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 administered mainly by injection [14]. 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 [14,15]. Patients unresponsive to such medication finally require surgery or interventional treatment [9,11,15,16].

Theophylline (3-methylxanthine) is a bronchodilator that has been used for nearly 80 years in human medicine typically as an add-on therapy for chronic obstructive pulmonary disorder (COPD) or asthma patients, in whom the disease is not well controlled [17,18]. The mechanisms of action of theophylline are unclear. On the other hand, the inhibition of phosphodiesterase, adenosine receptor antagonism, and activation of histone deacetylase, as well as some other mechanisms have been proposed to explain the actions of this agent [19-21]. Theophylline has multiple effects on inflammatory cells and structural cells. First, it acts on inflammatory cells to reduce the number of eosinophils, reduce cytokine expression and traffic in T-lymphocytes, reduce the chemical mediators in mast cells, decrease cytokine expression in macrophages, and reduce the recruitment of neutrophils [17]. Theophylline also acts on structural cells to cause bronchodilation in airway smooth muscle and reduce leakage through the endothelium, but the mechanisms by which it increases the strength of the respiratory muscles are unclear [22].

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

MATERIALS AND METHODS

Study population

In the present study, all patients were assessed retrospectively, 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 a fluoroscopic examination.

Inclusion criteria

A diagnosis of TC was based on the patient's clinical symptoms and physical examination. In particular, TC was confirmed by fluoroscopy with the region and grade of TC. Patients who met the following criteria were included: 1) presence of respiratory symptoms, including coughing; 2) undergoing theophylline-based treatment; and 3) being managed at SNU VMTH

for >3 months. If the patient had other concurrent diseases (e.g., myxomatous mitral valve degeneration, chronic kidney disease, Cushing's disease, renal or urinary bladder calculi, liver enzyme elevation, chronic bronchitis, and pancreatitis), they were included only if these diseases were stable.

Exclusion criteria

Dogs who underwent fluoroscopy preoperatively but had no symptoms, and dogs with other chronic conditions without TC (e.g., unstable, clinically important, and severe disease) were excluded because these could affect the clinical signs markedly. Patients with respiratory symptoms suspected of being due to cardiac disease, particularly pulmonary edema and marked lower respiratory problems, were excluded.

Radiographic and fluoroscopic evaluation

The patients were examined by X-ray imaging (EVA-HF525; Comed, Korea) and fluoroscopy (SPINEL 3G, GEMSS Medical, Korea). In addition, a 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. In addition to being used to diagnose TC and indicate the locations and gradings of TC in each area, fluoroscopy was also used to determine if there was lung herniation based on induced coughing in a humanoid position [6]. TC was evaluated in four 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) [2,6,7,11,16]. TC grade 0 represented a normal state. The mean TC grade at each region was determined as the sum of the product of the grade and number of dogs with that grade in that region, for grades 0–4, divided by the total number of dogs.

Medical records

The patients' information from the medical records in an electronic charting program (E-friends; pnV, Korea) was reviewed: breed, sex, age, body weight, body condition score (BCS, 1 to 9), general condition, respiratory symptoms, concurrent disease, and survival status. The patients' general condition was assessed using the canine Karnofsky score (CKS, 0 to 100) [23]. A CKS score of 0 means that the dogs are dead. Patients with a CKS score 100 participated normally in the activities of daily life with no clinical signs even with a small asymptomatic tumor [23].

The patient's medication history as well as improvements and side-effects after treatment were investigated during 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].

