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ORIGINAL ARTICLE

Beneficial effects of beta-blockers and angiotensin-converting enzyme inhibitors in Duchenne muscular dystrophy

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Summary
Background: Patients with Duchenne muscular dystrophy (DMD) often have severe heart failure with a high mortality rate. Most DMD patients with cardiomyopathy became symptomatic in their early to middle teens and usually die of congestive heart failure within 2—3 years from the onset of symptoms. It has been reported that the combination of an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker has additive benefits in patients with heart failure. The aim of this study was to assess whether the combination of an ACE inhibitor and a beta-blocker is associated with long-term survival of DMD patients with left ventricular (LV) dysfunction.
Methods: We retrospectively analyzed the outcomes of 52 DMD patients who had begun treatment for heart failure with an ACE inhibitor and a beta-blocker at National Yakumo Hospital during the period from 1992 to 2005. All patients used wheelchairs in their daily lives. Patients were classified as symptomatic or asymptomatic at the initiation of treatment with these two drugs. Twelve patients who had already had apparent symptoms due to heart failure were enrolled in a treatment group. Forty patients who had no symptoms with reduced LV ejection fraction ($\leq$45% in echocardiography) were enrolled in a prevention group.
Results: Five-year and 7-year survival rates of all patients were 93 and 84%, respectively. In the treatment group, 5-year and 7-year survival rate were 81 and 71%, respectively. Survival rate became zero at 10.9 years. In the prevention group, 5-year and 7-year survival rates were 97 and 84%, respectively, and 10-year survival rate was 72%. Nine patients in the prevention group remained event-free over 10 years.

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Conclusions: In this study, the combination of an ACE inhibitor and a beta-blocker had a beneficial effect on long-term survival of DMD patients with heart failure. The treatment was particularly effective for asymptomatic patients with LV dysfunction.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder occurring in one in 3500 male births. DMD is caused by mutations in the dystrophin gene that result in marked reduction or absence of the sarcolemnal protein dystrophin. Patients with DMD are characterized by progressive skeletal muscle wasting and become wheelchair-bound before 13 years of age [1]. Patients managed conventionally rarely survive beyond their teens because of respiratory and heart failure. Cardiomyopathy in most DMD patients is similar clinically to dilated cardiomyopathy (DCM). DMD is often complicated by severe heart failure and has a very high mortality rate. Severe heart failure occurs in DMD patients from their early teens and is very common in patients over 18 years of age [2,3]. Several studies have indicated that approximately 10—15% of patients with DMD die from cardiac failure caused by DCM [3,4]. Most patients with DMD remain asymptomatic for many years in spite of the progression of cardiac dysfunction, because their energy expenditure and oxygen consumption are severely curtailed by muscle weakness. Patients with DMD might therefore have severe cardiac dysfunction when they initially experience cardiac symptoms. Non-invasive ventilation (NIV) has improved the rate of survival to 25 years from 0 to 53%. Nevertheless, the mean age of survival in the presence of cardiomyopathy has been reported to be 16.9 years [5]. It is known that combination therapy with an angiotensin-converting enzyme (ACE) inhibitor and a beta-adrenergic blocking agent improve the survival of patients with left ventricular (LV) dysfunction [6—15]. However, the benefit of beta-blockers and ACE inhibitors for long-term survival of DMD patients with heart failure is not clear. An ACE inhibitor and a beta-blocker began to be used from 1992 in DMD patients with heart failure whose treatment was managed at National Yakumo Hospital. At that time, both of the drugs were prescribed when symptoms of heart failure were apparent. We often experienced rapid worsening of heart failure in DMD patients. We tried to begin the treatment with an ACE inhibitor and a beta-blocker when LV dysfunction was diagnosed even if patients had no symptoms. The purpose of this study was to assess the effects of therapy with a beta-blocker and an ACE inhibitor on survival rate in DMD patients with heart failure and to determine the efficacy of the combination therapy in asymptomatic patients.

