

Therapeutic Efficacy of Carvedilol and Hawthorn Extract in Management of Dilated Cardiomyopathy in Dogs

Basava Reddy K.^{1*}, Ansar Kamran C.¹, Ramesh P.T.¹, Upendra H.A.¹, Suguna Rao², Mahesh V.³

ABSTRACT

The present study was undertaken to evaluate the effect of carvedilol and hawthorn extract in managing dilated cardiomyopathy (DCM) to limit the treatment cost and improve the quality of pet life. Total 165 dogs were subjected to detailed clinical and physical examination, electrocardiography and echocardiography. Out of 165 dogs, 61(36.96%) were diagnosed as DCM, out of which 30 were allocated randomly to three treatment groups comprising ten dogs in each group. Group-I dogs were treated with pimobendan, digoxin, enalapril and furosemide. In Group-II and III, pimobendan was replaced with carvedilol and hawthorn extract, respectively. Dogs with ventricular arrhythmias (Ventricular Premature Complexes, Ventricular fibrillation) were excluded from the treatment groups as digoxin is contraindicated in ventricular arrhythmias. A noticeable improvement in clinical signs, thoracic radiographic findings, left ventricular dimensions and left ventricular contractility indices was observed in the three treatment groups after 28 days of treatment when compared to the pre-treatment values. The drug's therapeutic efficacy was evaluated based on comparative assessment of post-treatment left ventricular contractility indices (fractional shortening and ejection fraction). Group I had longer survival time with mean of 375 ± 14.25 days followed by Group III (264.67 ± 41.22 days) and Group II (214.57 ± 31.32 days) dogs.

Keywords: Dilated Cardiomyopathy, Dogs, Pimobendan, Carvedilol, Hawthorn Extract

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INTRODUCTION

Cardiac diseases are common in dogs, as that of human beings. Most of the cardiac cases are successfully managed by early detection and initiation of treatment. Well-managed dilated cardiomyopathy(DCM) dogs maintain good quality of life for many years and others have short survival time despite treatment (Martin *et al.*, 2010). Addition of pimobendan to standard triple therapy (digoxin, frusemide and enalapril) to cardiac patients significantly improved symptoms of heart failure, regardless of the breed (Fuentes *et al.*, 2002). Beta-blockers such as carvedilol have been reported to be of better choice in humans with DCM and congestive heart failure (Watanabe *et al.*, 2011). There is scanty literature about the beneficial effects of carvedilol in DCM dogs (Oyama *et al.*, 2007). Recent advances suggested that natural remedies (hawthorn extract) along with the conventional treatment prolong the survival time of dogs with DCM (Bhargavi., 2020). The herbal drug hawthorn extracted from leaves of Crataegus plant belongs to Rosaceae family native to temperate regions of the Northern Hemisphere in Europe, Asia, North Africa and North America. It has positive inotropic, vasodilatory effects, increases myocardial perfusion, reduces afterload, and is similar to class III antiarrhythmic agents (Brenyo and Aktas., 2014). Even though several treatment options are available for managing DCM, most dog owners request euthanasia rather than treatment owing to further complications, expensive treatment and animal management. Given the above factors, the present study evaluated the efficacy of carvedilol and hawthorn in managing DCM in Dogs to limit the treatment

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cost and improve the quality of life.

MATERIALS AND METHODS

The present study was conducted at the Department of Veterinary Medicine, Veterinary College, Hebbal, Bengaluru from November 2019 to July 2021.

Dogs presented (n=165) with clinical signs suggestive of cardiac insufficiency were screened for the DCM using the specially designed cardiology data sheet. They were subjected to detailed clinical and physical examination,

electrocardiography and echocardiography. The dogs with fractional shortening (FS) below 25 % in M- mode echocardiogram and ejection fraction (EF) below 40 % in biplanar Simpson's method of discs were selected for the study (Fig. 1, 2). Simpson's Method of Disc (SMOD) was used to measure the chamber volumes as per the standard procedure described by Boon (2011) (Fig 3). The LA and AO were measured in M-mode using a short axis view at the aortic valve level to calculate the LA/AO ratio as per the standard method described by Hansson *et al.* (2002) (Fig 4).

Dogs diagnosed with DCM were randomly allotted to the three treatment groups irrespective of age, sex and breed. Dogs of Group I were administered with pimobendan @ 0.25 mg/kg b.wt, PO, bid, before food, digoxin @ 0.005 mg/kg b.wt, PO, bid, after food, enalapril @ 0.5 mg/kg b.wt, PO, bid, after food and furosemide @ 2 mg/kg b.wt, PO, bid, after food. In Group-II and III dogs pimobendan was replaced with carvedilol @ 0.3 mg/kg b.wt, PO, bid, after food and hawthorn extract @ 25 mg/kg b.wt., PO, b.i.d, after food, respectively.

