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Benefits of glucocorticoids in non-ambulant boys/men with Duchenne muscular dystrophy: A multicentric longitudinal study using the Performance of Upper Limb test

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Abstract

The aim of this study was to establish the possible effect of glucocorticoid treatment on upper limb function in a cohort of 91 non-ambulant DMD boys and adults of age between 11 and 26 years.

All 91 were assessed using the Performance of Upper Limb test. Forty-eight were still on glucocorticoid after loss of ambulation, 25 stopped steroids at the time they lost ambulation and 18 were GC naïve or had steroids while ambulant for less than a year.

At baseline the total scores ranged between 0 and 74 (mean 41.20). The mean total scores were 47.92 in the glucocorticoid group, 36 in those who stopped at loss of ambulation and 30.5 in the naïve group ($p < 0.001$).

The 12-month changes ranged between −20 and 4 (mean −4.4). The mean changes were −3.79 in the glucocorticoid group, −5.52 in those who stopped at loss of ambulation and −4.44 in the naïve group. This was more obvious in the patients between 12 and 18 years and at shoulder and elbow levels.

Our findings suggest that continuing glucocorticoids throughout teenage years and adulthood after loss of ambulation appears to have a beneficial effect on upper limb function.

Keywords: Upper limb; Glucocorticoids; Duchenne muscular dystrophy; Non ambulant; PUL

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1. Introduction

Duchenne muscular dystrophy (DMD) is a progressive X-linked neuromuscular disease, affecting 1 in 3600 live male births. Classically untreated boys lose ambulation by 9.5 years (range 6–12), with respiratory, cardiac and orthopedic complications following in the second decade and premature death. Recent studies have, however, demonstrated that there is a 'new natural history' of the disease [1–3], mainly related to improvements in standards of care [1,4,5], and glucocorticoid (GC) treatment. The effect of GC has also been confirmed by Cochrane reviews concluding that GC treatment should be considered the gold standard as demonstrated by placebo controlled studies that are not available for any other treatment [6]. Recent longitudinal studies have clearly shown a delay in loss of ambulation in boys treated with GC compared to untreated boys [1]. The outcome appears to be also related to the regime of GC with a reported median age at loss of ambulation of 12 years for boys on intermittent regime and of 14.5 years for those on daily treatment [7].

While in the past GC treatment was often only started at the time when DMD boys were showing more difficulties in getting up from the floor or climbing stairs [8], the recently published standards of care suggest that GC treatment should be started earlier, ideally between 4 and 6 years [4,5], with some studies suggesting that GC should be started even before the age of 4 years [9].

There is even less agreement on the time when GC treatment should be discontinued. For many years in several centers the treatment was discontinued at the time boys lost ambulation as it was felt that the risk of gaining weight in patients who were less active was bigger than the possible beneficial effects. A few recent studies, however, have reported a possible beneficial effect of GC [1], but no systematic study has been performed using a scale assessing functional abilities. This is probably also related to the paucity of clinical tools assessing upper limb function in DMD [10].

The Performance of Upper Limb (PUL) test, recently developed as part of an international effort to provide a disease specific assessment for upper limb function in DMD, has proved to be a reliable tool, also suitable in a multicentric setting, for both ambulant and non-ambulant DMD boys and young adults [11,12]. The PUL allows to follow the proximal to distal progression of involvement observed in DMD by assessing various functional abilities in three domains (shoulder, elbow, distal).

The aim of this study was to establish the possible effect of GC treatment on upper limb function by using the PUL in a cohort of non-ambulant DMD boys and adults.

2. Patients and methods

2.1. Patients

The patients included in this study are part of a larger prospective longitudinal study aimed at assessing upper limb function in a larger cohort of ambulant and non-ambulant DMD boys and adults involving 13 tertiary neuromuscular centers. Preliminary cross sectional data of the study at baseline have already been reported [11]. The previous study also reports inter rater reliability. **All clinical evaluators were trained by the same lead physical therapist to ensure standardization of equipment, assessment procedures and scoring.** The study has been approved by the Ethic Committee of each center. Informed consent was obtained from each patient.

As we aimed to establish the possible effect of GC in patients who maintained it after loss of ambulation compared to those who stopped GC at the time when they lost ambulation, in this study we only included non-ambulant patients who had lost ambulation for at least two years. Patients were retrospectively subdivided into three subgroups: a) those who were still on GC after loss of ambulation, b) those who stopped GC at the time they lost ambulation; c) those who were never on GC or who had them while ambulant for less than a year. In order to make the groups comparable we did not include 4 patients above the age of 26 years as they were all untreated.

2.2. PUL

The PUL includes 22 items with an entry item to define the starting functional level, and 21 items subdivided into shoulder level (4 items), middle level (9 items) and distal level (8 items) dimensions. For weaker patients a low score on the entry item means high-level items do not need to be performed. Scoring options vary across the scale between 0–1 and 0–6 according to performance. Each dimension can be scored separately with a maximum score of 16 for the shoulder level, 34 for the middle level, and 24 for the distal level [11]. A total score can be achieved by adding the three level scores (max total score 74).

2.3. Statistical analysis

Baseline PUL was compared across the 3 GC groups adjusting for age using a global test based on a repeated measures ANOVA, considering shoulder, middle and distal PUL assessments as repeated measures on the same subject, with age (<18 and ≥18 years) and GC subgroups as factors. This global test approach gives a unique p value for a difference across GC subgroups of PUL assessments. Post-hoc comparisons using an ANOVA model were run separately for assessing the impact of age and GC subgroup on shoulder, middle and distal assessments.

Twelve-month change was evaluated as a % decrease from baseline; patients with PUL = 0 at baseline were excluded from the analysis of change; patients with a PUL increase over 12 months were set as stable patients (decrease = 0). Differences among 12-month changes were assessed by the non-parametric Kruskal–Wallis test.

3. Results

Ninety-one patients fulfilled the inclusion criteria. Their age ranged between 11.1 and 26.9 years (mean 16.95; SD ± 3.52). Forty-eight were still on GC: 7 of the 48 were on daily steroids (mean dose 0.45 mg/kg/day) and 41 on intermittent (mean dose 0.49 mg/kg/day). Another 25 patients stopped GC at the time when they lost ambulation. The mean age when they stopped

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