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Steroid Therapy and Cardiac Function in Duchenne Muscular Dystrophy

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Abstract. Duchenne muscular dystrophy leads to progressive deterioration in skeletal and cardiac muscle function. Steroids prolong ambulation and improve respiratory muscle strength. The authors hypothesized that steroid treatment would stabilize cardiac muscle function. Echocardiograms performed from 1997 to 2004 for 111 subjects 21 years of age or younger with Duchenne muscular dystrophy were restrospectively reviewed. The medical record was reviewed for steroid treatment. Untreated and steroids-treated subjects did not differ in age, height, weight, body mass index, systolic and diastolic blood pressure, or left ventricular mass. The shortening fraction was lower in the untreated group. Of those treated, 29 received prednisone and 19 received deflazacort. There was no difference in the shortening fraction between the two treated subgroups. Treated subjects not receiving steroids still had a normal shortening fraction, which was no different from the shortening fraction of those still receiving treatment. As compared with the treated subjects, the untreated subjects 10 years of age or younger were 4.4 times more likely to have a shortening fraction less than 28% ($p = 0.03$), and the untreated subjects older than 10 years were 15.2 times more likely to have a shortening fraction less than 28% ($p < 0.01$). This retrospective study suggests that the progressive decline in cardiac function of patients with Duchenne muscular dystrophy can be altered by steroid treatment. The effect appears to be sustained beyond the duration of treatment and independent of steroid type.

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Duchenne muscular dystrophy (DMD) is an inherited myopathy characterized by progressive skeletal muscle weakness leading to loss of ambulation, respiratory failure, and death in the second to third decade of life [2]. Myocardial involvement results in a decline in cardiac function with age, ultimately leading to dilated cardiomyopathy, which contributes to early death from heart failure [14, 16, 19].

Currently, there is no cure for DMD. Oral steroids are the only effective long-term therapy. The benefits of prednisone therapy have been advocated for more than 15 years [3, 6]. The report of less weight gain led to the use of deflazacort, an oxazoline derivative of prednisolone [13]. The addition of chronic steroid therapy, using either deflazacort or prednisone, has prolonged ambulation, stabilized pulmonary function, and reduced scoliosis [1, 5, 12, 20, 21]. It also has been suggested that deflazacort has beneficial effects on cardiac function [18]. However, several side effects from long-term steroid treatment are predicted to be detrimental to cardiac function including obesity, ventricular hypertrophy, hypertension, and lipid abnormalities. Consensus has been reached regarding the benefit observed with steroid therapy [4]. However, there has been no consensus regarding a standard dose, treatment age, or treatment length [4]. The choice of steroid often is determined by cost and family preference, and treatment regimens are frequently altered on the basis of side effects. Thus, analysis of the various treatment regimens is difficult.

The purpose of this retrospective study was to evaluate the effect of the steroid treatment in current clinical practice on the natural history of cardiac function in Duchenne muscular dystrophy patients.

We hypothesized that steroid treatment, regardless of type, would stabilize cardiac muscle function.

Methods

Subjects

All subjects with DMD undergoing an evaluation of cardiac function by echocardiogram from 1997 to 2004 at one of two institutions were included in this study. The inclusion criteria required a clinical diagnosis of DMD, current age younger than 22 years, availability of complete echocardiographic data, and medical records complete and available for assessment of steroid exposure. The study criteria were fulfilled by 111 subjects.

The basic medical data including age, height, weight, and systolic and diastolic blood pressures at the time of the echocardiogram were collected for each subject. The medical record was reviewed for steroid exposure. The subjects were assigned to the "treated" group if steroids were administered longer than 6 months. Subjects never exposed or treated for less than 6 months were categorized as "untreated." For all the treated subjects the age at initiation, the duration of treatment, and the type of steroid (deflazacort or prednisone) were noted. Treatment dose was not evaluated secondary to variability within the study group. The institutional review board approved the review of collected data, analysis, and reporting.

Echocardiographic Analysis

Transthoracic echocardiogram comprised evaluation of left ventricular systolic function and cardiac geometry. M-mode measurements included left ventricular end diastolic and systolic dimensions, left ventricular posterior wall thickness, and interventricular septal thickness at end diastole. The measures allowed for calculation of fractional shortening and left ventricular mass [7]. The shortening fraction was considered normal if it was greater than 28% [9].