Dogs having ventricular arrhythmias (Ventricular premature complexes and Ventricular fibrillation) were excluded from treatment groups as digoxin is contraindicated in ventricular arrhythmias. The drug's therapeutic efficacy was evaluated based on a comparative assessment of left ventricular contractility indices, fractional shortening (FS) and ejection fraction (EF) in Group I, II and III dogs on the day of presentation and on 28th day of post-treatment.

Survival time was calculated (days) from the day of initiation of treatment (when DCM diagnosis was made) to the death or euthanasia. Dogs lost to follow-up or still alive at the end of the study were excluded.

Statistical Analysis

Data was analyzed statistically on SPSS-16.0 (SPSS Inc., Chicago, IL USA) software package as per standard method (Snedecor and Cochran., 1994) and with Graph pad prism software (8 version). Paired t-test was performed to compare the means of dogs with DCM before and after treatment in each group and their statistical significance was tested. One-way ANOVA was used to test the significance between the three groups after treatment.

RESULTS AND DISCUSSION

Highest occurrence of DCM was noticed in the age group of 4 to 8 years of male Labrador Retrievers.

Clinical Examination

The therapy was aimed to ameliorate the clinical signs, quality of life and prolong survival time to the extent possible by controlling congestive heart failure (CHF) signs, improving cardiac output, managing secondary complications and arrhythmias as suggested by Ware (2009).

The dogs in Group-I showed clinical improvement within ten days of treatment. Clinical signs were improved with

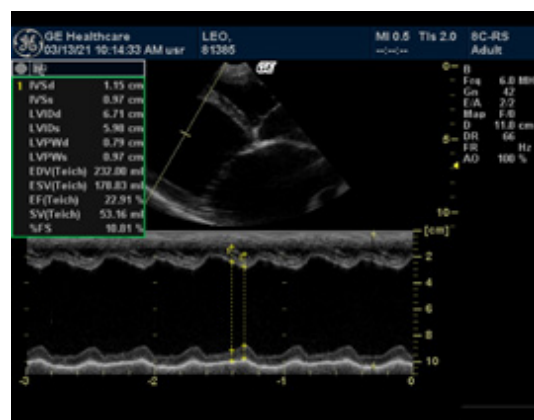


Fig 1: M-mode echocardiography in DCM dog showing enlarged left ventricle with FS10.81%.

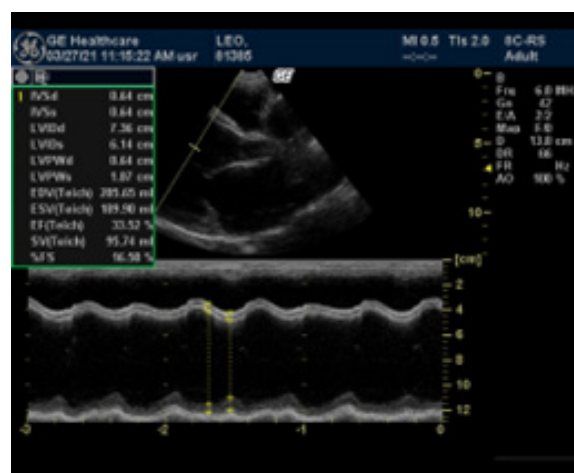


Fig2: M-mode echocardiography in the same dog of fig (1) showing decreased LVIDd and increased FS (16.50%) after initiation of treatment in Group I.

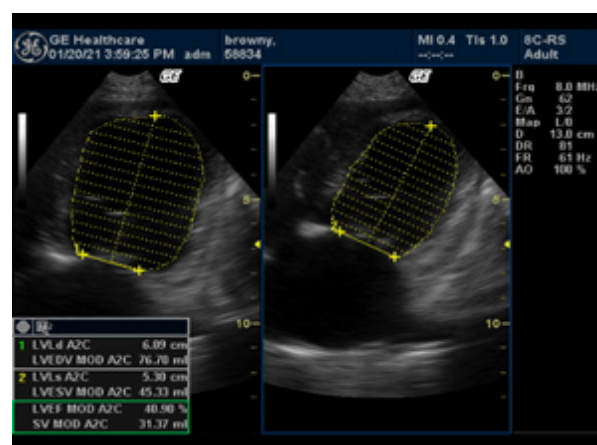


Fig 3: Measurement of EDV, ESV and EF in biplanar Simpson's method of discs in DCM dog.

