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High dose weekly oral prednisone improves strength in boys with Duchenne muscular dystrophy

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Abstract

Daily prednisone improves strength in boys with Duchenne muscular dystrophy, but side effects are almost universal. We used a different dosing regimen of prednisone to determine if benefit to boys with Duchenne muscular dystrophy might be maintained with fewer side effects. Twice weekly oral prednisone was given each Friday and Saturday (5 mg/kg/dose). This total dose is twice as high as the daily low dosage prednisone regimen (0.75 mg/kg/day). Twenty boys (8.0 ± 1.2 years) were treated. Historical control groups included 18 untreated boys (6.1 ± 1.6 years) and four boys (7.3 ± 0.6 years) treated with daily prednisone. Strength (using a hand-held manometer and grip meter) and timed functional testing were measured. There was an improvement in upper extremity strength for 95% of boys ($n = 20$) at 6 months using quantitative strength testing. Improvement in lower extremity strength occurred in all boys with antigravity quadriceps strength (17/17). The improvement ($P = 0.001$ for proximal upper extremities; $P = 0.002$ for grip; and $P < 0.0001$ for proximal lower extremities) was significant compared to untreated boys. Sixteen boys were treated continuously for more than 12 months (22 ± 1.5 months). Of these, 15 remained significantly stronger than prior to treatment and 8/16 showed additional gains in strength after six months of treatment. Six boys were on the weekly prednisolone 2 years or longer without interruption. All six had upper and lower extremity strength at follow-up that was as good or better than at baseline. Functional testing improved in boys less than 8 years without contractures. Three boys without antigravity quadriceps strength at the start of treatment lost the ability to walk unassisted within 6 months. Eight other boys lost the ability to ambulate unassisted between 12 and 24 months of treatment. In each, progressive contractures developed. Linear growth was maintained in all boys on weekly treatment. Obesity rates did not differ from untreated boys. Twice weekly prednisone improved strength over 6–12 months in the majority of boys, but did not slow contracture development. Sustained benefit beyond 12 months is possible with fewer side effects compared to daily prednisone.

Keywords: Duchenne muscular dystrophy; Prednisone; Obesity; Contracture

1. Introduction

Daily prednisone stabilizes or improves the strength of boys with Duchenne muscular dystrophy (DMD). This was first reported by Drachman et al. in an open trial of 2 mg/kg/day [1]. This finding was duplicated in open design trials [2,3] and subsequently, through the collaboration of the Clinical Investigation of Duchenne Dystrophy (CIDD) investigators, in double-blinded placebo-controlled trials [4–6]. Effective doses include both 1.5 and 0.75 mg/kg/day. The duration of the improvement extends as long as 3 years in those children who maintained doses of 0.5 and 0.6 mg/kg/day [7].

Despite the elegant work demonstrating that daily prednisone benefits 80% of boys with DMD, many boys are not treated until they are beginning to fall. One reason for the delay in treatment is the known steroid side effects. Side effects including weight gain, cushinoid facies, and behavioral changes occur in 60–100% of treated boys. Daily deflazacort shows a similar benefit in strength with fewer side effects [8]. However, weight gain and cushinoid features also occur in boys treated with deflazacort compared to placebo. In our experience, more than 50% of boys treated with daily corticosteroids develop significant enough side effects that medication is decreased or discontinued. Lower dose regimens including alternate day corticosteroids and treatment for the first 10 days of the month have demonstrated efficacy with fewer side effects [5,9–11]. Other immunosuppressive medications have mixed results.

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While azathioprine shows no benefit [6], cyclosporine was shown to improve strength in boys with DMD [12]. The objective of this pilot study was to determine if a high dose twice weekly oral prednisone dosing regimen would improve strength in boys with DMD. Side effects using this dose in children with epilepsy have been minimal [13–15]. The study demonstrates improved strength beyond 6 months in the majority of boys treated.