Theophylline-based therapy

Theophylline (Theolan-B SR Cap.; Alvogenkorea Co., Ltd., Korea; Etheophyl Cap.; Lindopharm, Germany) was prescribed at a dosage of 7.5–30 mg/kg PO q12h, depending on the patient's status, with monitoring of the theophylline serum concentrations. Theophylline serum concentrations were measured 2–4 weeks after starting the medical treatment by a commercial laboratory (Neodin; Neodin BioVet Laboratory, Korea); the 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 were also prescribed according to the SNU VMTH treatment protocol. Prednisone was used in the short-term to reduce several side effects. The medication was prescribed at a dosage of 0.5–1 mg/kg PO q12h for 3–5 days and then tapered over a period of three weeks, while codeine was prescribed at a dosage of 1–2 mg/kg q12h orally. Additional drugs, such as bromhexine, acetyl cysteine, streptokinase, ambroxol, acepromazine, cetirizine, and tulobuterol patch, were used depending on the symptoms.

Assessment and scoring of coughing

Coughing was assessed at various time points, such as at diagnosis (pre-treatment), in the early stages 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, which are analogous to the cough scoring used in humans [24,25]. This study evaluated the presence or absence of symptoms, and the intensity, duration, and interval of cough in the canine patients.

The 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), 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 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 to be the product of the duration score and number of dogs, plus the product of the interval score and the number

Table 1. Protocol for the 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 treatment	2–6 mo treatment
Duration	1	Less than a minute	34	37	46
	2	1–5 min	2	1	1
	3	5–10 min	1	2	0
	4	10–20 min	0	1	0
	5	Over 20 min	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 h	3	10	6
	4	Every 8–12 h	2	1	0
	5	Every 6–8 h	1	0	1
	6	Every 4–6 h	5	1	0
	7	Every 2–4 h	2	3	1
	8	Every 1–2 h	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; SD, standard deviation.

*{(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).

of dogs, plus the product of the intensity score and the number of dogs, divided by the total number of dogs.

SFP analysis

The asymptomatic period from improvement to recurrence with theophylline-based therapy was investigated from the medical records. In this case, SFP analysis was excluded if there was no recurrence history but survival was unknown. This study also excluded patients that 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. The SFP was set to 0 days if symptoms were waxing and waning within a short period (30 days).

In addition, the survival status of the patients up to February 18, 2019, was investigated by a telephone survey. The owners were asked about the dog's survival, date of death, cause of death, and 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.

Statistical analysis

Statistical analysis was performed using commercial software (R package, ver. 3.1.1; The R Foundation for Statistical Computing, Austria). The numerical data are presented as the mean \pm standard deviation. The correlations of symptoms, serum theophylline concentrations, fluoroscopic images, and SFP were analyzed. Logistic regression analysis was applied to the categorical response variables, such as the presence or absence of side-effects and an increase or decrease in theophylline dosage; the correlation of SFP with these variables was determined. On the other hand, linear regression models were used for the continuous response variables, such as the period until symptoms improved. Furthermore, cumulative logistic regression analysis was performed for the categorical variables using a stepwise process, such as the degree of symptom improvement. Linear regression models were used to analyze the association between the SFP and sex, TC grading, and age. They were also used to confirm the association between the TC grading and final theophylline dose. Cumulative logistic models were used to analyze the relationship between the TC grade and degree of symptom improvement. The value of $p < 0.05$ were considered significant.

RESULTS

Study animals

In total, 488 dogs underwent fluoroscopy over a period of five 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, weight, and BCS were 11.28 ± 3.14 years (range, 1–15 years), 4.51 ± 2.5 kg (range, 1.41–16 kg), and 5.87 ± 1.15 (range, 4–8), respectively (**Table 3**). The subjects were 21 females and 26 males (15 neutered females, six intact females, 22 castrated males, four intact males) (**Table 3**). The CKS ranged from 60 to 90 with a mean score of 78.09 ± 8.25 (**Table 4**). A CKS score 60 means that the dogs have at least one major disease with moderate lethargy, and mild anorexia. Patients with a CKS score 90 participated normally in the activities of daily life and had minor and localized disease [23]. The study focused on dogs with cough or chronic cough (more than two months) and other clinical signs, such as dyspnea, nasal discharge, syncope, tachypnea, lethargy and cyanosis (**Table 5**) [9,10].