respect to exercise tolerance, cough, dyspnea, polypnea, physical activity and reduced abdominal distension. The present findings agree with Fuentes *et al.*, (2002) and Amberger *et al.*, (2004). On the other hand, the dogs in Group-II and Group-III showed clinical improvement by fifteen to twenty days after initiation of treatment. The delay

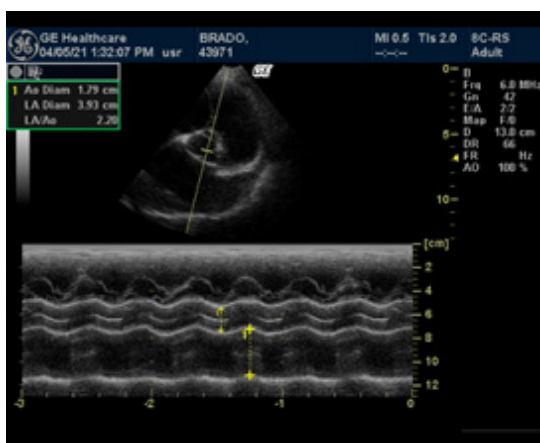


Fig 4: M-mode measurement of LA/AO ratio in DCM dog.

in the clinical improvement in the Group-II and Group-III dogs over Group-I might be due to modest positive inotropic action of carvedilol (Ware and Keene, 1999) and hawthorn. The use of hawthorn extract as an adjunctive treatment was found to produce a significant benefit in the control of symptoms such as improvement of exercise tolerance, dyspnea and fatigue associated with heart failure (Chang *et al.*, 2005 and Rastogi *et al.*, 2016).

Thoracic Radiography

Thoracic radiography revealed reduction in pulmonary oedema in all the three Groups by the end of study period. The progressive reduction in pulmonary oedema in the DCM dogs might be due to the control of fluid retention by furosemide and blocking of aldosterone induced renal retention of sodium and water, reduction of the pulmonary capillary wedge pressure and improvement in the heart failure by enalapril (Martin, 2003).

Left Ventricular Internal Dimension at End Diastole and End Systole

A significant reduction in left ventricular internal dimensions at end-diastole and end-systole (LVIDd and LVIDs) was

observed in all three Groups of dogs following treatment (Table 1). This might be due to a reduction in afterload and improved systolic function of myocardium. The present findings agree with earlier studies (Feuntes *et al.*, 2002; Martin, 2003; O'Grady *et al.*, 2008 and Summerfield *et al.*, 2012).

Left Ventricular Contractility Indices

There was highly significant ($p < 0.01$) increase in the left ventricular contractility indices (fractional shortening and ejection fraction) following treatment in Group I dogs (Table 1). The present findings agree with the observations of Fuentes *et al.* (2002). This may be due to positive inotropic and vasodilatory effects of pimobendan, negative chronotropic action of digoxin and reduction of afterload caused by enalapril and furosemide.

There was significant increase in left ventricular contractility indices (FS and EF) following treatment in Group-II dogs (Table 1). Similarly, Nikolaidis *et al.* (2006) also reported improved cardiac output, stroke volume and decreased left ventricular end diastolic pressure with oral administration of carvedilol in dogs with dilated cardiomyopathy. The addition of carvedilol to the standard therapy (digoxin, frusemide and benazepril) improved echocardiographic indices of systolic function (FS and EF), reduced NT-pro BNP levels but statistically there was no significant improvement over standard therapy (Kumar *et al.*, 2018).

There was significant ($p < 0.01$) increase in left ventricular contractility indices (FS and EF) following treatment in Group-III dogs. Tankanow *et al.* (2003) reported no evidence of any pharmacodynamic interaction in the co-administration of hawthorn with digoxin in heart failure patients. The significant increase in left ventricular contractility indices associated with positive inotropic and vasodilatory effects of hawthorn increasing myocardial perfusion and reducing afterload was supported by findings of Brenyo and Aktas (2014) and Chang *et al.* (2005).