2. Patients and methods

2.1. Patients (Table 1)

All boys presented with weakness between 3 and 5 years of age. The diagnosis of DMD was made based on physical examination, elevated creatine kinase, and genetic ($n = 12$), biopsy ($n = 7$), or both ($n = 1$) confirmation of dystrophin mutation or absence. Three of the boys (#10, 13, and 18) had contractures at the start of the study and were falling several times a day. Twice weekly oral prednisone was given every Friday and Saturday (5 mg/kg/dose). During treatment, all the boys were followed every 3–6 months. Sixteen boys continued treatment uninterrupted for more than 1 year (mean 22 ± 1.5 months; range 12–32 months). Six boys continued treatment for 2 or more years. Four boys interrupted or stopped treatment. In two, the reason was irritability on the days after taking the prednisone. One, child # 9, did not continue. The other, child #14, resumed medication after about 3 months when he noted worsening weakness. He took the doses at night and the irritability was less. In the other two, # 7 and 15, the cause for interruption was non-compliance as parents did not fill the prescriptions. The historical comparison groups included 18 boys (6.1 ± 1.6 years) who were not treated and four boys (7.3 ± 0.6 years) treated with daily prednisone. The untreated boys were followed for 94 visits or 47 intervals (mean duration between visits was 7.7 ± 0.6 months). The untreated group consisted of those examined during the 5 years prior and of children whose parents chose not to use prednisone during the course of the study. Analysis of this retrospective data allowed us to generate natural history data for the expected decline in quantitative strength (Fig. 1a–c).

2.2. Quantitative strength testing

Strength in pounds was measured in proximal upper extremity muscles groups (bilateral elbow flexion and extension) and proximal lower extremity muscles groups (bilateral knee extension and flexion) [16,17]. A hand-held Chatillon dynamometer and a Jamar grip meter were used and all measurements were made by the same examiner (A.M.C). This method relies on the presence of a Medical Research Council (MRC) scale strength score higher than 3/5. With the child sitting, elbow flexion and extension were measured with the elbow flexed to 90 degrees. Knee flexion

Table 1
Age, duration of followup, contractures and outcome of boys given twice weekly prednisone (10 mg/kg/week)[a]

Pt#	Age Rx started (years)	Age at last follow-up	Time Rxed prednisone (months)	Contractures	Surgical release (Age)	Outcome
1	5.2	8.0	34	–		Walks/runs/hops
2	6.5	8.4	23	–		Walks
3	6.7	8.7	24	–		Walks
4	7.0	8.0	12	–		Walks
5	7.4	9.4	24	–		Walks/runs/hops
6	7.4	9.4	24	–		Walks/runs
7	7.8	9.9	3**(6)	+ 9.9 (h, k, a)	No	Wheelchair
8	7.8	9.4	19	+ 9.0 (a)	Yes	Stands-LLB
9	7.8	8.5	8	+ 8.5 (h, itb, a)*	No	Wheel chair (8.5 years)
10	8.1	9.6	18	+ 8.7 (h,k,a) *	Yes	Stood-LLB 6 months; wheelchair (9.2 years)
11	8.1	9.9	22	–	-	Walks
12	8.3	10.3	24	–	-	Walks
13	8.5	10.1	19	+ 9.5 (h, itb, k, a)	No	Wheel chair (9.5 years)
14	8.6	11.9	3**(15)	+ 9.8 (k, a)	Yes	Walk 12 months; wheelchair (10.8 years)
15	8.6	11.5	10**(12)	+ 10.9 (h, a)	Yes	Walks-LLB
16	8.6	9.9	15	+ 9.5 (h, k, a)	Yes	Stands-LLB
17	9.2	11.7	30	+ 9.5 (k, a)	Yes	Walks-LLB
18	9.2	10.8	19	+ 9.7(h, itb, k, a)*	No	Wheelchair (9.7 years)
19	9.6	10.7	13	+ 9.5(h, itb, k, a)	No	Wheelchair (10.1 years)
20	10.7	12.5	21	–	–	Walks

[a] *Patients #10, 13, and 18 did not have measurable quadriceps at the start of treatment, but had contractures at the beginning of treatment and lost the ability to ambulate independently during first 6 months on prednisone. **Patients #7, 14, and 15 had interrupted therapy and then resumed therapy. LLB: long leg braces; h = hip; itb = iliotibial band; k = knee; a = ankle.

