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Efficacy of pimobendan on survival and reoccurrence of pulmonary edema in canine congestive heart failure

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ABSTRACT. The aim of this study was to evaluate the efficacy of pimobendan with conventional therapies on survival and reoccurrence of pulmonary edema in dogs with congestive heart failure (CHF) caused by myxomatous mitral valve disease (MMVD). Records of 197 client-owned dogs from 14 veterinary hospitals were included in this study. Dogs were administered conventional treatments with or without pimobendan. Sixty-four dogs received a standard dose of pimobendan (0.20–0.48 mg/kg every 12 hr (q12hr)), 49 dogs received a low dose of pimobendan (0.05–0.19 mg/kg q12hr), and 84 dogs received conventional therapy alone. Dogs in the standard-dose and low-dose pimobendan groups had significantly longer median survival times than dogs in the conventional group (334, 277 and 136 days, respectively; $P<0.001$). The reoccurrence rate of pulmonary edema in the standard-dose group was significantly lower than in the low-dose and conventional groups (43%, 59% and 62%, respectively; $P<0.05$). Combination of pimobendan with a conventional treatment regimen significantly prolonged survival time after an initial episode of pulmonary edema in dogs with CHF caused by MMVD. There was no difference in survival between dogs administered standard and low doses of pimobendan, but pimobendan did prevent the reoccurrence of pulmonary edema in a dose-dependent manner.

KEY WORDS: angiotensin-converting enzyme inhibitor, calcium sensitizer, canine, mitral regurgitation

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Mitral regurgitation (MR) secondary to myxomatous degeneration of the mitral valve apparatus is the most common cause of heart failure in small breed dogs [8]. Progressive MR secondary to myxomatous mitral valve disease (MMVD) causes volume overload of the left atrium (LA) and left ventricle (LV) and can result in dilation and hypertrophy of LA and LV [21]. Once the increased diastolic pressure from the regurgitated volume exceeds the compensatory mechanisms of the heart, congestive heart failure develops. At the initial diagnosis of MMVD, a cardiac murmur may be detected, but the patient may not present with any clinical signs. From the first onset of clinical sign of cardiac murmur, it may take few years to develop congestive heart failure (CHF). Confirmation of MMVD is often performed via an echocardiographic examination, which shows valvular thickening, abnormalities in the left atrial to aortic root ratio (LA/Ao) and E-wave transmitral peak velocity (Emax) [5]. The median survival time of dogs with severe MR is 6–7 months [5, 19].

Conventional treatment regimen for CHF in dogs includes diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and digoxin [20]. ACEIs have been shown to improve quality of life (QOL) and prolong survival times compared to a placebo in dogs with MMVD [11], and therefore, ACEIs are widely used in dogs with progressive MMVD. More recently, pimobendan has often been added to conventional therapy for the treatment of CHF in dogs. Pimobendan is an inodilator that exhibits both inotropic and mixed peripheral vasodilatory properties (affects both the arterial and venous vasculature) via both calcium sensitization and inhibition of phosphodiesterase [12]. Pimobendan has been shown to improve QOL and prolong the survival times of dogs

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with MMVD compared to treatment with ACEIs [16, 22]. In addition, the QUEST study showed that treatment with pimobendan prolonged the survival time to a greater extent when compared to benazepril in dogs with CHF caused by MMVD [14]. Multiple studies have shown that dogs treated with a multidrug regimen that included pimobendan have longer survival times when compared to dogs receiving a conventional therapy without pimobendan [10, 14].

The recommended dose of pimobendan varies greatly and can range from 0.1 to 0.3 mg/kg every 12 hr (q12hr) [6]. In Japan, some of veterinarians had prescribed lower dosage (0.1–0.2 mg/kg) of pimobendan for human (Acardi®, Boehringer Ingelheim Japan, Tokyo, Japan) which was before animal pimobendan coming (Vetmedin®, Boehringer Ingelheim Japan). The positive inotropic effects of pimobendan have been observed when 0.1 mg/kg is administered orally [25]. To the authors' knowledge, there is no literature available on the optimum dose of pimobendan when given as part of the conventional treatment regimen. The present study had two objectives: 1) to retrospectively evaluate the efficacy and dose dependence of pimobendan when combined with a conventional therapy on the survival times and 2) to measure the recurrence rate of pulmonary edema in dogs with CHF caused by MMVD.

