Intermittent Prednisone Therapy in Duchenne Muscular Dystrophy

A Randomized Controlled Trial

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Background: Prednisone treatment is used to prolong ambulation in patients with Duchenne muscular dystrophy (DMD). However, since severe adverse effects often accompany prednisone treatment, it is debatable whether the benefits of prednisone treatment outweigh its adverse effects.

Objectives: To study the effects of prednisone on muscle function and to determine the extent of steroid-related adverse effects and their influence on the quality of life of ambulant patients with DMD.

Design: A randomized, placebo-controlled, crossover trial with 6 months of treatment: prednisone or placebo (0.75 mg/kg daily) during the first 10 days of each month. After a washout period of 2 months, patients received the other regimen for an additional 6 months.

Setting: University hospital and rehabilitation center in the Netherlands.

Results: The increase in time needed to run 9 m (P = .005) and to climb 4 standard-sized stairs (P = .02) was significantly lower during the prednisone period.

Conclusions: Prednisone slowed deterioration of muscle function and muscle force in ambulant patients with DMD. Although adverse effects were present, patient quality of life was not affected. Therefore, short-term prednisone treatment can be recommended to preserve motor functions in ambulant patients with DMD.


Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder characterized by progressive weakness of the limb girdle musculature. This disorder is caused by a deficiency of dystrophin, a cytoskeleton protein that is associated with the sarcolemma. Patients die in their late teens or early 20s from respiratory failure or cardiomyopathy. Many drugs have been used to slow disease progression, but a beneficial effect of steroids on muscle force has only been shown in randomized controlled trials.

In trials that report the effect of prednisone on DMD, the main outcome measure has been muscle force or has not been specifically mentioned. Since muscle force and muscle function are only related indirectly, muscle force might change without accompanying change in functional status. Therefore, steroids should only be used if a beneficial effect on muscle function can be shown. Despite the introduction of intermittent treatment schedules and reduced dosage schemes, adverse effects such as weight gain, cushingoid appearance, and behavioral changes are frequently reported in prednisone-treated patients. This is probably why the use of steroids is still controversial, hampering universal acceptance as supportive therapy in DMD.

Some important questions still need to be resolved. First, although a positive effect of steroids on muscle force has been established, the effects on functional status are not clear. Second, the extent to which the quality of life (QoL) of patients is influenced by the inevitable adverse effects of steroids is unknown. The objectives of this study are to determine in a randomized, double-blind, placebo-controlled, crossover trial the effect of prednisone on...
Ambulant patients with DMD aged 5 to 8 years were considered for inclusion in the study. Patients were included if their clinical picture demonstrated classic DMD, their serum creatine kinase level was grossly elevated, a muscle biopsy specimen showed (almost) no dystrophin, except for an occasional muscle fiber (less than 5% of fibers), and they could walk without assistance. Patients were excluded if they had used steroids within 2 months before the start of the trial. The study received approval from the local ethics committee. All parents provided written informed consent. In all cases, primary care physicians agreed with the patients’ participation. The study had a randomized, double-blind, placebo-controlled, crossover design in which all patients received prednisone (0.75 mg/kg daily) or placebo for 6 months during the first 10 days of each month. In the remaining 20 days, no prednisone was prescribed. Dosages were rounded to the nearest 5 mg. After a subsequent washout period of 2 months, patients received the other regimen for an additional 6 months. Randomization was performed by the pharmaceutical chemist.

The primary outcome measure was a change in muscle function assessed by timed functional testing (running 9 m with bare feet as fast as possible, climbing 4 standard-sized stairs, and rising from a supine position to a standing position on the floor). The secondary outcome measures were changes in quantified muscle force, weight, blood pressure, functional grade, and QoL. Changes in muscle force were measured by handheld dynamometry. To determine patterns of muscle weakness, individual muscles were grouped together to calculate (changes in) clinically relevant summed scores. We distinguished total muscle force (all muscle scores added), proximal muscle force (shoulder abductors, elbow flexors and extensors, hip flexors and abductors, knee flexors and extensors), distal muscle force (wrist extensors and 3-point grip), arm muscle force (all arm muscle groups), and leg muscle force (all leg muscle groups).

The functional grade of both upper and lower extremities was measured using the grading system by Brooke et al. All measurements were performed each month on days 1, 10, and 30 by one of us (E.A.C.B.). The QoL was measured at the start and end of both 6-month trial periods with the DUX-25, which is a QoL questionnaire that covers 4 domains: physical, emotional, social, and home functioning. The items are scored using a 5-point scale. Evaluation of adverse effects was performed at each visit by using a standard list that described steroid-related adverse effects. Patients were examined for the presence of cushingoid appearance, cataracts, and skin changes (acne, hirsutism, easy bruising, etc). Patients and parents were interviewed for the presence of blurred vision, behavioral changes (hyperactivity, irritability, insomnia, euphoria, depression, etc), and gastrointestinal symptoms (increased appetite, nausea, stomach discomfort, etc).