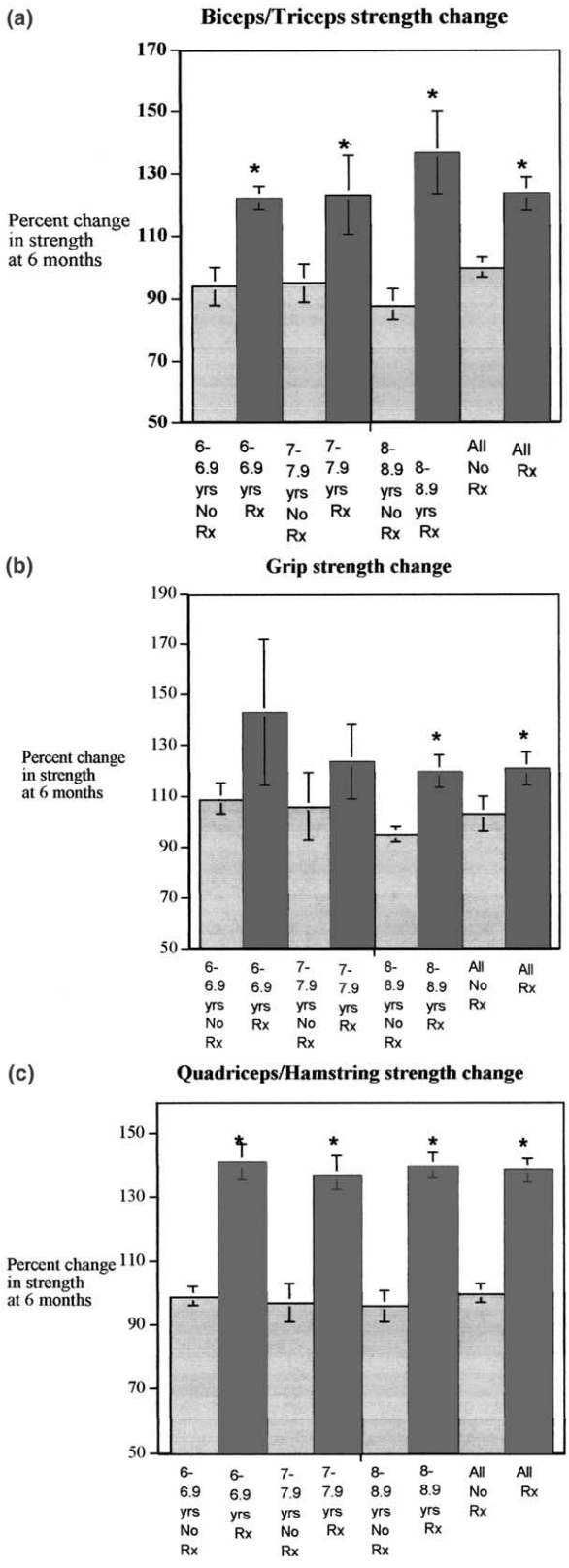


Fig. 1. Proximal upper extremity, Grip, and Proximal lower extremity strength at 6 months for treated and untreated boys with DMD. Proximal strength in both arms (a) and legs (c) improved for all ages with treatment compared to untreated boys. Grip strength (b) increased at all ages but the change was only significant at age 8–8.9 years and in the group as a whole.

and extension were measured with the hip and knee flexed to 90 degrees [18]. The quantitative strength examination of each child was performed without referencing the prior examination's results. Results in pounds were averaged in two groups: upper extremity (elbow flexion and extension) and lower extremity (knee flexion and extension). Grip strength was measured bilaterally and averaged.

It is known that boys with DMD of similar ages may vary significantly in strength. It was important to report each boy's strength in a way that reflected his own baseline. Therefore, changes in strength were calculated as a percent for each treated boy over the first 6 months ($n = 20$). Thus, if strength increased between visits, the value would be greater than 100%. If strength declined, the value would be less than 100%. This method also allowed us to compare groups of treated boys to age-matched untreated boys (Fig. 1a–c). All data were entered into a spreadsheet (Excel from Microsoft). Descriptive and comparative statistics were done within this program. P values equal to or less than 0.05 were considered significant.

2.3. Evaluation of strength longitudinally

In order to express the variability between boys' responses, we also analyzed the course of absolute strength across time for each treated boy. The numeric averages from the upper and lower extremity muscle groups were plotted across time (Fig. 2a, b). This analysis demonstrates graphically the variation in starting strength and in the benefit between boys.

2.4. Timed functional testing

Timed functional testing was performed in a subset of boys. This was performed using a stop watch (J.S., R.R. and J.F.) and included time to stand from a supine position, time to run or walk 30 ft, and time to climb four steps. Twelve boys were tested prior to and after 6 months of therapy.

2.5. Determination of obesity or excessive weight gain

Weight by height was determined for each visit using the National Center for Health Statistics percentiles [19]. For this study, the operational definition of obesity was a weight by height greater than the 80%ile. Linear growth was maintained in every boy treated with weekly prednisone. Therefore, weight by height analysis provided a better assessment of obesity or excessive weight increase than would absolute increase in weight. Excessive weight gain was noted if weight by height increased by more than 20 percentile points or, in boys who were already two standard deviations above the mean, if weight by height increased by more than one standard deviation.

