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Long-term effects of pentoxifylline in heart failure therapy

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ABSTRACT

The aim of the present study is to investigate the effects of pentoxifylline on left ventricular ejection fractions (EF) and volumes, New York Heart Association (NYHA) functional class, left ventricular diastolic parameters and hospitalization for heart failure in patients with ischemic or non-ischemic cardiomyopathy. A total of 60 patients were randomised to either peroral 1200 mg/day pentoxifylline or control group. All patients were on optimal heart failure therapy and their EF was <40% by transthoracic echocardiography. The patients were followed up for 12 months. Twenty-one patients (70%) in pentoxifylline group and 20 (66.7%) in control group completed the study. Baseline and 12 months' end-diastolic volume, end-systolic volume, EF and NYHA class were as follows in pentoxifylline group; 160.5±51.3 mL vs 156.6±43.1 mL, 109.1±40 mL vs 106.1±33.4 mL, 32.4±5.7% vs 33.2±5.2%, 2.4±0.5 vs 2.2±0.5, p=0.5411, 0.5257, 0.4099 and 0.1037; respectively. There were also no difference in baseline and follow-up diastolic parameters. Mean hospitalization numbers for heart failure were similar between groups (1.26±0.71 vs 1.60±1.04, p=0.1717). Contrary to previous reports, no beneficial effect of pentoxifylline was observed on clinical or echocardiographic parameters.

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1. Introduction

Congestive heart failure with the features of high frequency, prevelance, morbidity and mortality is one of the most important health problems (Del Carlo and O'Connor, 1999). Most common cause of hospitalization over sixty five years old patients is congestive heart failure (Narula et al., 2001). Although incidence of numerous cardiovascular diseases decreased in the last 20 years, the incidence of heart failure has increased (O'Connell and Bristow, 1994). While one year-mortality in mild and moderate heart failure is 15-25%, mortality in severe heart failure is between 40-50%. Heart failure caused by myocardial, valvular, pericardial and non-cardiac pathologies affects various organs such as renal, pulmonary, endocrinological and musculoskeletal systems. Pathophysiology and medical treatment of heart failure is well known (Silistreli and Oto, 1999). Current medical treatment modalities (digoxin, diuretics, angiotensin converting enzyme (ACE) inhibitors, beta blockers and phosphodiesterase inhibitors) aim reducing afterload and increasing contractility (Durdu et al., 2003).

Pentoxifylline, a derivative of metilxanthine, inhibits phosphodiesterase enzyme and shows haemorrhagical and antiinflammatory effects. Pentoxifylline reduces the viscosity of blood, decreases aggregation of thrombocytes and improves tissue oxygenation. Hypoxia and ischemia are important in the occurence of inflammation. It has been speculated that pentoxifylline can reduce inflammation by enhancing tissue oxygenation. It was shown that pentoxifylline inhibits tumor necrosis factor (TNF) and interleukin-2 (IL-2) production which are derived from monocytes and T-cells via polysaccharide signalling and supresses cytokine replication (Ward and Clissold, 1987; Sullivan et al., 1988; Edwars et

Table 1. Baseline clinical characteristics

	Pentoxifylline group (n=30)	Control group (n=30)	p
Age (year)	60.8±11.7	62.9±10.7	0.4910
Sex			
Female	13 (43.3%)	7 (23.3%)	0.1709
Male	17 (56.7%)	23 (76.7%)	
Averaged NYHA class	2.7±0.7	2.8±0.6	0.3079
NYHA class			
2	13 (43.3%)	8 (26.7%)	
3	14 (46.7%)	19 (63.3%)	0.2998
4	3 (10%)	3 (10%)	
Hypertension			
Present	12 (40%)	18 (60%)	0.164
None	28 (60%)	12 (40%)	
Diabetes Mellitus			
Present	10 (33.3%)	12 (40%)	0.035
None	20 (66.7%)	18 (60%)	
Ischemic CMP			
Present	13 (43.3%)	15 (50%)	0.7958
None	17 (56.7%)	15 (50%)	
Smoking			
Smoker	3 (10%)	9 (30%)	0.1277
Non-smoker	18 (60%)	11 (36.7%)	
Ex-smoker	9 (30%)	10 (33.3%)	
SBP (mmHg)	131.6±21.4	121.4±25.4	0.1095
DBP (mmHg)	79.5±13.1	76.6±14.8	0.4402
Rythm			
Sinus	27 (90%)	24 (80%)	0.4696
AF	3 (10%)	6 (20%)	

NYHA: New York Heart Association; **CMP:** Cardiomyopathy; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **AF:** Atrial fibrillation.

al., 1991; Schandene et al., 1992). In the treatment of heart failure immunological mechanisms are suggested to be substantial determinants and resistance to treatment is still an essential problem. In this paper we investigated the efficacy of a new hemorheological and immunomodulator agent, pentoxifylline.