Methods

Study patients

We reviewed the records for 56 patients diagnosed with DMD who were diagnosed with LV dysfunction and had begun treatment for heart failure with an ACE inhibitor and a beta-blocker at National Yakumo Hospital during the period from 1992 to 2005. Two patients who did not have routine follow-up at National Yakumo Hospital were excluded. Another two patients whose diagnosis was suggestive of an intermediate or Becker muscular dystrophy, because they walked over the age of 13 years, were also excluded. Fifty-two consecutive patients with DMD were enrolled in this study. In all patients, diagnosis of DMD was confirmed either by DNA analysis that revealed deletion of exons in the dystrophin gene or by muscle biopsy that showed the absence of dystrophin. All of the patients used wheelchairs in their daily lives. The patients were classified as symptomatic or asymptomatic when they begun the treatment with an ACE inhibitor and a beta-blocker and were enrolled in a treatment or a prevention group. The treatment group included patients who had already had apparent symptoms due to heart failure when they had begun treatment with these two drugs despite their wheelchair dependence. Their symptoms included cough, fatigue, palpitations, sweating, chest and abdominal discomfort, arthralgias, chills, decreased urinary output, irritability, and difficulty in concentration [16]. The prevention group included patients who had no apparent symptoms with reduced LV ejection fraction (LVEF, $\leq$45% in echocardiography) at the beginning of treatment with an ACE inhibitor and a beta-blocker.

Patients were administered a beta-blocker within 3 months after starting treatment with an ACE inhibitor. Doses of both drugs reached maintenance doses within 3 months after starting administration. Echocardiography had been routinely performed once or twice a year. Echocardiographic variables were determined according to the standards of the American Society of Echocardiography.

End points

All-cause mortality was used as the primary end point in this study. For the present analysis, deaths due to pump failure include deaths due to ''worsening heart failure with or without arrhythmia''; arrhythmic deaths include only deaths due to ''arrhythmia without worsening heart failure'' [13]. Mortality was censored on 31 December 2005.

Statistical analysis

Data are expressed as means ± S.D. Chi-square analysis was used for categorical variables. Paired or unpaired *t* tests were used for evaluation of differences between the two groups. Differences were regarded as statistically significant at $P < 0.05$. Outcomes were assessed by Kaplan–Meier survival analysis and log-rank test statistics. Variables included in the univariate analysis for the prevention group were age, LV end-diastolic diameter (LVDd), LV fractional shortening (%FS), LVEF, and plasma brain natriuretic peptide (BNP) level at the start of treatment.

Results

Patient population

Characteristics of the 52 patients are shown in Table 1. Thirty-eight (70%) of the 52 patients used ventilators in their daily lives. Eight (15%) of the 52 patients had a past history of pulmonary edema. Most of the patients (83%) received bisoprolol as a beta-blocker, and 4% of the patients received carvedilol. The mean follow-up period was 6.8 ± 3.2 years.

Actuarial survival for all patients

Patients taking both an ACE inhibitor and a beta-blocker could achieve long-term survival. The 5-year survival rate for all 52 patients was 93% and the 7-year survival rate was 84% (Fig. 1). Eleven patients survived for more than 10 years.

Table 1 Baseline characteristics.

Characteristic	Patients with DMD $n = 52$
Age at starting treatment (years)	19.5 ± 5.8
Duration (years)	6.9 ± 3.3
NIV use	37 (71%)
Past history of pulmonary congestion	8 (15%)
Echocardiographic measurements	
LVDd (mm)	58 ± 9
FS (%)	16 ± 5
LVEF (%)	36 ± 8
BNP (pg/ml)	135 ± 277
Treatment dose per day for maintenance (mg)	
ACE inhibitors	
Enalapril	39 (75%) 3.7 ± 1.8
Lisinopril	7 (13%) 6.1 ± 4.3
Others	6 (12%)
Beta-blockers	
Bisoprolol	43 (83%) 3. ± 1.3
Metoprolol	7 (13%) 20.8 ± 2.0
Carvedilol	2 (4%) 10 ± 0
Diuretics	38 (73%)
Digoxin	49 (94%)

DMD: Duchenne muscular dystrophy; ACE: angiotension-converting enzyme; NIV: non-invasive ventilation; LVDd: left ventricular end-diastolic diameter; FS: fractional shortening; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide.