3. Results

3.1. Quantitative strength in untreated boys with DMD (Fig. 1)

3.1.1. Proximal upper extremity strength

Untreated boys between 5 and 6 years of age had an average interval increase in upper extremity strength of 122 ± 9%. Between 6 and 9 years, average strength in the upper extremity did not change. The expected increases associated with normal growth did not occur. All boys maintained antigravity elbow flexion and extension strength through 9 years of age.

3.1.2. Grip strength

Grip testing showed that between 6 and 8 years mild improvement in grip did occur. The increase was 109 ± 6% for 6–6.9 years of age and 106 ± 13% for boys 7.0–7.9 years of age. Between 8 and 9 years there was, on average, a modest decline (95%).

3.1.3. Lower extremity strength

Lower extremity strength in untreated boys between 6 and 7 years of age on average remained stagnant (98%) but no boy lost antigravity quadriceps strength or the ability to walk independently. However, between 7 and 8 years of age, two boys lost antigravity quadriceps strength and the ability to ambulate independently. Three more untreated boys lost antigravity quadriceps strength and stopped walking independently between 8 and 9 years of age. Thus, the values of 97% (for 7–7.9 years) and 96% (for age 8–8.9 years) are overestimates as they refer only to boys who maintained antigravity quadriceps strength. No untreated boy lost antigravity knee flexion before 9 years of age.

3.2. Quantitative strength in boys with DMD treated with twice weekly prednisone (Fig. 1a–c)

Boys treated with twice weekly prednisone showed significant increases in upper and lower extremity strength on prednisone. The degree of improvement varied. Most boys and their parents reported functional improvement within 2–4 weeks of the first dose. Parents reported decreases in the frequency of falling for older boys and walking or running faster for younger boys. Two boys gained the ability to ride two wheel bicycles without training wheels.

Nineteen of 20 boys had improved proximal upper extremity strength over the first 6 months (Fig. 1a). Improvement was significant at 6–6.9 years of age ($P = 0.001$); 7–7.9 years ($P = 0.003$) and 8–8.9 years compared to untreated controls and in the group as a whole ($P = 0.001$).

Grip strength improved in all the 20 boys at 6 months. However, untreated boys between 6 and 7.9 years also showed improvement in strength and the difference in grip strength was not significant for hand grip until 8–8.9 years. The changes were also significant for the entire group ($P = 0.002$) (Fig. 1b).

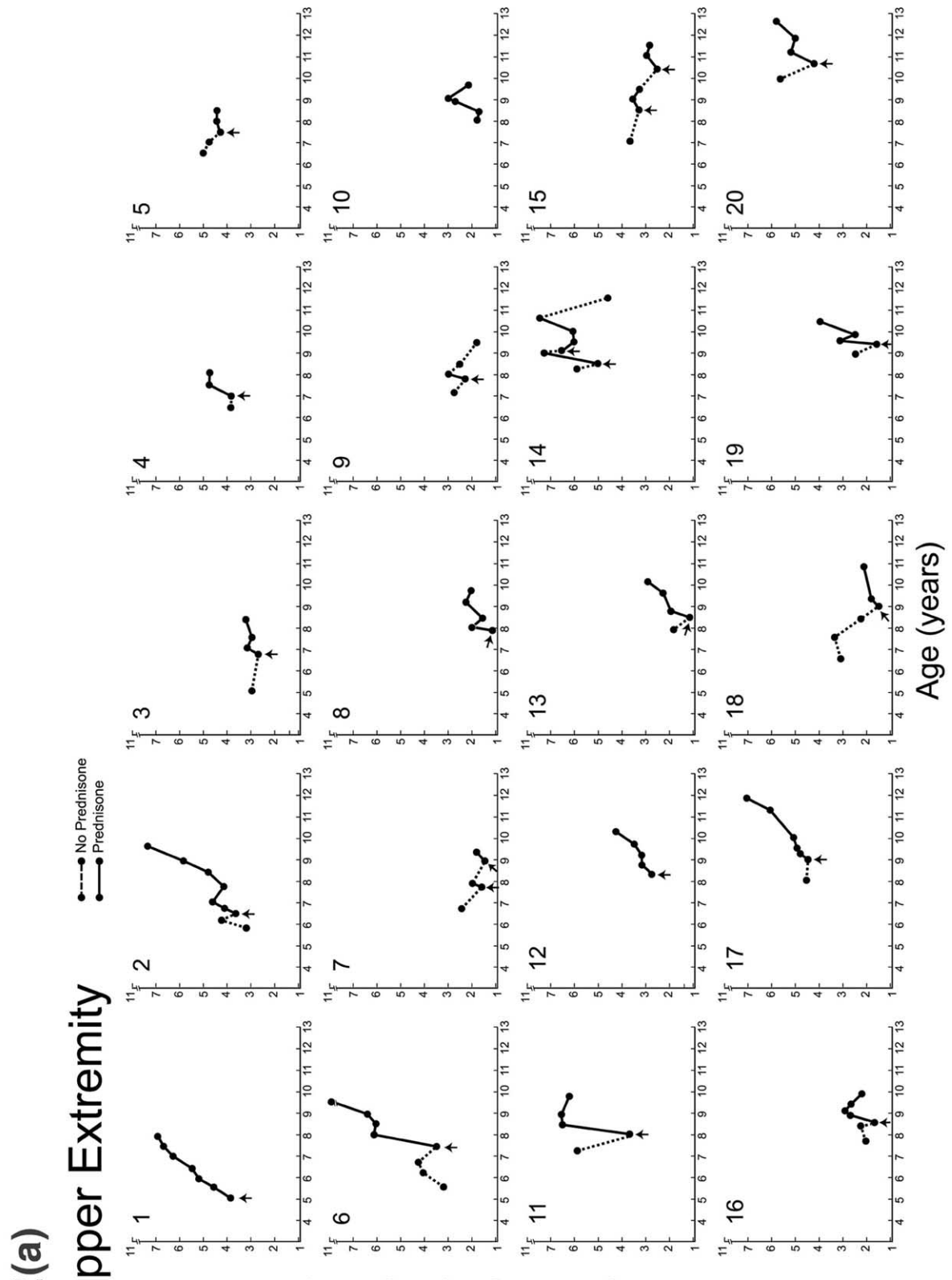
Seventeen of 17 (100%) boys who could be measured showed improvement in lower extremity proximal strength by 139 ± 3% ($P < 0.0001$) compared to untreated boys. This difference was present despite the fact that treated boys were significantly older and that all had either measurable ($n = 14$) or historical ($n = 6$) evidence for decline prior to starting weekly prednisone. This benefit compared to untreated children was significant at each age analyzed (6–9 years of age) (Fig. 1c).