MATERIALS AND METHODS

A retrospective study was performed using clinical data from 14 veterinary hospitals in Japan. Records were collected between November 2004 and February 2010, from 197 client-owned dogs with documented pulmonary edema.

We evaluated the records of the first onset of pulmonary edema (dyspnea, cough and tachypnea) in dogs with mitral regurgitation, retrospectively. Dogs were included, if they had been diagnosed with MMVD via a 2-D echocardiographic examination which showed thickening of the mitral valve leaflets, +/− evidence of chordal rupture and left ventricular and left atrial dilatation within the first 3 days of hospitalization. Measurements, including fractional shortening [4] and the LA/Ao ratio, were obtained from the right parasternal short axis using the 2D view [13]. Mitral regurgitation and eventual tricuspid regurgitation were detected using the color flow Doppler method. Thoracic radiographs (standard lateral and dorsal–ventral (DV)/ventral–dorsal (VD) views) had to be taken within the initial 3 days of hospitalization for CHF to verify the presence of pulmonary edema. The patients were required to have current radiographic evidence of pulmonary edema and cardiomegaly (vertebral heart score (VHS) ≥10.5) [7]. During the initial hospitalization period for stabilization of the left side CHF (L-CHF), any registered drug was permitted for therapy.

Dogs were excluded from the study, if they died without responses to acute therapy during the initial onset of pulmonary edema.

After treatment and recovery of CHF, the dogs were treated with a combination of diuretics, ACEIs, digoxin, pimobendan, antiarrhythmics as needed and cough suppressants. The dogs were divided into one of the following treatment groups for the study:

Conventional therapy group (n=84): ACEIs administered according to the manufacturer's recommended dosages, furosemide (≥2 mg/kg q12hr) or other loop diuretics at the manufacturer's recommended dosages, and other drugs as needed. Pimobendan (Vetmedin, Boehringer Ingelheim Japan) was not permitted.

Low dose pimobendan (low-pimo) group (n=49): ACEIs administered according to the manufacturer's recommended dosages, furosemide (≥2 mg/kg q12hr) or other loop diuretics at the manufacturer's recommended dosages, pimobendan at half the manufacturer's recommended dose (0.13 mg/kg [range 0.05–0.19 mg/kg]) q12hr, and other drugs as needed.

Standard dose pimobendan (standard-pimo) group (n=64): ACEIs administered according to the manufacturer's recommended dosages, furosemide (≥2 mg/kg q12hr) or other loop diuretics, pimobendan at the recommended dose (0.24 mg/kg [range 0.20–0.48 mg/kg]) q12hr, and other drugs as needed.

The dogs were followed individually, and drug dosages were adjusted according to the needs of each patient. However, neither the ACEIs nor the pimobendan dosages (low or standard dose) were changed.

Seventy dogs (29 from the low-pimo group and 41 from the standard-pimo group) were treated with pimobendan immediately after the initial onset of pulmonary edema. Eleven dogs (eight from the low-pimo group and three from the standard-pimo group) were treated with pimobendan more than 1 month after initial onset of pulmonary edema. Thirty-two dogs (12 from the low-pimo group and 20 from the standard-pimo group) were treated with pimobendan after the reoccurrence of pulmonary edema.

Endpoints of the study

The primary endpoint was defined as death resulting from an underlying mitral regurgitation, i.e., death at home with signs of fatal pulmonary edema, or sudden cardiac death likely to have been caused by a fatal arrhythmia or rehospitalization with L-CHF and severe pulmonary edema considered unmanageable following up to 3 days of intensive therapy, leading to euthanasia. Survival was calculated as the number of days from the first occurrence of L-CHF until the verified day of all cause death.

The secondary endpoint of the study was defined as the reoccurrence (second episode) of clinical and radiographic signs of L-CHF. Additionally, a log-rank test was used to evaluate whether the reoccurrence of pulmonary edema was associated with a worse prognosis.