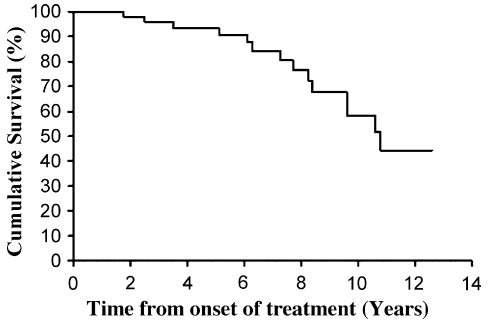

Figure 1 Kaplan–Meier survival curve for all patients treated with a beta-blocker and an ACE inhibitor.

Treatment and prevention groups

Patients were classified as symptomatic ($n = 12$, 23%) or asymptomatic ($n = 40$, 77%) at the start of therapy and enrolled in the treatment or the prevention group (Table 2). Patients in the treatment and the prevention groups were followed for an average of 7.1 ± 3.4 and 6.7 ± 3.2 years, respectively. LVDd was large and contractility of the left ventricle decreased significantly in the treatment group compared with those in the prevention

Table 2 Basic characteristics of study groups.

Characteristic	Treatment $n=12$	Prevention $n=40$	P-value
Age at starting treatment (years)	17.6 ± 3.8	20.1 ± 6.3	NS
Duration (years)	7.1 ± 3.4	6.7 ± 3.2	NS
NIV use	8 (67%)	29 (73%)	NS
Echocardiographic measurements			
LVDd (mm)	67 ± 6	56 ± 7	<0.001
FS (%)	11 ± 5	18 ± 4	<0.001
LVEF (%)	28 ± 8	38 ± 7	<0.001
BNP (pg/ml)	474 ± 468	42 ± 47	<0.05
Treatment			
Beta-blockers			
Bisoprolol	12 (100%)	31 (78%)	
Dose per day for maintenance (mg)	3.0 ± 1.0	3.2 ± 1.4	NS
Metoprolol	0	7(18%)	
Dose per day for maintenance (mg)		20.8 ± 2.0	
Carvedilol	0	2(4%)	
Dose per day for maintenance (mg)		10.0 ± 0	
ACE inhibitors			
Enalapril	8 (67%)	31(78%)	
Dose per day for maintenance (mg)	2.6 ± 1.2	4.0 ± 1.8	<0.05
Lisinopril	3 (25%)	4 (10%)	
Dose per day for maintenance (mg)	7.5 ± 6.7	5.0 ± 2.0	NS
Others	1 (8%)	5(12%)	
Diuretics	12 (100%)	37 (88%)	NS
Digoxin	12 (100%)	26 (62%)	<0.05

DMD: Duchenne muscular dystrophy; ACE: angiotensin-converting enzyme; NIV: non-invasive ventilation; LVDd: left ventricular end-diastolic diameter; FS: fractional shortening; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide.

group. All patients in the treatment group received diuretics.

Actuarial survival for patients in the two groups

Prognosis was improved remarkably in both the treatment group and prevention group (Fig. 2). In the treatment group, 5-year survival rate was 81% and 7-year survival rate was 71%. Survival rate became zero at 10.9 years. In the prevention group, 5-year survival rate was 97% and 7-year survival rate was 84%. Furthermore, 10-year survival rate was 72% in the prevention group. Patients in the prevention group tended to have better survival than patients in the treatment group ($P < 0.001$ by log-rank test). Nine patients in the prevention group remained event-free over 10 years.

Modes of death

Patients in the prevention group were less likely to die than were patients in the treatment group (Table 3). Three patients in the prevention group died of apparent cardiac events.

