OPEN ACCESS
Advances in Animal and Veterinary Sciences
Research Article

Management of Dilated Cardiomyopathy with Enalapril and Losartan

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Abstract | The present study was undertaken to evaluate the efficacy of angiotensin converting enzyme inhibitor (Enalapril) and angiotensin II receptor antagonist (Losartas) along with a diuretic and supplemental therapy in dogs with idiopathic dilated cardiomyopathy. A total of 30 dogs with dilated cardiomyopathy were randomly allotted to treatment groups i.e., group I and II (15 dogs in each group). The echocardiographic left ventricle dimensions of the dilated cardiomyopathy affected dogs of group I and II showed significantly (P<0.01) increased LVEDd and LVEDs when compared with the mean values of healthy dogs. The other dimensions viz., LVPWd, LVPWs, IVSd and IVSs noted on day 0 among the different group of affected dogs were significantly low (P<0.05). There was significant increase in EPSS value (<0.01). With respect to Ejection Fraction and Fractional Shortening, the values on day 0 were significantly low (P<0.01). Group I was treated with Enalapril and group II with Losartan along with common diuretic torsemide in both the groups. All the dogs in group I showed recovery where as two dogs died in group II during the treatment period. The present findings reveal that dogs suffering with dilated cardiomyopathy can be treated with a combination of traditional ACEi like enalapril, superior diuretic like torsemide and supplemental neutraceuticle like L-carnitine, for earlier clinical recovery with no adverse drug reactions.

Keywords | Canine, Dilated cardiomyopathy, Enalapril, Losartan, Torsemide

Received | January 05, 2019; **Accepted** | June 21, 2020; **Published** | June 25, 2020
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Citation | Haritha GS, Kumar S.K, Kumar AVVV (2020). Management of dilated cardiomyopathy with enalapril and losartan. Adv. Anim. Vet. Sci. 8(7): 777-781.
DOI | http://dx.doi.org/10.17582/journal.aavs/2020/8.7.777.781
ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331

INTRODUCTION

Despite the recent advances in the management of patients with heart failure, morbidity and mortality rates remain high. Common causes of heart failure are ischaemic heart disease, uncontrolled hypertension and valvular disease. However, in up to 50 % of the cases its exact cause remains initially unknown; this condition is called idiopathic dilated cardiomyopathy (DCM) (Hazebroek et al., 2012). Dilated cardiomyopathy (DCM), characterized by chamber dilatation and myocardial systolic and diastolic dysfunction, is one of the most common heart diseases in dogs. The clinical diagnosis is based on findings on echocardiographic and Doppler examinations, with the active exclusion of other acquired or congenital heart diseases (Tidholm and Jonsson, 1997). The management of patients with dilated cardiomyopathy (DCM) starts with the determination of the underlying diagnosis, definition of the hemodynamic character (eg, systolic, diastolic, valvular, right and left-sided heart dysfunction) and recognition of complicating factors (eg, atrial fibrillation, renal dysfunction). Angiotensin-converting enzyme inhibitors, beta-blocking agents, digoxin, and judicious diuretic administration make up the therapeutic plan for patients with symptomatic DCM heart failure (Carl, 2001).

MATERIALS AND METHODS

Out of 201 dogs suspected for cardiac ailment at College of Veterinary Science, Hospital, Bhoiguda, Hyderabad during 2012-14, 113 dogs were diagnosed for various cardiac disorders. A total of 30 male Labrador retriever patients with a mean weight of 41.5 Kg (39-44kg) and mean age of 9.5 years (8-11yrs) confirmed for dilated cardiomyopathy alone were selected for therapeutic trial. They were randomly allotted to one of the treatment groups viz., group I and II with 15 dogs in each. In all the dogs a thorough physical examination, complete blood count,

biochemical analysis, radiograph, electrocardiograph and echocardiograph were carried out (Varshney et al., 2008). The dogs under treatment trial were monitored for a period of 90 days and the therapeutic efficacy was assessed at frequent intervals based on improvement in the clinical signs, hemato-biochemical findings and echocardiographic features.

However, treatment was also continued even after 90 days, but not considered for the study. Further, all the other dogs diagnosed for various cardiac diseases and hypothyroid associated DCM were also treated with respective therapeutic agents for significant period. Arrhythmias were tackled by suitable treatment. Blood Urea Nitrogen and serum creatinine were monitored in the course of treatment.

Dogs in group I were treated with enalapril at the initial dose rate of 0.25 mg/kg twice daily for 10 days which was increased to 0.5 mg/kg, thereafter; torsemide at the dose rate of 0.2 mg/kg twice daily, orally (Oyama et al., 2011); and L-Carnitine at the dose rate of 50 mg/kg, once daily, orally, for 90 days (Vykunta et al., 2008).

