Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomised controlled trial.
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Abstract

Prednisone treatment is used to prolong ambulation in Duchenne muscular dystrophy (DMD). However, since severe side effects often accompany prednisone treatment it is debatable whether the benefits of prednisone treatment outweigh its side effects. The objectives of this trial were to study the effects of prednisone on muscle function and to determine the extent of steroid related side effects and their influence on the quality of life (QoL) in ambulant DMD patients.
The study design was a randomised placebo-controlled crossover trial with 6 months of treatment. Prednisone (0,75 mg/kg/d) or placebo was given for 6 months during the first 10 days of each month. After a washout period of 2 months, patients received the other regime for further 6 months.
Seventeen ambulant DMD patients aged 5-8 years were included.
The main outcome measure was change in muscle function assessed by timed functional testing; running 9m, climbing 4 standard-size stairs and rising up from the floor to a standing position.
The increase in time needed to run 9m and to climb 4 standard-size stairs was significantly lower during the prednisone period (p = 0,005, p = 0,023).
In conclusion: prednisone slowed deterioration of muscle function and muscle force down in ambulant DMD patients. Although side effects were present, the QoL was not affected. Therefore, short-term prednisone treatment can be recommended to preserve motor functions in ambulant DMD patients.
Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder characterised by progressive muscle weakness of the limb girdle musculature. DMD is caused by a deficiency of dystrophin, a cytoskeleton protein that is associated with the sarcolemma. Patients die in their late teens or early twenties due to respiratory failure or cardiomyopathy.1

Many drugs have been used to slow down disease progression, but a beneficial effect on muscle force has only been shown in randomised controlled trials for steroids.2,3 In trials reporting the effect of prednisone in DMD the main outcome measure was muscle force2,3 or it was not specifically mentioned.4 Since muscle force and muscle function are only related indirectly, muscle force might change without accompanying change in functional status. It can be stated that steroids are only worth the effort, if a beneficial effect on muscle function can be shown.

Despite the introduction of intermittent treatment schedules and reduced dosage schemes4,5 side effects such as weight gain, cushingoid appearance and behavioural changes were frequently reported in prednisone treated patients.2,3 This is probably the reason why the use of steroids is still regarded as controversial, hampering universal acceptance as supportive therapy in DMD.6 Therefore, some important questions still need to be resolved. Firstly, although a positive effect of steroids on muscle force has been established, the effects on functional status are not clear. Secondly, the extent to which the quality of life (QoL) of patients is influenced by the inevitable side effects of steroids is unknown.

The purpose of this study was to determine in a randomised double-blind placebo controlled crossover trial the effect of prednisone on functional status in ambulant DMD patients and to monitor the number and extent of side effects and their influence on the quality of life.

Patients and methods

Ambulant DMD patients aged 5-8 years were included. Patients were included, if their clinical picture demonstrated classical DMD, serum CK level was grossly elevated, muscle biopsy showed (almost) no dystrophin, except for an occasional muscle fibre (less than 5% of fibres)15 and if they could walk without assistance. Patients were excluded if steroids had been used within 2 months before the start of the trial.

The study received approval from the local ethical committee. All parents provided written informed consent. In all cases, primary care physicians agreed with the subjects’ participation. The study had a randomised double-blind placebo controlled crossover design in which all patients received prednisone (0,75 mg/kg/d) or placebo...
for 6 months during the first 10 days of each month. In the remaining 20 days no prednisone or placebo was prescribed. Dosages were rounded off to the nearest 5 mg. After a subsequent washout period of 2 months, medication was switched over for another 6 months. Randomisation was carried out by the pharmaceutical chemist. 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-size stairs and rising up from a supine position to a standing position on the floor). Secondary outcome measures were changes in quantified muscle force, weight, blood pressure, functional grade and quality of life. 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 three-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 of Brooke et al.. All measurements were performed each month at day 1, 10 and 30 by the first author. QoL was measured at the start and end of both 6 month trial periods by using the DUX-25. This is a QoL questionnaire that covers four domains: physical, emotional, social and home functioning. The items are scored using a five-point scale. Side effect evaluation was carried out at each visit by using a standard list, which described steroid related side effects. Patients were examined for the presence of cushingoid appearance, cataracts and skin changes (acne, hirsutism, easy bruising). Patients as well as parents were interviewed for the presence of blurred vision, behavioural changes (hyperactivity, irritability, insomnia, euphoria, depression) and gastrointestinal symptoms (increased appetite, nausea, stomach discomfort).

Statistics

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 (β) was calculated for both periods. Data were analysed according to the sequence in which the medication was given. Group I consisted of patients who received prednisone first (phase 1), group II of patients who received prednisone during the second period (phase 2). To test for a treatment effect we calculated the difference in mean β 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. To test for a period effect the mean β for group I and II were added, 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 II (placebo as first treatment).

Results

Seventeen ambulant DMD patients were included. The mean age was 6.29 years (SD 0.92). After randomisation 7 patients started with prednisone whereas, the other 10 started with placebo (Figure 1). One patient dropped out after 10 days due to 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 up test, since three patients had too many missing values due to disease related deterioration.

During the prednisone period the time needed to run 9 m and the time to climb 4 standard-size stairs increased significantly slower compared to the placebo period (p = 0.005 and 0.023, 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 versus 0.81 seconds in the placebo period (Figure 2). For climbing stairs this was 0.37 seconds (prednisone period) versus 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 placebo period, there was no statistical difference between both periods (p = 0.136).

During the prednisone period total muscle force (p = 0.023), proximal muscle force (p = 0.016) and arm muscle force (p = 0.024) improved significantly compared to 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 versus a decrease of 28.65 N in the placebo period (Figure 4). For proximal muscle force and arm muscle force this was respectively 48.18 N versus -40.41 N and 41.83 N versus 3.53 N. 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 to the placebo period (2.37 kg versus 1.47 kg respectively). Blood pressure remained stable during both periods.