Statistical analysis

Age, body weight, grade of heart murmur, VHS, LA/Ao and FS are expressed as the mean ± standard deviation. StatMate III (StatMate III, ATMS, Co., Ltd., Tokyo, Japan) was used to perform basic statistical analyses and log-rank tests. All continuous baseline variables were compared using Bartlett's test and one-way analysis of variance (one-way ANOVA). For categorical data, a χ^2 or Fisher's exact test was used. The Kaplan-Meier method was used to estimate the median time to end point for each treatment

Table 1. Initial clinical data from dogs in the three treatment groups

	Conventional group	Low-dose pimobendan group	Standard-dose pimobendan group	*P*-value
Age (years)	11.7 ± 2.5	11.8 ± 2.5	11.9 ± 2.5	0.89
Body weight (kg)	5.9 ± 3.8	6.1 ± 3.6	6.5 ± 3.7	0.68
Sex (M/NM/F/NF) (%)	42/12/12/18 (50/14/14/22)	28/4/12/5 (57/8/25/10)	34/11/10/9 (53/17/16/14)	0.35
Grade of heart murmur	4.2 ± 0.8	4.0 ± 0.6	4.0 ± 0.7	0.23
Thoracic radiography				
VHS (v)	11.9 ± 1.1	11.9 ±1.0	12.1 ±0.8	0.40
Echocardiography				
LA/Ao	2.3 ± 0.6	2.4 ± 0.4	2.1 ± 0.4	0.08
FS (%)	47.2 ±10.1	47.7 ± 9.9	45.5 ± 7.8	0.53
Presence of TR (%)	38	26	51	0.09

M, Male; NM, Neutered Male; F, Female; NF, Neutered Female.

group and to plot time to event curves. A log-rank test was used to determine whether there were any significant differences between each group. A *P* value less than 0.05 was considered significant.

RESULTS

Population characteristics

The study population comprised of 197 client-owned dogs. The most commonly recruited breeds were Shih Tzu (n=49), Maltese (n=36), Chihuahua (n=18), Cavalier King Charles Spaniel (n=12), Yorkshire Terrier (n=11), Miniature Dachshund (n=8), Toy Poodle (n=7) and Pomeranian (n=7). There were 15 additional breeds and 34 mixed-breed dogs. The median age at initial presentation was 11.8 years (range, 4.9–18.1 years), and the median body weight was 6.1 ± 3.7 kg (range, 1.5–21.1 kg). There were no statistically significant differences in the signalment, physical examination, heart size or echocardiographic findings between the 3 groups at initial presentation. (Table 1).

There was a significant difference in the number of dogs in the low-pimo group (28/49: 57%) treated with spironolactone compared to the standard-pimo group (16/64: 25%) and the conventional group (5/84: 6%) ($P<0.001$). There were significantly fewer dogs ($P<0.01$) treated with bronchodilators in the standard-pimo group (9/64: 14%) than in the low-pimo (15/49: 31%) and conventional (31/84: 37%) groups.

Eighty percent of the dogs recruited reached the primary endpoint (158/197). 150 dogs (76%) died spontaneously of cardiac related causes, 2 dogs (1%) were euthanized for cardiac related causes, 5 dogs (3%) died of renal failure, and 1 dog (0.5%) died from a neoplasm. Thirty-nine dogs (21%) were censored, because 37 dogs (19%) were alive at the termination of the study and 2 dogs (1%) had received mitral valve repair surgery.

Impact of pimobendan combination therapy on the survival rate

In both of the groups administered pimobendan, the survival times were significantly prolonged compared to the conventional group ($P<0.001$) (Fig. 1). The median survival times for the standard-pimo, low-pimo and conventional groups were 334, 277 and 136 days, and the 1-year survival rates were 46%, 37% and 23%, respectively. There was no significant difference between the standard- and low-pimo groups.