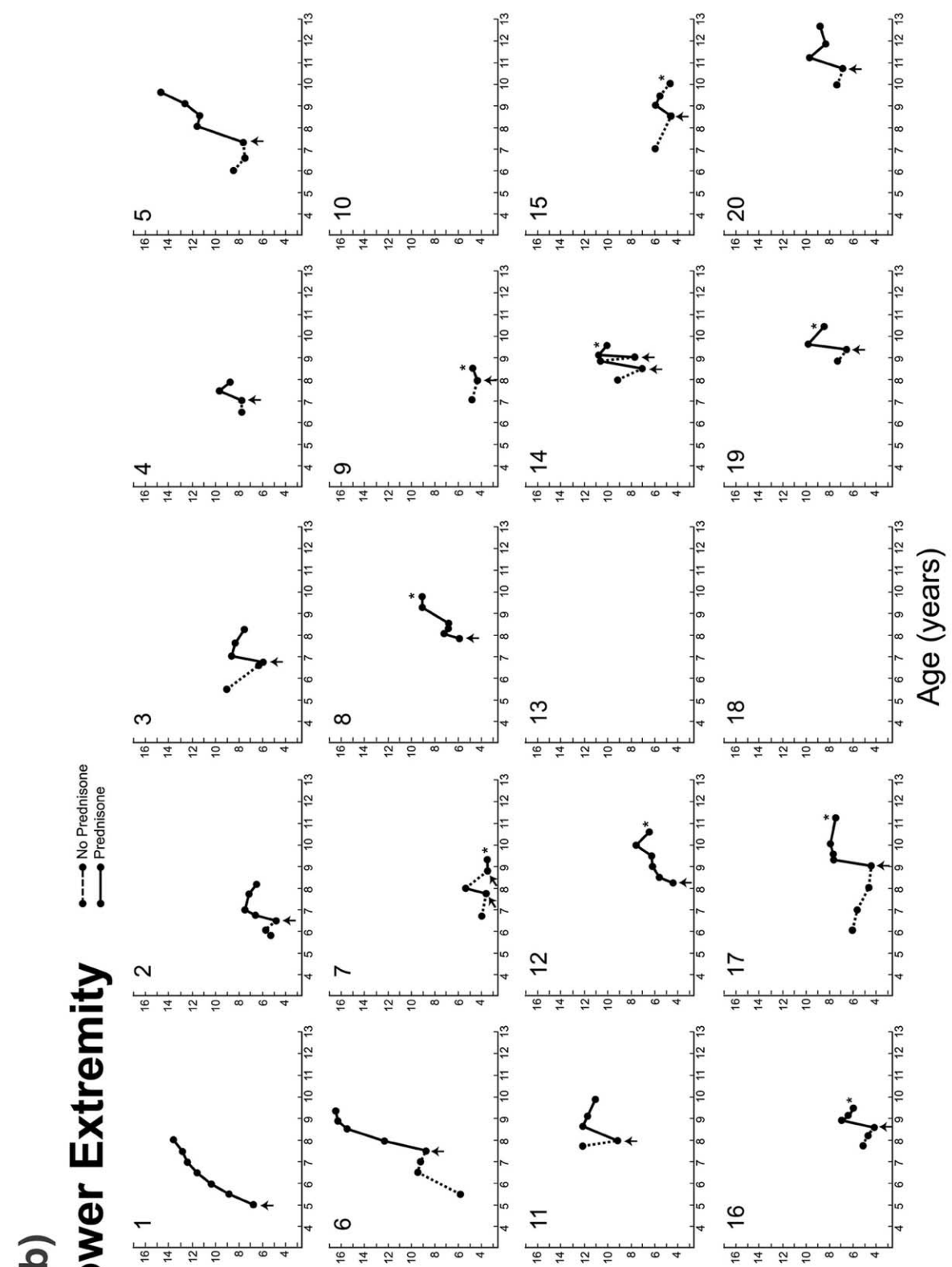
We also compared the improvement seen in the boys given twice weekly prednisone with the four boys given daily prednisone. The average improvement in upper extremity strength at the first follow-up did not differ between these groups ($P = 0.6$). Grip strength also did not differ significantly between daily and weekly treated boys ($P = 0.14$). The improvement in lower extremity strength in boys treated daily was slightly less than those treated twice weekly (119% versus 140%; $P = 0.01$).