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 the patients with tracheal collapse in the present study

Signalments	Value
Age (Mean \pm SD yr, range)	11.28 \pm 3.14, 1–15
BW (Mean \pm SD kg, range)	4.51 \pm 2.5, 1.41–16
BCS (Mean \pm SD, range)	5.87 \pm 1.15, 4–8
Sex	
Female (No., %)	6, 12.8
Spayed female (No., %)	15, 32.0
Male (No., %)	4, 8.5
Castrated male (No., %)	22, 46.8

BW, body weight; BCS, body condition score.

Table 4. Karnofsky score of the 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 et al. [23].

Table 5. Clinical signs of the 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.

Tracheal collapse evaluation through fluoroscopic examination

This study examined whether the TC grade of each region, determined by fluoroscopy, had effects on the symptoms, and consequently on treatment. In the cervical region, TC grade 0 (n = 21, 44.7%) was predominant and the mean TC grade in this region was 1.64 \pm 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

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)	

SD, standard deviation.

*TC grade 0 represented the normal state; † $\{(0 \times \text{the number of dogs with grade 0 in that region}) + (1 \times \text{the number of dogs with grade 1 in that region}) + (2 \times \text{the number of dogs with grade 2 in that region}) + (3 \times \text{the number of dogs with grade 3 in that region}) + (4 \times \text{the number of dogs with grade 4 in that region})\} / \text{the total number of dogs}$.

thoracic inlet and in the intrathoracic region. In the area of the carina, TC grade 4 ($n = 37$, 78.7%) was most common and TC grade 1 was not observed. The mean grades 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).

Outcomes of the 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 this study, prednisone ($n = 17$, 36.17%) and codeine ($n = 12$, 25.53%) were also prescribed, and some patients ($n = 7$, 14.89%) used all three 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 treatment for 2–4 weeks. 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 treatment 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 the 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), the cough intervals differed significantly from the initial serum

Table 7. Patients' characteristics after treatment

Variables	Mean ± SD (range)
Symptom-free period (d)	189.7 ± 194.45 (0–720)
Survival time (d)	1,028.19 ± 551.08 (127–2048)
Final dosage of theophylline (mg/kg)	16.01 ± 4.34 (7.5–22)

SD, standard deviation.

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.

concentrations based on the cumulative logistic regression model (coefficient -0.13 , p value 0.018), whereas the cough duration and intensity had not changed significantly.

Fourteen patients (29.8%) experienced side-effects with the theophylline treatment in this study. Most 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.

Correlations between the TC grade through a fluoroscopy examination and factors

First, the correlation between the TC grade and cough improvement was assessed. The cough duration and intensity in the early stages (2–4 weeks treatment) showed a statistically significant correlation with the TC grades of the thoracic inlet and intrathoracic region, respectively (**Table 9**;

Table 9. Correlation between the TC grade through a fluoroscopic examination and degree of symptom improvement

Treatment time points	Coughing variables	Region	Coefficient	p value*	
Early stage (2–4 wk treatment)	Duration	Cervical	0.47	0.139	
		Thoracic inlet	-1.22	0.049*	
		Intrathoracic	0.51	0.498	
	Interval	Carina	-0.01	0.994	
		Cervical	0.24	0.266	
		Thoracic inlet	-0.26	0.283	
	Intensity	Intrathoracic	Intrathoracic	0.27	0.440
			Carina	-0.35	0.353
			Cervical	0.22	0.347
		Thoracic inlet	Thoracic inlet	-0.19	0.467
			Intrathoracic	0.79	0.045*
			Carina	0.23	0.589
Stable stage (2–6 mo treatment)	Duration	Cervical	3.74	0.994	
		Thoracic inlet	-3.01	0.987	
		Intrathoracic	2.73	0.993	
		Carina	4.41	0.988	
	Interval	Cervical	-0.22	0.329	
		Thoracic inlet	-0.35	0.244	
		Intrathoracic	0.46	0.224	
		Carina	0.26	0.449	
	Intensity	Cervical	-0.02	0.938	
		Thoracic inlet	-0.14	0.679	
		Intrathoracic	0.11	0.793	
		Carina	0.45	0.272	

TC, tracheal collapse.