Linear regression analysis was used to show changes of the primary and secondary outcome measures in time. For all timed functional tests, muscle force sum scores, weight, and (systolic) blood pressure, the regression coefficient ($\beta$) was calculated for both periods. Data were analyzed according to the sequence in which the medication was given.

Group 1 consisted of patients who received prednisone first (phase 1); group 2 consisted of patients who received prednisone during the second period (phase 2). To test for a treatment effect, we calculated the difference in mean $\beta$ values between phase 1 and 2 for each treatment group separately. These differences were subsequently statistically compared between both groups. If data were distributed normally, paired $t$ tests were used; otherwise, the Wilcoxon signed-rank test was used. $P \leq .05$ was considered statistically significant. To test for a period effect, we added the mean $\beta$ values for groups 1 and 2 and tested for the presence of a statistical difference from zero. We defined a placebo effect as a parameter change opposite to the clinical expectation (improvement of functional tests, force increase, etc). This was tested only in group 2 (placebo as first treatment).

Seventeen patients with a mean (SD) age of 6.29 (0.92) years were included in the study. After randomization, 7 patients started taking prednisone, whereas the other 10 started taking placebo (Figure 1). One patient dropped out after 10 days because of a traumatic fracture of his right femur. This patient was not included in the statistical analysis. Therefore, all analyses are based on 16 patients. Results of only 13 patients are used for the rising from the floor to a standing position test, because 3 patients had too many missing values due to disease-related deterioration.

During the prednisone period, the time needed to run 9 m ($P = .005$) and the time needed to climb 4 standard-size stairs ($P = .02$) increased significantly more slowly compared with the placebo period (Table 1). This implies, if both groups are pooled, an average increase of the mean time needed to run 9 m of 0.08 seconds in the prednisone period vs 0.81 seconds in the placebo period (Figure 2). For climbing stairs, this increase was 0.37 seconds (prednisone period) vs 2.43 seconds (placebo period) (Figure 3). The change in time needed to rise from the floor increased during both trial periods. Although the increase was slightly larger during the pla-
placebo period, there was no statistically significant difference between both periods (P = .14).

During the prednisone period, total muscle force (P = .02), proximal muscle force (P = .02), and arm muscle force (P = .02) improved significantly compared with the placebo period, whereas distal and leg muscle force remained stable. This implies an increase of total muscle force of 77.65 N in the prednisone period vs a decrease of 28.65 N in the placebo period (Figure 4).

For proximal muscle force and arm muscle force, these increases were 48.18 N vs −40.41 N and 41.83 N vs 3.53 N, respectively. During the placebo period, all summed force scores decreased, with the exception of arm muscle force. Body weight did not increase significantly faster during the prednisone period compared with the placebo period (2.37 and 1.47 kg, respectively). Blood pressure remained stable during both periods.

Table 1. Mean Treatment Effects for the Prednisone and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prednisone Group</th>
<th>Placebo Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Running 9 m, s/d</td>
<td>4.675 × 10^{-4}</td>
<td>4.90 × 10^{-4}</td>
<td>.005</td>
</tr>
<tr>
<td>Climbing stairs, s/d</td>
<td>2.050 × 10^{-3}</td>
<td>13.52 × 10^{-4}</td>
<td>.02</td>
</tr>
<tr>
<td>Rising, s/d</td>
<td>5.995 × 10^{-3}</td>
<td>12.43 × 10^{-4}</td>
<td>.14</td>
</tr>
<tr>
<td>Weight, kg/d</td>
<td>13.14 × 10^{-3}</td>
<td>8.148 × 10^{-4}</td>
<td>.06</td>
</tr>
<tr>
<td>Blood pressure, mm Hg/d</td>
<td>3.607 × 10^{-3}</td>
<td>2.087 × 10^{-4}</td>
<td>.19</td>
</tr>
<tr>
<td>Total muscle force, N/d</td>
<td>4.314 × 10^{-4}</td>
<td>−1.592 × 10^{-4}</td>
<td>.02</td>
</tr>
<tr>
<td>Proximal muscle force, N/d</td>
<td>2.677 × 10^{-4}</td>
<td>−2.245 × 10^{-4}</td>
<td>.02</td>
</tr>
<tr>
<td>Distal muscle force, N/d</td>
<td>16.97 × 10^{-2}</td>
<td>3.847 × 10^{-2}</td>
<td>.06</td>
</tr>
<tr>
<td>Arm muscle force, N/d</td>
<td>23.24 × 10^{-2}</td>
<td>1.959 × 10^{-2}</td>
<td>.02</td>
</tr>
<tr>
<td>Leg muscle force, N/d</td>
<td>17.87 × 10^{-2}</td>
<td>−2.056 × 10^{-2}</td>
<td>.15</td>
</tr>
</tbody>
</table>

*Statistically significantly different at P ≤ .05.

All patients scored Brooke grade 1 for upper extremities (abducting the arms in a full circle until they touch above the head). During the placebo and prednisone periods, the functional status of the upper extremities did not change in any patient. For the lower extremities, grade 1 (walks and climbs stairs without assistance), grade 2 (walks and climbs stairs with aid of railing), and grade 3 (walks and climbs stairs slowly with aid of railing during 12 seconds for 4 standard-size stairs) scores were noted.