Impact of pimobendan combination therapy on the reocurrence of pulmonary edema

Thirty-two dogs (12 from the low-pimo group and 20 from the standard-pimo group) were excluded from the analysis, because pimobendan was initiated after the reoccurrence of pulmonary edema. The reoccurrence rates of pulmonary edema for the standard-pimo, low-pimo and conventional groups were 43% (19/44), 59% (22/37) and 62% (52/84), respectively. The standard-pimo group showed a significant reduction in the reoccurrence of pulmonary edema compared to the low-pimo and conventional groups. The death rates from the reoccurrence of pulmonary edema were as follows: standard (9%), low (11%) and conventional (24%) therapy. Thus, the inclusion of pimobendan in addition to conventional therapy for CHF was negatively correlated to death as a result of reoccurring pulmonary edema.

The group that had reoccurrence of pulmonary edema (n=93) had significantly shorter survival times compared with the group that had non-reoccurrence (n=72) ($P<0.05$).

DISCUSSION

Pimobendan is frequently added to the conventional treatment regimen in dogs with clinical signs associated with MMVD. However, there has been no study documenting the efficacy of pimobendan in combination therapy. We retrospectively investigated

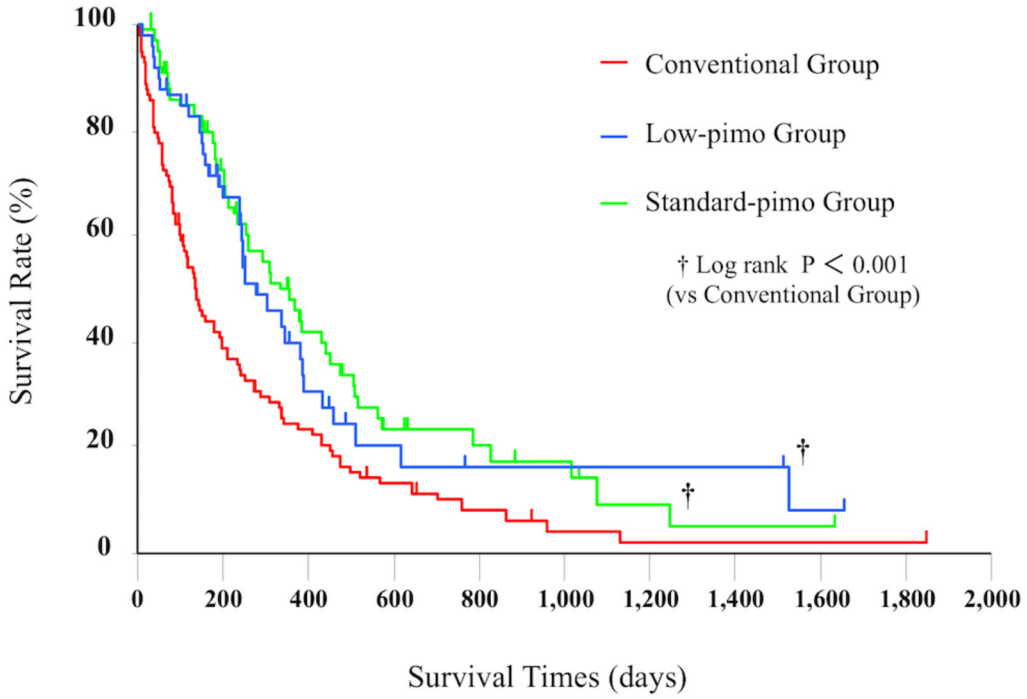

Fig. 1. Kaplan-Meier Survival Curve. In both of the groups administered pimobendan, the survival times were significantly longer than those in the conventional group.

the survival times after the initial onset of pulmonary edema in dogs with MMVD. The present study compared the impact of two different dose ranges of pimobendan with the efficacy of conventional treatment.