2. Materials and methods

Study protocol

This is a single centered, randomised and prospective study. Inclusion criteria are: Left ventricular ejection fraction less than 40% via echocardiographic assesment, presence of New York Heart Association (NYHA) functional class II-IV heart failure symptoms, having a high quality echocardiographic view and having optimal medical treatment for heart failure. Severe liver disease is defined as elevated liver enzymes twice or more, serum creatinine level more than 2.5, conditions that may effect serum cytokine levels except cardiomyopathy (sepsis, rheumatoid arthritis, acquired immunodeficiency syndrome) and age less than 18 are considered as exclusion criteria. The study protocol was approved by Ankara Numune Education and Research Hospital (ANEAH) ethical committee and all patients signed the informed consent before the study. Between September 2010 April and 2011, 60 heart failure patients who were under optimal medical treatment adjusted according to heart rate and blood pressure measurements were randomised to study and control groups consisting of 30 patients. Assessment of NYHA functional capacity of patients initially and after follow up was performed by a physician unaware of the study protocol (Chacko, 1995).

Pentoxifylline (400 mg three times a day) was added to routine treatment protocol in the study group while control group continued to take existing medical therapy. Baseline characteristics, functional capacity and echocardiographic parameters were recorded in the beginning and after 12 months follow up, they were re-evaluated. The primary endpoint of the study is to investigate the affects of pentoxifylline treatment in 12 months period on left ventricular ejection fraction, end-diastolic and end-systolic volumes and NYHA functional class in patients with heart failure. The secondary endpoints are comparison of two groups about hospitalization for heart failure and diastolic parameters.

Echocardiographic assesment

The echocardiographic assessments of all patients initially and at the end of the study were performed by an experienced physician unaware of study groups using Vivid 7 echocardiography device (GE Ultrasound, Horten, Norway) equipped with a 1.5 MHz-3.3 MHz probe.

Measurements were taken from parasternal long axis, parasternal short axis, apical four chamber, apical two chamber views in the left lateral decubitis position and from subcostal view in supine position in the guidance of American Echocardiography Association guideline (Sahn et al., 1978). Modified Simpson method was used to calculate ejection fraction, and left ventricular volumes and diastolic mitral flow parameters were acquired by pulsed-wave (PW) Doppler from apical four chamber view. Isovolumetric relaxation time was obtained by measuring time from closure of aortic valve to opening of mitral valve with placement of PW Doppler on the point of mitral and aortic flows. Peak systolic pulmonary pressure was calculated using modified Bernoulli equation from tricuspid regurgitant flow. Three measurements in patients with sinus rhythm and ten in patients with atrial fibrillation were averaged.

Table 2. Baseline echocardiographic parameters

	Pentoxifylline group (n=30)	Control group (n=30)	p
EDV (ml)	165.1±57.8	186.4±65.1	0.1906
ESV (ml)	115.2±45.6	132.9±54.5	0.1811
EF (%)	31.2±6.3	29.7±6.5	0.3801
EDD (mm)	63±8.5	63.7±8.9	0.7745
ESD (mm)	54.1±7.2	53.2±10.5	0.8030
FS (%)	15.9±4.1	16.9±4.9	0.5625
Left atrium (mm)	50.1±7.5	48.9±6.3	0.5341
Right ventricle (mm)	33.1±7.7	31.8±6.2	0.5278
Mitral E (m/s)	0.78±0.23	0.79±0.25	0.8004
Mitral A (m/s)	0.67±0.23	0.75±0.18	0.2401
E/A ratio	1.25±0.63	1.12±0.48	0.4806
EDT (ms)	169.2±53.2	193.3±61.4	0.1642
IVRT (ms)	94.1±24.6	95.5±22.6	0.8861
PAP (mmHg)	38.1±15	37.1±12.7	0.8067

EDV: Left ventricle end diastolic volume; **ESV:** Left ventricle end systolic volume; **EF:** Left ventricle ejection fraction; **EDD:** Left ventricle end diastolic diameter; **ESD:** Left ventricle end systolic diameter; **FS:** Fractional shortening; **EDT:** E deceleration time; **IVRT:** Isovolumetric relaxation time; **PAP:** Peak systolic pulmonary artery pressure.