Dogs in group II were treated with losartan potassium at the initial dose rate of 1.25 mg/kg twice daily for 10 days which was increased to 2.5 mg/kg, thereafter; torsemide at the dose rate of 0.2 mg/kg twice daily, orally; and L-Carnitine at the dose rate of 50 mg/kg, once daily, orally, for 90 days (Jeyaraja et al., 2008).

The pet owners were advised to restrict dog's physical activity and to give low salt or salt free diet.

RESULTS AND DISCUSSION

All the 30 dogs considered for therapeutic trial showed similar clinical manifestations like exercise intolerance, cough, dyspnoea at rest, going down in condition, anorexia and ascites, pale mucosa with pedal oedema, cyanotic tongue and syncope in few dogs which were similar to that of findings of (Jeyaraja et al., 2015; Satish et al., 2011).

There was no significant difference in the hematological findings (Table 1). However, in contrast, Reece (2004) and Sesh et al. (2013) who suggested that decrease in Hb, PCV and TEC was due to ischemia indicating cardiovascular disorder. De Morais (2000) suggested that, though the hematology was not particularly helpful to diagnose, but it could be used to investigate potential concurrent diseases. Biochemically (Table 2), increase in CKMB and LDH and significant decrease in total protein, albumin, sodium and potassium levels were noticed. Singh et al. (2012) who were of the opinion that in CHF patients routine biochemical parameters may remain within the normal range except for an elevation in the levels of lactate dehydrogenase and creatine kinase MB. Mild hypoproteinaemia and hypoalbuminemia in the affected dogs could be attributed to increased protein loss from the intestines due to bowel and pancreatic oedema and poor absorption due to decreased splanchnic perfusion (Ettinger, 2000) or it is usually ascribed to high levels of vasopressin causing water retention (Paul, 2010). Low levels of sodium and potassium were also similar to the findings of Sesh et al. (2013) who opined that hyponatremia and hypokalemia might be due to the drainage of sodium and calcium from the blood into cardiac tissue for depolarization and excitation of cardiac muscle respectively, which is one of the physiological responses at the time of cardiac arrest (Guyton, 2011).

The echocardiographic left ventricle dimensions of the dilated cardiomyopathy affected dogs of group I and II revealed a significantly ($P<0.01$) increased LVEDd and LVEDs when compared with the mean values of healthy dogs. The other dimensions viz., LVPWd, LVPWs, IVSd and IVSs noted on day 0 among the different group of affected dogs were significantly low ($P<0.05$). There was significant increase in EPSS value ($P<0.01$). With respect to Ejection Fraction and Fractional Shortening, the values on day 0 were significantly low ($P<0.01$) (Table 3). Gamcarz (2007) stated that echo cardiographic evaluation of diastolic parameters in dogs with dilated cardiomyopathy revealed a significant difference in the left ventricle dimensions when compared with that of the healthy dogs. However, Singh et al. (2012) reported that in late dilated cardiomyopathy, both systolic and diastolic left ventricular dimension and EPSS ratio were increased with reduced fractional shortening (FS). Mild mitral regurgitation was observed in some cases of late DCM. In early DCM there was normal diastolic dimension (LVIDd) but increased systolic left ventricular dimension (LVIDs) and hence reduced FS was found.

When therapy was instituted, alleviation of clinical signs of group I dogs was noticed in 05-15 days with no mortality. Clinical signs among the dogs of group II alleviated in 10-25 days. Inspite of every effort, two dogs of this group died during the course of therapy. There is no significant difference in blood parameters of group I and II dogs' pre and post therapy. A significant decrease was noticed in the values of CKMB and LDH by day 90 after treatment in both the groups. There was also a significant increase in TP, albumin, sodium and potassium levels post therapy. However, these serum chemistry levels differed significantly between the groups. i.e., the DCM affected Labrador dogs of group I showed a quicker and much improvement when compared to that of group II cases that were relatively slower with less improvement. Whereas, no significant difference was noticed with the values of ALT, BUN, creatinine and chloride in between the groups by day 90 (Table 2). In both the DCM affected groups the

Table 1: Mean ± SE of hematological findings in healthy and all Groups of DCM dogs before and after therapy