Predictors of long-term survival in asymptomatic patients

In this study, univariate analysis revealed that only %FS was a significant predictor of long-term survival for patients in the prevention group ($P < 0.05$). The patients in the prevention group were stratified

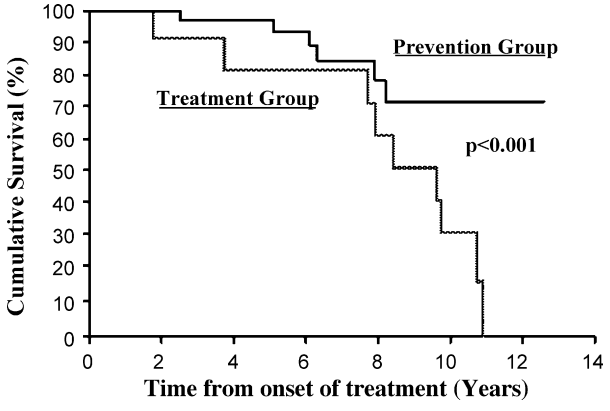

Figure 2 Kaplan—Meier survival curve for study groups. Patients in the prevention group are represented by the solid line, those in the treatment group by the dotted gray line.

Table 3 Modes of death.

Treatment group ($n = 12$)	
All-cause mortality 58% (7 patients)	Number of patients
Arrhythmia with worsening heart failure	4
Worsening heart failure	1
Respiratory complication	2
Prevention group ($n = 40$)	
All-cause mortality 15% (6 patients)	Number of patients
Arrhythmia with worsening heart failure	2
Arrhythmia without worsening heart failure	1
Respiratory complication	1
Unknown	2

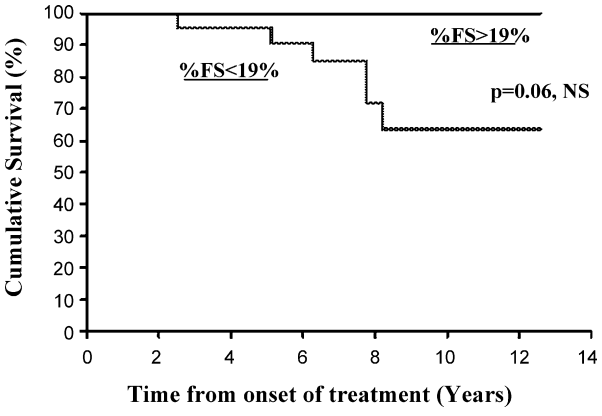

Figure 3 Kaplan—Meier survival curve for 40 patients in the prevention group subdivided into two groups according to the median %FS (19%). %FS: %fractional shortening.

into two groups based on median %FS (19%) at the start of treatment and a cumulative survival curve was constructed according to Kaplan—Meiyer survival methods. Long-term survival of patients with %FS > 19% tended to be better than that of patients with %FS < 19%, but the difference was not statistically significant (Fig. 3).

Discussion

The present study demonstrated that the combination of an ACE inhibitor and a beta-blocker has a beneficial effect on long-term survival of DMD patients with LV dysfunction. Moreover, the effect was greater in asymptomatic patients than in symptomatic patients. Most DMD patients with cardiomyopathy become symptomatic in their early to middle teens and usually die of congestive heart failure within 2—3 years from the onset of symptoms [3]. In a previous study on survival of DMD patients with congestive heart failure, of eight patients who were 17.6 ± 3.9 years of age and were treated with only digitalis and diuretics, three survived for 1 year, one survived for 4 years, and none survived for 5 years [17]. They died at 13.7—25.1 years of age (mean age of death, 18.9 ± 4.2 years). It has been reported that the mean survival period for DMD patients with congestive heart failure was 26.0 months when LVEF had decreased to 30.1% and that the mean survival period was only 15.4 months when LVEF had decreased to 23.2% [16]. Eagle et al. reported that NIV improved the rate of survival to 25 years from 0 to 53%. Nevertheless, the mean age of survival in the presence of cardiomyopathy is still only 16.9 years [5]. Most patients with DMD remain asymptomatic for many years in spite of the progression of cardiac dysfunction because of their wheelchair-bound state. Cardiac function in DMD patients might therefore be NYHA III or IV when they initially experience cardiac symptoms. In our experience, when the main therapy consisted of digitalis, diuretics, and catecholamines, heart failure was aggravated rapidly and most patients died within 2 years from the start of therapy.