Statistical Analysis

Basic medical and echocardiographic data were entered into an electronic database and analyzed with the statistical software package SAS, version 8.2 (SAS Institute, Cary, NC, USA). Results are reported as mean ± standard deviation. The continuous variables were compared using *t*-tests. Correlation analysis was used to determine the associations of age, treatment age and length, height, weight, body mass index, systolic and diastolic pressure, left ventricular geometry, and mass with shortening fraction. Logistic regression was used to calculate the odds of shortening fraction between the groups. Statistical significance was inferred by a p value less than 0.05.

Results

Population

The treated ($n = 48$) and untreated ($n = 63$) subjects ranged in age from 3 to 21 years (treated 11 ± 4 years; untreated, 12 ± 5 years). The basic medical data are outlined in **Table 1.** The groups did not differ in age, height, weight, body mass index, systolic and diastolic blood pressure, or indexed left ventricular mass. The shortening fraction was lower in the untreated group than in the steroid-treated group (30% ± 7% vs 36% ± 5%; $p < 0.001$). Age and left ventricular end diastolic dimension were negatively associated with shortening fraction ($p < 0.01$). However, height, weight, body mass index, systolic and diastolic pressure, and indexed left ventricular mass were not associated with shortening fraction. Only 4.5% of the subjects younger than 10 years had a shortening fraction less than 28%. In the second decade, there was a dramatic increase in the number of boys, mainly those untreated, with demonstrable abnormalities in cardiac function and 32% of our subjects older than 10 years had a shortening fraction less than 28% (Fig. 1).

Table 1. Characteristics of untreated and treated subjects

	Untreated ($n = 63$)	Treated ($n = 48$)	p Value
Age years (range)	12 ± 5 (3–21)	11 ± 4 (3–21)	NS
BMI (kg/m^2)	21.1 ± 6	20.9 ± 6	NS
SBP (mmHg)	111 ± 13	108 ± 13	NS
DBP (mmHg)	65 ± 10	64 ± 10	NS
LVMi (g/ht$^{2.7}$)	32 ± 13.6	31.9 ± 9.3	NS

BMI, body mass index; DBP, diastolic blood pressure; LVMi, left ventricular mass index; SBP, systolic blood pressure.

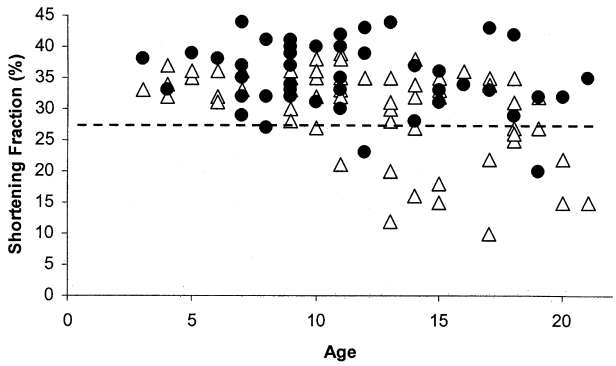

Fig. 1. Shortening fraction and age for untreated and treated subjects. Untreated subjects are represented by the open triangles. Steroid-treated subjects are represented by the closed circles. The horizontal dashed line represents the cutoff for normal shortening fraction of 28%.

Steroid Treatment

The mean age at initiation of steroid treatment was 6.7 ± 2.5 years. The mean length of treatment was 3 ± 2.5 years. Neither the age of initiation nor the

Table 2. Shortening fraction (SF) and odds ratio by age for untreated and treated subjects

Age Group	Untreated SF (%)	SF < 28% (%)	Treated SF (%)	SF < 28% (%)	Odds Ratio	*p* Value
3–10 years	33.9 ± 2.5	5	36 ± 4	4	4.4	0.02
11–21 years	28 ± 7	42	35 ± 5.5	13	15.2	0.01

duration of treatment was associated with shortening fraction. There were 10 subjects (age, 16.3 ± 3 years) who had been treated with steroids for 4.2 ± 1.6 years (range, 2–8 years), but for whom steroids had been discontinued because of side effects. Despite discontinuation of steroid use for 6 ± 4 years (range, 2–11 years), these subjects had a normal shortening fraction (35% ± 6%) greater than that of the untreated subjects ($p < 0.001$) and no different from that of the subjects still receiving treatment. As compared with the steroid-treated subjects, the untreated subjects 10 years of age or younger were 4.4 times more likely to have a shortening fraction less than 28% ($p < 0.03$), and the untreated subjects older than 10 years were 15.2 times more likely to have a shortening fraction less than 28% ($p < 0.01$) (Table 2). For each year, the odds of a shortening fraction less than 28% increased by 30% for the untreated subjects, as compared with the shortening fraction of the steroid-treated subjects ($p < 0.001$).