The prognosis of dogs diagnosed with severe mitral regurgitation is very poor, and the median survival time is less than 7 months [5, 19]. Therefore, the efficacy of new treatment regimens was evaluated by observing whether there was an increase in survival times. In the present study, the median survival times for the standard-pimo, low-pimo and conventional groups were 334, 277 and 136 days, respectively. This study showed that pimobendan administered in addition to conventional treatment increased the survival of dogs with CHF due to MMVD by 2.5 times. These results are consistent with previously reported studies that have examined the effects of pimobendan monotherapy. At similar doses, pimobendan increased survival by 1.9 times when compared to ACEI therapy [14]. Although it is difficult to directly compare previous studies due to the differences in study criteria, our data suggest that the combination therapy of pimobendan with conventional treatment (including ACEIs) is more effective than conventional therapy alone (including ACEIs).

A previous study suggested that pimobendan may increase MR under clinical conditions and may induce ventricular hypertrophy [24]. Another study reported that pimobendan may worsen valve regurgitation in dogs with asymptomatic MMVD compared to ACEIs [9]. The standard doses of pimobendan were used in these two studies. The efficacy of pimobendan in asymptomatic dogs with MMVD still needs to be confirmed. In our study, symptomatic dogs with MMVD demonstrated a longer survival time when on either the standard dose or low dose pimobendan. The clinical signs associated with high-dose (2.6–21.3 mg/kg) pimobendan toxicosis have been reported [18] and include cardiovascular abnormalities, such as severe tachycardia, hypotension and hypertension. However, these adverse effects of pimobendan were not observed in any of the dogs in this study.

The other drugs did not show any influence on the survival time in the multivariate analysis. Previous reports have indicated the effectiveness of ACEIs as a medical treatment for MMVD [2, 11], and the guidelines for diagnosis and treatment of canine chronic valvular heart disease recommend the use of diuretics and ACEIs in the treatment of CHF [1]. At present, these medications make up the standard drug treatment regimen for dogs with CHF. ACEIs and loop diuretics were used in the treatment of many dogs in this study. Thus, the current study is important in clarifying the efficacy of combining pimobendan with other conventional therapies.

Traditionally, the positive inotrope digoxin has been used in CHF treatment. The positive inotropic effect of digoxin leads to increased oxygen consumption by the myocardium, however, studies on the effect of combined pimobendan and digoxin therapy have not yet been published. Spironolactone is an aldosterone antagonist that has a positive effect on survival in dogs with naturally occurring MR caused by MMVD [3]. Spironolactone also improved rehabilitation in dogs with moderate to severe CHF [17]. Our study does not address the effect of combination therapy with pimobendan and digoxin or aldosterone antagonists, such as spironolactone or torsemide, and further studies are required to address the impact of combined pimobendan and concomitant drug therapy.

Pulmonary edema is associated with poor prognosis in dogs diagnosed with MMVD [19]. Our study showed that the reoccurrence rate of pulmonary edema was associated with a shorter survival time. The present study investigated the efficacy of

combination therapy including pimobendan to reduce the reoccurrence of pulmonary edema. We found that the standard dose range of pimobendan (0.20–0.48 mg/kg) was associated with a significantly lower rate of reoccurrence of pulmonary edema compared to conventional treatment. These data are consistent with the fact that pimobendan reduces left atrial diameter [15] and left atrial pressure [23]. The positive inotropic effects of pimobendan have been observed using 0.1 mg/kg administered orally [25], and pimobendan was administered at this concentration. In addition, a higher dose (0.5 mg/kg) of pimobendan has been shown to decrease left atrial pressure to a higher degree [23]. This dose-dependent effect of pimobendan is consistent with our results. This retrospective study supports the benefits of adding the standard dose (0.25 mg/kg q12hr) of pimobendan to a conventional therapy regimen to reduce pulmonary edema and improve disease prognosis.

The main limitation to this study is the study design. This was a retrospective study, and therefore, we did not have any control over the composition and dosage of the conventional treatment or of the dosage and timing of pimobendan introduction into the treatment regimen. These factors brought considerable variability into the analysis of the combination treatment. Nonetheless, this study confirmed the benefits of pimobendan and supports the use of standard-dose pimobendan and combination therapy over conventional treatment. Another limitation in this study is that Sodium intake in each individual patient was not measured.

In conclusion, pimobendan in combination with conventional therapy significantly prolongs the survival time after the initial onset of pulmonary edema in dogs with CHF caused by MMVD.

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