ACE inhibitors have been shown to remarkably improve the prognosis of patients with heart failure [18—21]. Meta-analyses of randomized clinical trials suggest that beta-blocker therapy has benefits for survival in heart-failure patients. In these trials, beta-blockers were conventionally administered with ACE inhibitors [6—11]. It has been reported that the combination of a beta-blocker and an ACE inhibitor is beneficial for survival of patients with LV dysfunction [12—15]. Reports about efficacy of the combination of these two drugs for treatment of heart failure in DMD patients are rare [16]. Results of controlled clinical trials on the efficacy of the combination of an ACE inhibitor and a beta-blocker for heart failure in DMD have not been reported. In this study, the 5-year survival rate of all DMD patients with heart failure exceeded 90%. Moreover, some patients survived for more than 10 years. It is therefore possible that treatment with an ACE inhibitor and a beta-blocker will remarkably improve the survival rate of DMD patients with heart failure as has been shown for patients with heart failure caused by other diseases.

Early use of a beta-blocker and an ACE inhibitor

Ishikawa et al. reported the effectiveness of the combination of these two drugs in 11 DMD patients with symptomatic heart failure for relief of symptoms and decrease of activated neuroendocrine level during 5-year follow-up [16].

Long-term efficacy of an ACE inhibitor and a beta-blocker in DMD patients with reduced LVEF and no symptoms has not been reported.

In this study, we classified patients as symptomatic (treatment group) or asymptomatic (prevention group) at the start of therapy and investigated prognosis in the two groups. It has been reported that beta-blockers are effective for patients with NYHA class III or IV heart failure caused by other diseases [9]. In this study, patients in the treatment group achieved long-term survival compared with that previously reported. However, in most of the patients in the treatment group, heart failure gradually worsened about 7 years after the start of therapy. Patients with DMD are at risk for developing heart failure. Early therapeutic intervention would be beneficial for DMD patients with LV dysfunction even if they are asymptomatic [22]. We therefore started the treatment with an ACE inhibitor and a beta-blocker in asymptomatic patients. The 5-year survival rate was maintained at more than 90%. The survival rate of patients in the treatment group decreased rapidly about 10 years after starting medication. In the prevention group, the 10-year survival rate was 73% and 9 patients were free from symptoms of heart failure even more than 10 years after starting therapy. Starting treatment with an ACE inhibitor and a beta-blocker in the asymptomatic stage seems to be effective for improving prognosis of patients with heart failure. A post-hoc analysis of results of studies on LV dysfunction has shown that the combination of an ACE inhibitor and a beta-blocker reduces the risk of death in asymptomatic patients with heart failure [13]. In this study, criteria for early treatment to obtain the better prognosis in asymptomatic DMD patients with LV dysfunction were not identified. Long-term survival of patients with %FS > 19% tended to be better than that of patients with %FS < 19%, but the difference was not statistically significant.

ACC/AHA guidelines recommend that treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed [15]. Duboc et al. reported that early treatment with perindopril monotherapy delayed the onset and progression of LV dysfunction in DMD patients with normal LV function [23]. Further investigation is needed to determine the appropriate timing of early treatment.

Study limitations

This was a retrospective analysis at a single center, and there may be a patient selection bias. The relationship between systolic cardiac parameters determined by ultrasound echocardiography and the timing of drug therapy to obtain longer survival was not identified in this study. Evaluation of diastolic parameters by LV filling pattern in echocardiography was not done sufficiently because of deformity of the thoracic cavity or difficulty in maintaining the left lateral decubitus position. Most patients in this study used NIV constantly. It is well known that NIV has a favorable effect on heart failure [24]. It is expected that NIV contributes to improvement in prognosis of DMD patients. We could not evaluate the effect of NIV and medication independently in this study.

Conclusion

The combination of an ACE inhibitor and a beta-blocker has a beneficial effect on long-term survival of DMD patients with heart failure. The treatment was particularly effective for asymptomatic patients with LV dysfunction. In DMD patients with LV dysfunction, treatment with the combination of a beta-blocker and an ACE inhibitor should be started as soon as possible.

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