Prednisone and Deflazacort

Of the 48 steroid-treated subjects, 29 received prednisone and 19 received deflazacort. The prednisone group was older at the time of cardiac evaluation than the deflazacort group (12 ± 5 years vs 9 ± 4 years; $p < 0.02$). The groups did not differ in treatment age or length, weight, body mass index, systolic and diastolic pressure, or left ventricular end diastolic dimension. There was no difference in the shortening fraction (prednisone, 35% ± 5.5% vs deflazacort, 36.6% ± 3.5%) between the two treated groups.

Discussion

In Duchenne muscular dystrophy, cardiac function, as measured by shortening fraction, remains normal until approximately the age of 10 years in the majority of patients. Our findings demonstrate that treatment with either prednisone or deflazacort appears to have an impact on the decline in cardiac function seen with DMD. Shortening fraction was significantly lower in the untreated group than in the steroid-treated group. The untreated subjects older than 10 years were 15.2 times more likely to have a shortening fraction less than 28% as compared with the steroid-treated subjects. Deflazacort and prednisone were equally effective at preserving cardiac function in this study. These data support the hypothesis that the progressive decline in cardiac muscle function can be altered by steroid treatment.

Cardiac muscle involvement in DMD, as demonstrated by electrocardiography, has been described for 50 years (11, 15, 17). Echocardiography has allowed the characterization of functional abnormalities before symptoms [8, 10]. The cardiac involvement seen in the untreated subjects of this study is comparable to that previously documented before the use of steroids. Our study represents a large cohort of boys with DMD and is unique in that it involves subjects from two major medical centers. Our work serves to confirm the conclusion of Biggar et al. [18] who evaluated the effect of deflazacort on cardiac function in 21 DMD boys and demonstrated preservation of cardiac function with treatment. However, this is the first study to compare steroid type and to demonstrate the same treatment effect on cardiac function from either prednisone or deflazacort. The natural history of cardiac dysfunction is altered by the use of steroids.

Treatment duration and the risk of side effects from chronic steroid use are questions faced by clinicians and families. Despite the theoretical adverse effects of steroid use to cardiac function, such as obesity, ventricular hypertrophy, hypertension, and lipid abnormalities, the benefits appear to outweigh these risks. Importantly, the data suggest that the beneficial impact of steroid treatment on cardiac function may be sustained beyond the duration of treatment. Patients forced to stop treatment because of complications from the chronic use of steroids may be afforded some longer-term benefit. The mean treatment duration of 4 years in the group of patients for whom steroids were discontinued appears to have provided preservation of cardiac function up to 6 years after discontinuation of steroid treatment.

Our study was limited by its retrospective nature, and the proof of benefit would require a prospective, randomized trial. Such a trial would now likely be unethical because of the overall proven benefits of steroids to the musculoskeletal system of these patients. Nevertheless, our results demonstrate that cardiac function should be an important outcome measure in the future testing of new therapies for DMD. Additionally, because fractional shortening is

dependent on preload and afterload as a measure of cardiac function, the benefits of steroids will need to be substantiated in a prospective study by other load-independent measures of cardiac function.

Despite a lack of knowledge regarding the mechanism of benefit from steroids, there is growing evidence of multisystem improvement in Duchenne muscular dystrophy. Natural history studies of DMD show that a substantial deterioration tends to occur at about the age of 10 years, when boys lose ambulation, develop scoliosis, and have a decline in pulmonary function. This natural history is clearly altered by steroid therapy. Our data indicate that the steroid-related clinical improvement in DMD patients extends to cardiac function, both during and beyond treatment duration, By improving respiratory and cardiac function, steroid treatment has the potential to prolong survival for patients with this disease.

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