Table 3. Comparison of findings in pentoxifylline and control groups initially and at the end of 12 months follow-up

	Pentoxifylline group (n=21)			Control group (n=20)		
	Baseline	**1. year**	**p**	**Baseline**	**1. year**	**p**
NYHA class	2.4±0.5	2.2±0.5	0.1037	2.8±0.6	2.4±0.5	0.0541
EDV (ml)	160.5±51.3	156.6±43.1	0.5411	194.6±83.3	202.9±79.7	0.1615
ESV (ml)	109.1±40	106.1±33.4	0.5257	140.1±68.8	144.0±67.9	0.3086
EF (%)	32.4±5.7	33.2±5.2	0.4099	29.1±7.3	30.7±6.2	0.1418
EDD (mm)	61.3±8.4	62.4±9.2	0.0904	63.0±10.6	62.9±9.4	0.9344
ESD (mm)	51.2±5.2	54.2±5.1	0.0066	56.3±19.1	56.3±17.5	1.0000
FS (%)	17.3±3.9	15.7±2.1	0.2014	16.0±8.2	17.0±7.2	0.2254
Left atrium diameter (mm)	49.8±8.2	50.2±7.3	0.6580	48.5±6.6	49.3±6.4	0.5372
Right ventricle diameter (mm)	33.4±7.4	31.1±6.8	0.1809	30.8±6.8	29.1±3.8	0.2271
Mitral E (m/s)	0.73±0.24	0.77±0.22	0.1963	0.67±0.19	0.75±0.25	0.2262
Mitral A (m/s)	0.69±0.25	0.71±0.19	0.7468	0.76±0.17	0.79±0.19	0.6143
E/A ratio	1.99±0.71	1.11±0.43	0.4519	0.90±0.28	1.00±0.49	0.3932
EDT (ms)	188.6±59.2	200.7±47.3	0.3138	193±51.2	197±28.7	0.7699
IVRT (ms)	97.0±23.9	117.4±16.6	0.1613	95.0±14.1	104.5±5.5	0.5000
PAP (mmHg)	39.2±17.0	41.9±20.9	0.4548	35.3±15.5	38.2±22.6	0.6228

NYHA: New York Heart Association; **EDV:** Left ventricle end diastolic volume; **ESV:** Left ventricle end systolic volume; **EF:** Left ventricle ejection fraction; **EDD:** Left ventricle end diastolic diameter; **ESD:** Left ventricle end systolic diameter; **FS:** Fractional Shortening; **EDT:** E deceleration time; **IVRT:** Isovolumetric relaxation time; **PAP:** Peak systolic pulmonary artery pressure.

Statistical Analyses

Analyses were performed, using SPSS 11.0 (SPSS Inc., Chicago, IL, USA) package program. The continuous data were expressed as the mean±standard deviation (SD) while non-continuous variables were described as percentages (%). Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between patients were made using Student's independent t-test for normally distributed data. Difference between categorical variables was assessed using Chi-square or Fisher's exact test The results were regarded as significant when $p<0.05$.

3. Results

Baseline clinical characteristics and echocardiographic parameters of 60 patients evaluated in the study were given in Tables 1 and 2. There is no difference between two groups except diabetes mellitus frequency and diabetes mellitus is a little bit more in the control group ($p=0.035$). At the end of 12 months period, 9 patients in pentoxifylline group (death 4 patients, biventricular pacemaker placement 2 patients, leaving controls 3 patient) and 10 patients in control group (death 6 patients, biventricular pacemaker placement 2 patients, leaving controls 2 patients) could not complete the study and statistical analysis of variables were performed in the remaining 21 patients (mean age: 64±12.7), in pentoxifylline group and 20 patients (mean age: 64.9±8.9) in the control group ($p=0.4185$).

Consequently, there was no difference between two groups in the primary endpoints consisting of ejection fraction, left ventricular end-diastolic and end-systolic volumes and NYHA class that were evaluated in the begining and at the end of 12 months period (Table 3). At the end of 12 months, there was no significant difference between two groups in terms of left ventricular end-diastolic and end-systolic diameters, left atrial and right ventricular diameters, peak systolic pulmonary artery pressure, diastolic mitral flow velocities, E deceleration time and isovolumetric relaxation time.

Hospitalization for heart failure, the second endpoint of the study, also showed no significant difference between pentoxifylline and control groups (1.26±0.71 vs 1.60±1.04, $p=0.1717$).