3.3. Evaluation of strength longitudinally (Fig. 2)

While all the boys derived some benefit from weekly steroids, the degree to which they improved varied significantly. This variability is depicted in Fig. 2a, b. For example, two boys (#1 and #6) treated showed progressive improvement in strength at each visit over 32 and 24 months, respectively. These boys attained and maintained the ability to run and ride two wheel bicycles (aged 8.0 and 9.4 years at last follow-up). Other boys (e.g. # 5, 6, and 11) showed initial improvement in the first 6 months and then strength was stable. Four boys stopped treatment for various reasons. In two (#9 and 14), this was because of weekend irritability. In the other two (#7 and 15), the reason was parental non-compliance in filling the prescription. Three of these boys resumed treatment (#7, 14, and 15). The 'on–off' effect of prednisone in upper and lower extremity strength is evident for each of these boys (Fig. 2a, b). Of the 16 boys who were continuously treated for at least 12 months, all remained significantly stronger than prior to treatment and 8/16 (50%) showed additional gains in strength beyond 6 months of treatment.

Six boys were on the weekly prednisone 2 years or longer without interruption. All six (100%) had upper extremity strength at follow-up which was as good or better than at baseline and five of the six (83%) (Fig. 2a) showed additional gains in upper extremity strength beyond the first year of treatment. All six (100%) had quantitative lower extremity strength which was as good as or better than at baseline and three of the six showed additional gains in lower extremity strength beyond the first year (Fig. 2b). Two boys, (#1 and 5) were still able to run, jump and hop on either foot. Three boys, #3, 6, and 12 were able to walk. One boy (#17) was able to walk with long leg braces.


2(a)
Upper Extremity
No Prednisone
Prednisone
Average Strength (kilograms)
Age (years)


2 (b)
Lower Extremity
No Prednisone
Prednisone
Average Strength (kilograms)
Age (years)

3.4. Timed functional testing and ambulation

Twelve boys were tested before and after 6 months of treatment. The mean time to rise from supine to standing for untreated boys measured 11.0 versus 8.6 s for boys treated ($P = 0.13$). The mean time to walk 30 ft for untreated boys was 8.1 versus 7.2 s for treated boys ($P = 0.2$). There was no significant difference for the times to walk up four steps (9.4 vs. 9.0 seconds; $P = 0.42$)

We found the fact that all boys did not improve their functional times surprising given that all boys had improved lower extremity quantitative strength. However, when we analyzed which boys showed worsening of their functional testing, they were boys who also developed progressive contractures. The majority of these tended to be the older boys (Table 1). To test this hypothesis, we compared the timed functional testing of the youngest boys (ages 5, 6, and 7 years) before and after treatment. Most of these boys had no contractures (Table 1). All improved timed testing in at least two categories. No child worsened. Mean time for rising from supine in this younger subset improved from 7.3 to 3.1 s ($P = 0.01$); mean time for walking 30 ft improved from 5.5 to 3.7 s ($P = 0.05$); mean time for walking up four steps improved from 5.1 to 2.5 s ($P = 0.02$).