S. No.	Parameter	Apparently healthy dogs	Group –I (n=15)		Group –II (n=15)	
			BT	AT	BT	AT
1.	PCV (%)	38.86 ± 0.22	38.21 ± 0.02	38.36 ± 0.43	38.74 ± 0.09	38.44 ± 0.33
2.	Hb (g/dl)	13.02 ± 0.24	13.33 ± 0.24	13.25 ± 0.34	13.09 ± 0.42	13.68 ± 0.35
3.	TEC X 10^6/ µl	6.94 ± 0.12	5.13 ± 0.27	6.37 ± 0.20	5.02 ± 0.26	5.94 ± 0.22
4.	TLC X 10^3/ µl	8.12 ± 0.45	8.96 ± 0.21	8.68 ± 0.30	8.63 ± 0.27	8.39 ± 0.18
5.	Neutrophils (%)	69.25 ± 0.26	69.92 ± 0.42	69.50 ± 0.74	70.20 ± 0.50	69.99 ± 0.14
6.	Lymphocytes (%)	25.72 ± 0.5	25.32 ± 0.56	25.56 ± 0.85	25.22 ± 0.72	25.36 ± 0.22
7.	Eosinophils (%)	2.89 ± 0.23	2.74 ± 0.12	2.72 ± 0.44	2.56 ± 0.32	2.41 ± 0.14
8.	Monocytes (%)	2.14 ± 0.12	2.02 ± 0.36	2.22 ± 0.08	2.02 ± 0.76	2.24 ± 0.38
9	Basophils (%)	---	---	---	---	---

Table 2: Mean ± SE of Biochemical findings in healthy and all Groups of DCM dogs before and after therapy.

S. No.	Parameter	Apparently healthy dogs	Group –I (n=15)		Group –II (n=15)	
			BT	AT	BT	AT
1.	CKMB (U/L)	28.24 ± 0.14	69.95 ± 2.94**	36.2 ^{a} ± 1.35**	68.2 ± 3.05**	47.05 ^{b} ± 1.08**
2.	LDH (U/L)	88.25 ± 0.56	149.25 ± 4.55**	97.35 ^{a} ± 2.90**	145.5 ± 5.20**	124.7 ^{b} ± 2.32**
3.	ALT (U/L)	33.68 ± 0.24	33.51 ± 0.96	33.10 ^{a} ± 1.30	33.94 ± 0.34	33.38 ^{a} ± 1.50
4.	TP (g/dL)	6.12 ± 0.02	4.62 ± 0.11*	5.82 ^{a} ± 0.13*	4.98 ± 0.98*	5.98 ^{b} ± 0.16*
5.	Alb (g/dL)	3.98 ± 0.01	2.72 ± 1.10*	3.66 ^{a} ± 1.07*	2.81 ± 0.66*	2.99 ^{b} ± 0.07*
6.	BUN (mg/dL)	15.2 ± 0.12	15.93 ± 0.80	15.28 ^{a} ± 0.53	16.09 ± 0.88	15.87 ^{a} ± 0.77
7	Cr (mg/dL)	1.22 ± 0.24	1.09 ± 0.59	1.16 ^{a} ± 0.52	1.16 ± 0.66	1.19 ^{a} ± 0.42
8	Na (mEq/L)	134.82 ± 0.54	125.92 ± 0.57*	135.38 ^{a} ± 0.87*	127.12 ± 0.67*	135.26 ^{b} ± 0.56*
9	K (mEq/L)	5.62 ± 0.24	3.89 ± 0.12*	5.40 ^{a} ± 0.14*	3.81 ± 0.82*	4.40 ^{b} ± 0.13*
10	Cl (mEq/L)	103.78 ± 0.25	103.36 ± 0.59	103.35 ^{a} ± 0.79	103.22 ± 0.72	103.61 ^{a} ± 0.16

Means bearing same superscripts do not differ significantly; * Significant at (P<0.05); ** Significant at (P<0.01).

Table 3: Mean±SE of left ventricle dimensions in echocardiography of DCM dogs of all Groups before and after therapy.

S. No.	Parameter	Apparently healthy dogs	Group –I (n=15)		Group –II (n=15)	
			BT	AT	BT	AT
1.	LVEDd (mm)	39.12 ± 0.22	55.64 ± 1.18**	48.69 ^{a} ± 0.92*	56.44 ± 1.22**	51.52 ^{b} ± 1.77*
2.	LVEDs (mm)	24.52 ± 0.36	49.98 ± 1.57**	40.92 ^{a} ± 0.79*	50.18 ± 1.52**	45.00 ^{b} ± 0.59*
3	LVPWd (mm)	7.02 ± 0.42	5.20 ± 0.88*	6.45 ^{a} ± 0.12*	5.08 ± 0.72*	6.23 ^{b} ± 0.22*
4.	LVPWs (mm)	8.26 ± 0.64	7.16 ± 0.78*	8.0 ^{a} ± 0.32*	7.25 ± 0.31*	7.66 ^{b} ± 0.23*
5.	IVSd (mm)	6.92 ± 0.74	5.32 ± 1.36**	6.20 ^{a} ± 0.31*	5.25 ± 1.42**	5.5 ^{b} ± 0.25*
6.	IVSs (mm)	6.02 ± 0.38	5.39 ± 0.27*	5.90 ^{a} ± 0.24*	5.44 ± 0.28*	5.70 ^{b} ± 0.11*
7.	EPSS (mm)	4.02 ± 0.26	9.04 ± 1.13**	7.20 ^{a} ± 0.27*	8.98 ± 1.32**	7.78 ^{b} ± 0.20*
8.	EF (%)	61.28 ± 1.42	34.34 ± 2.68**	49.54 ^{a} ± 2.86**	32.86 ± 2.46**	43.66 ^{b} ± 2.02**
9.	FS (%)	32.42 ± 0.48	13.18 ± 1.98**	22.32 ^{a} ± 1.76**	12.98 ± 0.18**	19.70 ^{b} ± 1.32**