Table 1: Left ventricular dimensions and functional echocardiographic parameters before and after treatment (Mean \pm S.E)

Parameter	Group I			Group II			Group III		
	Before treatment	After treatment	p value	Before treatment	After treatment	p value	Before treatment	After treatment	p value
LVIDd (cm)	5.65 \pm 0.22	5.32** \pm 0.16	0.0049	5.01 \pm 0.39	4.95* \pm 0.39	0.035	4.88 \pm 0.41	4.67* \pm 0.38	0.0329
LVIDs (cm)	4.95 \pm 0.26	3.80** \pm 0.13	0.0037	4.13 \pm 0.32	3.99** \pm 0.33	0.002	4.08 \pm 0.37	3.67* \pm 0.32	0.0181
EDV (mL)	155.23 \pm 14.46	130.39** \pm 7.9	0.0043	128.43 \pm 19.68	120.47** \pm 18.1	0.002	147.49 \pm 16.10	128.86** \pm 13.1	0.0017
ESV (mL)	116.90 \pm 15.22	57.58** \pm 4.57	0.0022	82.03 \pm 13.11	74.81** \pm 11.96	0.005	96.11 \pm 12.43	73.00** \pm 7.96	0.0080
EF (%)	27.04 \pm 3.31	56.06** \pm 1.52	0.0048	36.33 \pm 2.03	38.39* \pm 2.43	0.013	34.62 \pm 2.89	43.16** \pm 3.19	0.0082
FS (%)	12.98 \pm 1.737	29.19** \pm 0.79	0.0042	17.54 \pm 1.10	19.34** \pm 1.27	0.005	16.92 \pm 1.56	21.87** \pm 1.72	0.0055
LA/AO	2.12 \pm 0.089	1.84** \pm 0.04	0.0026	2.04 \pm 0.071	2.02 NS \pm 0.07	0.096	1.93 \pm 0.089	1.85 NS \pm 0.08	0.1005
EPSS(cm)	1.75 \pm 0.156	1.55** \pm 0.09	0.0041	1.34 \pm 0.17	1.34 NS \pm 0.15	0.934	1.38 \pm 0.24	1.24 NS \pm 0.17	0.0982

Note:**indicates $P < 0.01$; *indicates $P < 0.05$; NS indicates no significant difference

Left ventricular contractile indices (FS and EF) were significantly increased following treatment in all the three groups, but Group-I showed highly significant difference ($P < 0.05$) when compared with Group-II and Group-III. In contrast, no significant difference was observed between Group-II and Group-III (Table 1). This might be due to inadequate drug dosages (carvedilol and hawthorn) and the brevity of follow-up time. Dahmer and Scott (2010) reported higher doses (600-1800 mg in two or three divided doses) of hawthorn may produce greater therapeutic effectiveness. Oyama *et al.* (2007) reported that the lack of effectiveness of carvedilol in DCM dogs might be related to severity of disease, dose or brevity of follow-up time.

LA/AO Ratio and EPSS

In the present study, there was significant ($p < 0.01$) decrease in LA/AO ratio and EPSS in Group I dogs following treatment but there was no significant difference in Group II and Group III dogs (Table 1). Decreased LA/AO ratio and EPSS in Group I following treatment indicates the reduction in preload and afterload at left ventricle. This might be due to decreased volume overload and increased stroke volume associated with vasodilatory effects of pimobendan.

Survival Period (days)

Group I had longer survival period with mean of 375 ± 14.25 days followed by Group III (264.67 ± 41.22 days) and Group II (214.57 ± 31.32 days) dogs. The present findings are in agreement with Fuentes *et al.* (2002) who reported DCM dogs showed significant improvement and survival time (Median=329 days) when pimobendan was added to standard therapy (digoxin, furosemide and enalapril). Pimobendan exerts its positive inotropic effects in the heart failure primarily through sensitization of the cardiac contractile apparatus to intracellular calcium and enhances the systolic function by improving the efficiency of contraction, leading to vasodilatation and reduction of both cardiac preload and afterload thereby safe augmentation of contractility is obvious in DCM (Boswood, 2010). Pimobendan is associated with reducing proinflammatory cytokines, thereby delaying the CHF and providing cardioprotection (Matsumoi *et al.*, 2001). Short survival time in Group II and Group III might be due to modest positive inotropic action of carvedilol and hawthorn respectively.

Group III dogs showed longer survival period with a mean of 264.67 ± 41.22 days compared with Group II (214.57 ± 31.32 days) DCM dogs. The use of hawthorn extract as an adjunctive treatment found to produce a significant benefit in the control of symptoms such as improvement of exercise tolerance, dyspnea and fatigue associated with heart failure (Rastogi *et al.*, 2016). Joseph and Pizzorono (2016) reported hawthorn was quite useful in early stages as sole agent and later stages in combination with digitalis cardioglycosides for managing CHF in humans.

CONCLUSION

Adding pimobendan to the standard therapy (digoxin, furosemide and enalapril) resulted in increased FS and EF in Group I, dogs with DCM therefore improving the longevity and quality of life. Hawthorn extract plus standard therapy in Group III showed better improvement compared with Group II regarding survival period. Hence this can be added to the standard therapy for managing DCM in dogs where pet owners cannot buy pimobendan as it is expensive.

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