Three boys, # 10, 13, and 18 did not have antigravity strength in quadriceps prior to starting prednisone. They were having frequent falls, contractures at the start of prednisone, and stopped walking independently during the first 6 months. Despite this, 1 year after treatment, all three had improved upper extremity strength and the two who underwent surgical releases were able to walk with long leg braces. Eight other boys (Table 1) developed or had progression of contractures during the time they were treated and lost the ability to ambulate beyond 6 months of treatment. Despite this, their quantitative strength was still clearly better than prior to starting prednisone (Fig. 1). Four of these six boys underwent surgical release of contractures and were able to stand or ambulate with long leg braces.

3.5. Obesity and linear growth in treated and untreated boys with DMD (Table 1)

3.5.1. Obesity in untreated boys with DMD

Obesity is common in boys with DMD. Nine of the 18 untreated boys (50%) had a weight by height ratio equal to or greater than the 80 percentile at the first evaluation. Over the period that followed (1.7 ± 0.3 years), four of these nine boys (44%), but only one of the nine non-obese boys (11%), increased weight by height by more than 20 percentile points or one standard deviation. Thus, in untreated boys with DMD, obesity or increased obesity was more likely to develop in those who were at or above the 80 percentile for weight by height at presentation ($P = 0.03$).

3.5.2. Obesity in boys treated with twice weekly prednisone

Nine of the 20 boys (45%) measured at or >80 percentile for weight by height prior to starting twice weekly prednisone. Six boys (patients # 4, 10, 11, 18, 19, and 20) or 30% increased their weight by height by more than 20 percentile points or one standard deviation. Five of these six boys had a weight by height >80 percentile at baseline while only one did not have ($P = 0.05$). In three boys, the weight gain occurred in the first 6 months of treatment; and in three others it occurred later in the course of treatment. Five of these six boys noted an increase in appetite during the days on prednisone. Two other children also noted an increase in appetite; one increased from the 75th to the 90th percentile and the other increased from the 95th to the 98th. Thus, obesity rates did not differ between the treated and untreated boys. The major risk for excessive weight gain in both groups was a weight by height at or above 80 percentile at baseline. Linear growth was maintained within 10 percentile points in all boys on weekly prednisone. Cushinoid features such as hirsuitism, acne, stria, and hypertension did not occur.

3.5.3. Obesity in boys treated with daily prednisone

Two boys were obese prior to starting daily prednisone. All four boys taking daily prednisone developed obesity or an increase in obesity and complained of an increase in appetite. Linear growth slowed or stopped in all four.

3.6. Other side effects and compliance

No child taking twice weekly prednisone developed hypertension or hyperglycemia during treatment. No child on weekly prednisone developed any infection requiring hospitalization. Electrolytes and glucose were drawn in most children at least once during the study. No child developed hypokalemia.

No child developed a pathological fracture and linear growth was maintained in all children. Two children had dual energy X-ray absorptiometry (DEXA scans) during the course of treatment. Patient #1 DEXA scans of femoral neck

Fig. 2. Longitudinal absolute strength for proximal upper extremity (a) and lower extremity strength (b) for boys with DMD. A quantitative decrease in strength prior to treatment (interrupted lines) was present in all boys for whom measurements were available. (a) Proximal upper extremity strength improved for 19/20 boys at first follow-up. Patient #10 did not show initial improvement in upper body strength, but at the time of second follow-up had improved strength. While the duration and magnitude of the benefit varied from child to child, most boys treated longer than one year were stronger than at the time they started prednisone. Patients # 7, 9, 14, and 15 demonstrate an 'on–off' effect for prednisone. (b) Seventeen of the 20 boys had antigravity quadriceps at the start of the treatment and their strength is depicted across time. Boys showed a parallel improvement in their lower extremity strength. Lines marked with * indicate that these boys developed contractures and stopped walking independently at this point.

and radius were performed after 2 years on weekly prednisone. These showed values of 0.650 and 0.379 g/cm^2 (−0.1 and + 0.9 SD compared to age-matched healthy controls). Patient #12 had DEXA scans of femoral neck and lumbar spine levels 2, 3, and 4 which showed values of 0.67 and 0.84 g/cm^2 (−1.43 and +0.84 SD compared to age-matched controls). These values (for patient #1 and for the lumbar spine of patient #12) compare very favorably with healthy children. The hip value for patient #12 is similar to what has been reported for untreated boys with DMD [20].