*Statistically significant difference: p value < 0.05 .

Table 10. Correlation between the TC grade through a fluoroscopic examination and the final dosage of theophylline

Factor	Region	Coefficient	p value*
The final dosage of theophylline	Cervical	-0.51	0.302
	Thoracic inlet	-0.22	0.683
	Intrathoracic	1.74	0.019*
	Carina	-0.52	0.517
	Lung herniation	-1.51	0.419

TC, tracheal collapse.

*Statistically significant difference: p value < 0.05.

coefficient -1.22, p value 0.049; 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 (Table 10; coefficient 1.74, p value 0.019).

Prediction of the SFP with theophylline-based therapy

The mean SFP in the TC patients was 189.7 ± 194.4 days (range, 0–720 days) (Table 7). This study examined whether sex, age, and fluoroscopic image features correlated with the SFP. The BCS was excluded from this evaluation because there were many missing values. No significant correlation of SFP with sex was observed (coefficient -10.27, p value 0.8828 in males) (Table 11). The SFP was evaluated according to the age at diagnosis (Table 12). Under 14 years of age, the mean SFP obtained with the treatment was 219.81 ± 202.00 days (range, 0–720 days) and 54 ± 52.99 days (range, 0–144 days) for a mean age of 14 years or older. The SFP was assessed by linear regression analysis using a cut-off age of 14 years; the regression coefficient was -165.81 and the p value was 0.057, but the sample size was small. Therefore, no statistically significant correlation was observed between the SFP and sex, age, or fluoroscopy results (Tables 11 and 12). Although higher intrathoracic region TC grades showed a lower SFP, this did not reach statistical significance (p value 0.294).

Table 11. 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	0.883
	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

SFP, symptom-free period; CI, confidence interval; TC, tracheal collapse.

*Statistically significant difference: p value < 0.05 (Therefore, all of the factors had no statistical significance with SFP); †In linear regression analysis, when there is no statistical significance for one variable (ex. male) for the biased variables (ex. male and female), there is no statistical significance for the other variable (ex. female). Therefore, there is no value for the other variable (ex. female).

Table 12. Mean symptom-free period after theophylline-based therapy according to age in 33 dogs in the present study

Age (yr)	Mean SFP to age (Mean ± SD day, range, No. *)		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	0.299
11	237.67 ± 223.79, 30–720, n = 12	162.24 ± 175.43, 0–510, n = 21	-75.43	-218.59 to 67.74	0.291
12	235.13 ± 214.00, 30–720, n = 16	146.88 ± 169.34, 0–510, n = 17	-88.24	-224.81 to 48.33	0.197
13	209 ± 214.91, 0–720, n = 18	166.47 ± 171.11, 0–510, n = 15	-42.53	-182.53 to 97.46	0.540
14	219.81 ± 202.00, 0–720, n = 27	54 ± 52.99, 0–144, n = 6	-165.81	-337.22 to 5.59	0.057

CI, confidence interval.

*Number of dogs; †Statistically significant difference: p value < 0.05 (Therefore, age had no statistical significance with SFP).

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 occurred mostly in middle-aged and older, obese, and small-breed dogs [2,4,8]. The theophylline serum concentrations were monitored to achieve a sufficient therapeutic response without inducing adverse effects. Nevertheless, some patients had side effects after being administered theophylline, even though the 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 1028.19 ± 551.08 days (range, 127–2048 days) (**Table 7**). Although this study investigated several factors as possible predictors of SFP, none had prognostic value.