The functional status of the lower extremities did not change in the 13 patients. Ten patients had their functional status classified as grade 1 and 3 patients as grade 2. In 1 patient, the functional status decreased from grade 1 to grade 2 during the prednisone period, and the functional status of 2 patients worsened from grade 2 to grade 3 during the placebo period.

The QoL did not change significantly during the prednisone period. With every new measurement, however, patients reported a slightly higher QoL, irrespective of the given medication, resulting in a significant improvement in the last measurement on 2 scales (emotional functioning and the total scale), possibly related to the attention of being involved in a trial.

In the prednisone period, 25 adverse effects were reported in 10 (63%) of 16 patients, whereas 6 adverse effects were reported in 5 (31%) of 16 patients in the placebo period. Combinations of adverse effects (irritability and cushingoid appearance and irritability and hyperactivity) were reported 4 and 3 times, respectively, and were only found in the prednisone period. The adverse effects were not clustered during the treatment days of each month. There were no dropouts because of the adverse effects. No period effects were seen for any variable. A placebo effect was found only for distal muscle force.

Figure 2. Time it took patients to run 9 m. Data points are based on the mean of all individual values. Error bars represent standard error of the mean.

Figure 3. Time it took patients to climb 4 standard-sized stairs. Data points are based on the mean of all individual values. Error bars represent standard error of the mean.

Figure 4. Adverse effects during both periods (P = .14).
The main results of this study are a significant difference between performance on functional tests between the prednisone and the placebo period. Prednisone stabilized the performance on the running test. The time needed to execute the climbing stairs and rising from the floor to a standing position test still increased with time, although clearly not as fast as during the placebo period. This finding provides evidence that prednisone slows disease progression. These results are consistent with other reports.2,3

During prednisone therapy, an increase in muscle force was found. Total muscle force and proximal and arm muscle force improved during the prednisone period. During the placebo period, all summed force scores decreased or remained stable. An increase in muscle force due to steroids has been reported earlier.2,3 The functional status of the upper extremities did not change during prednisone treatment. This apparent contradiction (ie, an increase in force together with a slight deterioration in performance on functional tests) can be explained by the effect of growth, probably outweighing the increase in force. This illustrates the indirect relation between muscle force and muscle function, arguing in favor of the use of functional tests as the main outcome measures in DMD therapeutic trials. We did not find evidence of a placebo effect. However, real testing of a placebo effect is not possible with our data, because we did not include nontreated patients, marking the natural course of the disease. Body weight increased slightly but not significantly during the prednisone period, which is inconsistent with other reports.2,3 probably because in these trials prednisone was not given intermittently. Consistent with the findings by Kinali et al,9 changes in blood pressure were not found.

Adverse effects were noted in 10 (63%) of 16 patients, despite the intermittent schedule and the use of a relatively low dose of prednisone (Table 2). Irritability and cushingoid appearance were the most frequently reported adverse effects during our study. However, there were no dropouts due to adverse effects.

Mendell et al1 reported these adverse effects previously in low-dose prednisone schedules (0.75 mg/kg daily). Alternative dosage schemes, such as alternate day schedules,3 were not able to prevent such adverse effects completely. Only Kinali et al9 reported no adverse effects in an intermittent regimen in which prednisolone, 0.75 mg/kg daily for 10 days on and 10 days off, was given. However, their study included only 4 patients.

The QoL was assessed by the DUX-25. This questionnaire has not been previously used in patients with DMD. In patients with DMD, the QoL was not affected in any of the scored domains, despite prednisone treatment. The scores are not different from those of healthy controls and patients with a stationary disease, such as spinal cord injury;10 but are clearly better than in patients with diabetes mellitus and juvenile chronic arthritis. This suggests that a (semi-) stationary disease has less effect on the QoL than diseases with short-term consequences, such as pain or regular injections. In addition, because the QoL is determined by the balance between adverse and treatment effects, it could be argued that adverse effects may be acceptable if associated with a positive treatment effect.

Eleven (69%) of 16 patients were 6 years or younger; therefore, this study comprises relatively young patients. In earlier trials, the mean age of included patients was higher (9.1 and 9.5 years). Because the mean age of becoming wheelchair bound is approximately 9.5 years,11 these studies included patients with relatively severe manifestations of disease. This might have impaired the beneficial effect of prednisone. However, although the progressive character of the disease argues in favor of early therapy, clear advice on which age group is most appropriate for prednisone therapy cannot be given on the basis of our study.

In conclusion, prednisone stabilizes muscle function in ambulant patients with DMD, which is likely to be due to an increase in muscle force. Despite the relatively low dose of prednisone (0.75 mg/kg daily), adverse effects were present. However, no patients dropped out of the study because of adverse effects. The QoL of patients with DMD was not affected by the use of prednisone. Therefore, short-term prednisone treatment can be recommended to preserve motor functions in ambulant patients with DMD.
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REFERENCES