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 period
Figure 1. Flow diagram of the randomised trial of intermittent prednisone in DMD patients.
Figure 2. Time running 9 m. Data points are based on the mean of all individual values. Error bar represents standard error of the mean (SEM).

Figure 3. Time climbing 4 standard-size stairs. Data points are based on the mean of all individual values. Error bar represents SEM. In the placebo period the SEM is relatively high, because one patient deteriorated during this period (his second trial period).
the functional status of the upper extremities did not change in any patient. For 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 over 12 seconds for 4 standard-size stairs) were noted. The functional status of the lower extremities did not change in 13 patients. Ten patients were graded as grade one and three as grade two. In one patient the functional status reduced from 1 to 2 during the prednisone period, and two patients worsened from grade 2 to grade 3 during the placebo period.

Quality of life 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 two scales (emotional functioning and the total scale), possibly related to the attention of being involved in a trial.

In the prednisone period 25 side effects were reported in 10 of 16 (62.5%) patients whereas this was 6 in 5 of 16 (31.3%) patients in the placebo period. Combinations of side effects (irritability and cushingoid appearance, irritability and hyperactivity) were reported 4 and 3 times, respectively, and were only found in the prednisone period. The side effects were not clustered during the treatment days of each month.

There were no dropouts because of the side effects. No period effects were seen for any variable. A placebo effect was only found for distal muscle force.

![Figure 4. Total muscle force. Data points are based on the mean of all individual values. Error bars represent SEM.](image-url)
Table 1.
Summarised results. Mean β in prednisone- and placebo period and treatment effect. *Significant difference at p ≤ 0.05. Seconds, sec.; day, d; kilogram, kg; millimeter mercury, mmHg; Newton, N.

<table>
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<tr>
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<th>mean β prednisone</th>
<th>mean β placebo</th>
<th>p treatment effect</th>
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</thead>
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<td>running 9 m</td>
<td>[sec./d]</td>
<td>4.675 $10^{-4}$</td>
<td>44.90 $10^{-4}$</td>
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<td>rising up</td>
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<td>12.43 $10^{-3}$</td>
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<td>8.148 $10^{-3}$</td>
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<tr>
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<td>[mmHg/d]</td>
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<td>2.087 $10^{-3}$</td>
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<td>[N/d]</td>
<td>17.87 $10^{-2}$</td>
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Table 2. Number of patients experiencing adverse events in each trial period.

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<th>Side effect</th>
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<th>Placebo (n = 16)</th>
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<td>none</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>cushingoid</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>hyperactivity</td>
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</tr>
<tr>
<td>irritability</td>
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<td>2</td>
</tr>
<tr>
<td>euphoria</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>increased appetite</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>hyperactivity, irritability</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>euphoria, increased appetite</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>euphoria, cushingoid</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>irritability cushingoid</td>
<td>4</td>
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</tr>
<tr>
<td>hyperactivity, irritability, increased appetite</td>
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Discussion

The main results of this study are a significant difference between performance on functional tests between the prednisone and the placebo period. Prednisone stabilised the performance on the running test. The time needed to execute the climbing stairs and rising-up test still increased with time, although clearly not as fast as during the placebo period. This provides evidence for prednisone in slowing down disease progression. These results are consistent with other reports.\(^2,3\)

During prednisone therapy an increase in muscle force was found. Total muscle force as well as proximal- and arm muscle force improved during the prednisone period. During the placebo period all force summed 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 (i.e. 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 favour of the use of functional tests as the main outcome measures in DMD therapeutic trials. We did not find evidence for a placebo effect. However, real testing of a placebo effect is not possible on our data, since we did not include non-treated 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 of Kinali et al.\(^9\) changes in blood pressure were not found. Side effects were noted in 10 of 16 (62,5\%) 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 side effects during our study. However, there were no dropouts due to side effects. Mendell et al.\(^3\) reported these side effects previously in low dose prednisone schedules (0,75 mg/kg/d). Alternative dosage schemes, such as alternate day schedules\(^5\), were not able to prevent such side effects completely. Only Kinali et al.\(^9\) reported no side effects in an intermittent regime in which prednisolone (0,75 mg/kg/d 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 used in DMD before. In DMD the QoL was not affected in any of the scored domains, despite prednisone treatment. The scores are not different from healthy controls and patients with a stationary disease such as spinal cord injury,\(^10\) but are clearly better than patients with diabetes and juvenile chronic arthritis. This suggests that a (semi) stationary disease, has less impact on the QoL than diseases with short-term consequences such as pain or regular injections.
Additionally, 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 of 16 patients (69%) were aged 6 years or less, therefore this study comprises relatively young patients. In earlier trials the mean age of included patients was rather high (9,1\textsuperscript{3} and 9,5 years\textsuperscript{2}). Since the mean age of becoming wheelchair bound is around 9,5 years\textsuperscript{11} these studies included relatively severe patients. This might have impaired the beneficial effect of prednisone. However, although the progressive character of the disease argues in favour of early therapy, clear advice on which age group is most appropriate for prednisone therapy can not be given on the basis of our study.

In conclusion, prednisone stabilises muscle function in ambulant DMD patients which is likely to be due to an increase in muscle force. Despite the relatively low dose of prednisone (0,75mg/kg/d) side effects were present. However, there were no dropouts due to the side effects. The QoL of DMD patients was not affected by the use of prednisone. Therefore short-term prednisone treatment can be recommended to preserve motor functions in ambulant DMD patients.

Acknowledgements

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Reference List