Cough can be caused by inflammation of the trachea but the cough itself can also induce inflammation [9]. Therefore, to reduce inflammation, prednisone (0.5 mg/kg PO q12h for 1–2 weeks and a 3 month interval) or fluticasone (125–250 mcg puff q12h) inhalation steroids are applied in long-term therapy in conventional TC treatments [15,16,26]. Therapy with stanozolol, an anabolic androgenic steroid, has also been proposed for canine TC [27]. In addition, antitussive agents have been recommended, including hydrocodone (0.22 mg/kg PO q12h) and butorphanol (0.55 mg/kg PO), to suppress cough [15]. Although bronchodilators (methylxanthines or beta-agonists) have also been used to relieve TC, there is insufficient evidence of their advantages. Therefore, as a follow-up treatment, it was common to add or withdraw theophylline while monitoring the therapeutic responses [15].

The TC patients in the current study might 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, particularly corticosteroids, repeatedly and for a long time in some patients (such as patients with Cushing's disease, diabetes mellitus, gastric ulcers, pancreatitis, and elevated liver enzymes). Therefore, 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 showed that theophylline inhibits glucocorticoid-induced hyperglycemia, thereby lowering the fasting blood glucose levels in patients and controlling interleukin-6 production by inhibiting the glucocorticoid receptor activity [28]. In addition, one study of the inflammation-suppressing mechanism found that theophylline inhibits NF- κ B activation by protecting I κ B α , thereby inhibiting the production of proinflammatory cytokines [29]. TC is a progressive disease; hence, continuous management is essential. Therefore, theophylline-based therapy has been used in patients that have shown a poor response to long-term therapy with previous drugs, or for whom there are concerns regarding severe side-effects of conventional drugs.

Theophylline has been administered in human patients with asthma and COPD [30]. On the other hand, a human study suggested that the use of methylxanthines should be avoided during COPD exacerbation because of the greater adverse effects and few benefits [18,31]. Recently, some studies reported that combination therapy involving low doses of theophylline and inhaled corticosteroids is effective in COPD patients, resulting in few side effects [32,33]. A non-bronchodilator effect of theophylline, involving the modulation of

steroid insensitivity, was found to play an important role in this effect [34]. In the present study, however, none of the patients showed such severe side-effects that resulted in the discontinuation of theophylline treatment.

The theophylline serum concentrations are associated with an improvement of the symptoms and side effects [30]. Several factors affect the clearance of the drug, which determines the serum concentration [17]. Various serum concentrations (0.2–25.6 mcg/mL) of theophylline at a dosage of 7.5–30 mg/kg PO q12h for 2–4 weeks were observed. Theophylline has a narrow therapeutic index of serum concentrations (10–20 mcg/mL) in humans and can easily cause side effects over the range [18,35,36]. On the other hand, dogs are less sensitive to high serum concentrations (above 20 mcg/mL) [35]. One study reported adverse effects at serum concentrations of 37–60 mcg/mL in dogs receiving theophylline [37]. A serum level of at least 8–10 mcg/mL is recommended for the therapeutic serum levels of theophylline in dogs [38]. In this study, the symptoms improved, even at serum concentrations < 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 [39–43]. In this study, an attempt was made to identify the early predictors of SFP, but no significant correlations were found between the SFP and several factors evaluated, including sex, age, and fluoroscopy images (**Table 11**). Therefore, the results of fluoroscopy are only used for a diagnostic examination and not to predict the SFP. A study in humans examined whether the laboratory results and clinical parameters were related to the SFP of hereditary angioedema, but no significant associations were found [39]. The relationship may differ according to the disease and factors investigated. Consequently, more study will be needed to examine the factors predicting SFP.

This study had some limitations, including the small sample number and missing values, such as the values for BCS and blood analysis. These limitations can be addressed by increasing the evaluation period and the size of the patient population, and the statistical significance can be clarified. Another limitation was the difficulty in controlling the living environment of individual patients. Because this was not a study of experimental animals, but rather a retrospective study of client-owned patients, exposure to environmental factors, such as humidity, ventilation, irritants, and environmental pollutants, may vary from patient to patient. For example, a study of chronic cough in canines identified environmental tobacco smoke and wood smoke as significant environmental factors related to chronic cough in canines [10].

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

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