4. Discussion

This paper revealed that pentoxifylline treatment had no effect on left ventricular ejection fraction, left ventricular diastolic and systolic volumes, NYHA class, left ventricular diastolic parameters and hospitalization in patients with heart failure.

Immune activation is one of the potential processes which is emphasised on the pathophysiology of heart failure. This was hypothesized after it was noticed in the observational studies that immune system activity is increased in patients with heart failure. Proinflammatory cytokines, especially TNF-alpha levels are elevated in patients with heart failure (Levine et al., 1990). In the light of these data, increased plasma proinflammatory cytokines are believed to be the result of immune process that is responsible for the progression of heart failure. Immunomodulatory agents, especially TNF-alpha, were investigated in order to prevent this process (Shaw et al, 2009). Randomized Etanercept Worldwide Evaluation (RENEWAL) study which was done with etanercept, a recombinant TNF receptor and inactivator of circulating TNF were early terminated due to adverse events (Mann et al., 2004). Similar results were acquired in the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) study which used infliximab, again a TNF-alpha monoclonal antibody (Chung et al., 2003).

These studies about immunomodulatory agents in heart failure therapy revealed unexpected outcomes (Levine et al., 1990; Shaw et al., 2009; Mann et al., 2004; Chung et al., 2003). Pentoxifylline is a peripheric vasodilator agent which reduces the viscosity of blood and it is in routine use in the treatment of peripheric vascular disease. Pentoxifylline became the focus of interest with its TNF-alpha inhibition effect in immunomodulation area. There are several small-scale randomised studies on this issue. In a study which was pre-

sented by Sliwa et al. (1998) pentoxifylline was applied to 28 idiopathic dilated cardiomyopathy patients with NYHA class II-III symptoms. Although there was no statistically significant difference between study and control groups, tendency to improvement in the functional capacity of study population was observed. When the number of patients was increased and 39 patients were evaluated, it was noticed that improvement in functional capacity in pentoxifylline group reached statistical significance. Improvement of ejection fraction was also remarkable in this study (Skudicky et al., 2000).

Another study evaluated 18 idiopathic dilated cardiomyopathy patients with NYHA class IV symptoms and revealed improvements in ejection fraction and functional capacity (Sliwa et al., 2002). Additionally 38 patients with ischemic heart disease and NYHA class I-IV symptoms had improvements in functional capacity and ejection fraction significantly with addition of pentoxifylline to routine heart failure treatment (Sliwa et al., 2004). On the other hand outcomes about mortality were not in the same direction with other parameters. Counterwise data was obtained in a different study Bahrmann et al. (2004) presented and pentoxifylline treatment derived no additional benefit on any clinical variable when used in 47 congestive heart failure patients. In this paper we aimed to investigate the effects of pentoxifylline on left ventricular ejection fraction, left ventricular volumes, NYHA functional class, left ventricular functional parameters and frequency of hospitalization. As in the previous studies we added 1200 mg/day pentoxifylline to routine optimal heart failure treatment protocol.

This study presented that addition of pentoxifylline to routine treatment protocol had no significant effect on clinical and echocardiographic parameters. While previous studies evaluated patients after 6 months follow up, in present study we planned a long term follow up to observe late period effects of pentoxifylline. Only patients with sinus rhythm were reviewed in the previous studies but we enrolled three patients with atrial fibrillation in pentoxifylline group and six patients in control group. Additionally a more extensive assessment including diastolic parameters and pulmonary artery pressure was performed not to overlook any significant variance. Another feature of this study that it lets us to make interpretation about frequency of hospitalization, which was not evaluated in the previous studies.

Beside these, our study has some limitations. The number of patients evaluated in the study is insufficient. Furthermore, levels of TNF-alpha and other cytokines that are asserted to be influenced by pentoxifylline could be investigated. In this study, we hypothesized that inhibition of TNF-alpha may provide improvement in heart failure because TNF-alpha levels are elevated in these patients. Because TNF-alpha contributes to progression of heart failure by accelerating apoptosis.

Significance of TNF-alpha in pathophysiology of heart failure is not well defined. Moreover, in the recent studies, although pentoxifylline treatment improved symptoms and ejection fraction, a notable reduction was not seen in the serum levels of TNF-alpha. Therefore it can be speculated that potential effects reported in the previous studies can act via different mechanisms.

Consequently, no additional benefit was observed in clinical and echocardiographic parameters with addition of pentoxifylline to standart treatment protocol in patients with heart failure. Despite existence of studies resulted positively, the potantial role of pentoxifylline in heart failure therapy is still controversial. As a result, more extensive clinical researches with larger study populations are needed.

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