Children were evaluated yearly by an ophthalmologist and none developed cataracts. Six (30%) children or their parents reported irritability or sleep disturbance during 1–2 days following medication. Two children (#7 and #14) developed irritability severe enough that the medication was discontinued. Child #14 resumed the medication when strength fell. Upon resumption, the child took the dose at bedtime and had no further difficulty. Four other children had the dose reduced by 25–30% and were then able to tolerate the irritability.

4. Discussion

4.1. Strength in boys treated with twice weekly prednisone

The results of this pilot study demonstrate that prednisone given in two high oral doses each week (10 mg/kg/week) significantly improves muscle strength in boys with DMD compared to untreated boys. Since the methods used here (quantitative strength testing) differ from those used in the CIDD group (MRC scale testing), it is difficult to directly compare the degree of improvement in the two studies. However, several important parallels exist. First, the onset of the improvement was similar with improvement reported in the first few weeks of treatment and measurable by 3–6 months. Second, in both studies, the majority of the boys benefited. In our study, sustained benefit beyond 1 year occurred in the majority.

Our work suggests that the strength benefit is similar to that achieved in boys treated with daily prednisone. However, as we did not follow any boys on either alternative day steroids or treatment for the first 10 days of the month, no comparisons can be made with those treatment strategies. Our work also shows that the youngest boys tended to have the greatest improvement in strength with gains in strength being maintained over several years (Fig. 2). Dubowitz et al. also found marked improvement in two young boys treated early with low dose, intermittent prednisone which was sustained over several years [21].

4.2. Ambulation and timed functional testing

In our study, timed functional testing improved in younger boys. However, this improvement was not as common in older boys. In fact, over the period of follow-up, 11 of the boys lost the ability to ambulate independently. Progression of contractures did not appear to be affected by the use of prednisone. In those who had progression of contractures, timed functional testing was more likely to worsen. This occurred even in boys who had definite improvement in quantitative strength. This discordance between strength and contractures was noted in the previous studies [2]. The mechanism of the development of the contractures is not clear. However, they are clearly a risk factor for the loss of ambulation.

4.3. The mechanism of the steroid benefit is not clear

We found that the benefit in some boys was more significant and persistent than in other boys. The most sustained benefit was in those children who started treatment early. At follow-up ages of 8–9.4 years, the six youngest children were able to walk well and three could run. It is known that muscle, for boys with DMD, becomes more fibrotic with age and it is possible that earlier treatment in a child plays a role in how much improvement occurs. Others have noted that earlier treatment (age 3–4) with prednisone 0.75 mg/kg per day for the first 10 days of the month was associated with dramatic improvement [11,21]. While our study does suggest that younger children benefited most, it does not address very young children as only three children were started at less than 7 years of age.

Biopsies obtained before and after prednisone clearly show a decrease in cellular infiltrates [22]. Based on limited benefit from alternative day steroids and no benefit from azathioprine, immmunosuppression has been considered by some to be an unlikely mechanism. The effects of weekly or pulse steroids may have not only transient effects on stabilizing membranes, but also have clear immunosuppressive effects. These effects are primarily directed at the humoral immune system and include antibody suppression and suppression of complement. It is well known that complement activation has an active role in the removal of necrotic tissue but it has also been recognized that complement deposition is present on non-necrotic fibers as well [23,24]. More extensive work regarding the mechanism of the benefit of weekly prednisone may allow better, and potentially earlier, treatment of this progressive dystrophy.

While the ultimate cure for DMD may well come from our increasing understanding of the genetic defect, there is a pressing need now to better treat this devastating, progressive muscular dystrophy. Immunocytochemistry [25] demonstrates progressive fibrosis over the first decade. Treatment with high dose twice weekly oral steroids appears to be at least as beneficial over the first 6–12 months as daily prednisone. While a larger trial with longer follow-up is necessary to validate these findings, twice weekly oral prednisone appears to be a safe method with a better side effect profile compared to giving prednisone daily. Younger boys without contractures had improved timed functional testing. The current study is clearly retrospective in nature. The side effect of irritability must be

considered as it was common (30%) and was time locked to the 2 days following prednisone. While all the boys maintained linear growth, formal assessment of bone density should also be carried out as this dose is higher than what the previous studies have used. However, the data are encouraging and show that the majority of boys did have an improvement in strength over 6 months. A subset of boys had benefit over more than 2 years.

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