Means bearing same superscripts do not differ significantly; * Significant at (P<0.05); ** Significant at (P<0.01).

left ventricle dimensions viz., LVEDd, LVEDs and EPSS were significantly decreased with a significant increase in other dimensions viz., LVPWd, LVPWs, IVSd and IVSs by the end of the therapy (day 90), when compared to pre-therapeutic values. Following therapy, Ejection fraction and Fractional shortening were significantly increased by day 90). Though improvement in various left ventricle dimensions of both the group dogs were significant when compared between before and after therapy, these dimensions and EF and FS also differed significantly

between the groups, i.e., the improvement in various parameters (LVEDd, LVEDs, EPSS, LVPWd, LVPWs, IVSd, IVSs, EF and FS) were significantly faster and more in group I cases compared to group II (Table 3). Lazaros et al. (2002) suggested beneficial effects of ACE inhibitors on the coronary circulation in DCM that are not shared by AT1 receptor antagonists. The ACE inhibitor enalapril improves transmural myocardial perfusion at rest and after chronotropic stress and restores impaired subendocardial coronary flow and vasodilator reserve in DCM. The effects of enalapril were bradykinin mediated and Nitric Oxide-dependent and were not recapitulated by losartan. However, Sharma et al., 2000 in a study to assess mortality in heart failure patients treated with losartan reported that beneficial effect was provided by losartan upon survival. However, he added that a large confirmatory study is needed to assess the mortality benefit of losartan compared with an ACE inhibitor. Torasemide is chosen as diuretic as it is a long-acting loop diuretic that combines the effects of both furosemide and spironolactone and may block the renin–angiotensin–aldosterone system and therefore it might attenuate myocardial remodelling accompanied by left ventricular dysfunction (Punniyakoti et al., 2008). Owners' compliance with respect to drug administration and the animal's acceptance to be medicated orally are the two important considerations in the successful management of DCM, which require chronic drug therapy (Roudebush and Freeman, 1999).

Table 4: Number of days taken for the alleviation of clinical manifestations in DCM affected dogs of both groups.

Manifestation	Time taken for disappearance of signs (days)			
	Group I (n=15)		Group II (n=15)	
	Range	Mean	Range	Mean
Exercise intolerance	08 – 15	11.5	15 – 25	20.0
Cough	10 – 15	12.5	12 – 20	16.0
Dyspnoea at rest	09 – 13	11.0	12 – 18	15.0
Ascites	08 – 15	11.5	10 – 20	15.0
Weight loss	10 – 15	12.5	12 – 20	16.0
Anorexia	05 – 10	7.5	10 – 18	14.0
Peripheral edema	06 – 12	9.0	10 – 15	12.5
Pale mucosae	08 – 15	11.5	10 – 15	12.5
Cyanotic mucosae	05 – 15	10.0	10 – 15	12.5

The efficacy of different therapeutic regimens was assessed based on resolution of clinical signs, improvement in the biochemical laboratory parameters and improvement in the echo cardiographic observations. Even though both the therapeutic regimens were found effective in treating DCM by alleviation of clinical signs, group I dogs showed faster recovery in terms of resolution of clinical signs in 7.5-12 days (Table 4) and with significant improvement in biochemical and echocardiographic findings and without any mortality in diseased dogs either during or after the completion of the course of therapy.

CONCLUSION

Despite the recent advances in the management of patients with heart failure, morbidity and mortality rates remain high. It may be concluded from the present findings that dogs suffering with dilated cardiomyopathy can be treated with a combination of traditional ACEi like enalapril, superior diuretic like torsemide and supplemental neutraceuticle like L-carnitine, for earlier clinical recovery with no adverse drug reactions. Qualitative improvement in the treatment was reflected by clinical findings and radiographic findings while quantitative improvement was reflected by echocardiography particularly by left ventricle indices viz., EF and FS.

AUTHORS CONTRIBUTION

All authors contributed equally.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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