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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

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 ambulation between the two subgroups was similar (11.2 and 11.1 years respectively).

The remaining 18 were GC naïve or had GC while ambulant for less than a year.

3.1. PUL

The total scores ranged between 0 and 74 at baseline (mean 41.20).

The mean total scores were 47.92 in the GC group, 36 in those who stopped GC at loss of ambulation and 30.5 in the GC naïve group (Table 1).

Baseline PUL significantly increased passing from shoulder (mean = 1.85) to middle (mean = 19.14) to distal (mean = 20.21, $p < 0.01$) domains (Fig. 1 and Table 1). Baseline PUL was significantly higher in those who never stopped GC than in those who stopped GC or never used GC (global test $p < 0.001$) and was lower in patients with age higher than 18 years (global test, $p < 0.001$).

While in the shoulder PUL was close to zero for all the patients (71% in those who never stopped, 80% in those who stopped and 100% in those who never used GC, $p = 0.006$), the difference was very evident in the middle region (mean in those who never stopped = 24.02, mean in those who stopped = 15.20 and mean in those who never used GC = 11.61, $p < 0.001$). The trend is still present in the distal PUL that is less affected (mean in those who never stopped = 21.17, mean in those who stopped = 19.32 and mean in those who never used GC = 18.89, $p = 0.04$). These differences were significant also adjusting for age.

Overall, shoulder PUL was = 0 in 79% of patients, while middle PUL was = 0 in 4 (4%) patients and distal PUL was higher than 0 in all the patients. Therefore 12-month PUL change was evaluated only in the middle and distal regions. The percentage decrease in the middle PUL was −10% in patients still using GC as compared to −34% and −36% in those who stopped and never used GC respectively ($p < 0.001$). The change was lower (mean = −4.5%) and not significantly different among the GC groups in the distal region ($p = 0.77$).

The 12-month changes ranged between −20 and 4 (mean −4.4). The mean changes were −3.79 in the GC group, −5.52 in those who stopped GC at loss of ambulation and −4.44 in the GC naïve group.

Table 2 and Fig. 2 show details of the changes in the whole cohort and in the subgroups subdivided according to GC treatment.

4. Discussion

The issue of continuing GC treatment after loss of ambulation has not yet reached a full consensus with, until recently, relative lack of available information on efficacy and safety data from the literature. This is also acknowledged by the DMD care guidelines published in 2010 that identify the use of GC therapy in non-ambulatory individuals as an area in need of further research. In the last few years a few studies have provided more evidence of the efficacy of GC treatment on cardiac [13] and respiratory functions and on strength and other functional measures [1,14], but many clinicians still feel that there is not enough evidence to justify the use of GC after loss of ambulation. This is mainly due to the concern that the side effect such as increased weight gain following a reduction of physical activity secondary to loss of ambulation may outweigh the possible beneficial effect.

Our results, using the PUL, a tool specifically developed to assess upper limb function in DMD, suggest that GC has a beneficial effect on upper limb function after loss of ambulation. The GC treated group had an overall better baseline function than the untreated ones. Not surprisingly those who had been on GC until loss of ambulation had better baseline scores than the GC naïve group. The overall difference was more obvious on the middle domain with GC treated patients having significantly higher scores than in the other groups, especially between the age of 12 and 18 years. In this age range most GC treated patients were still able to perform most of the activities exploring functional aspects from the elbow and also had some functional activities at shoulder level that were less present in those who stopped GC steroids at loss of ambulation and even less in the GC naïve group. This trend was confirmed, even if to a lesser extent, also in the patients older than 18 years.

The difference between the GC treated and untreated groups was also obvious in the 12-month changes as the treated group had a slightly slower deterioration than the untreated ones. This again was most obvious in the middle domain and between 12 and 18 years. In contrast at shoulder level the treated group appeared to have more negative changes compared to the untreated ones. This is, however, only due to the fact that the treated group had better baseline shoulder subscores and was therefore more likely to lose points related to the residual shoulder activity while the untreated groups had much lower baseline shoulder subscores (0 in the naïve group) and therefore were more unlikely to lose any further point.

The PUL did not appear to be equally sensitive to capture the differences in the distal domain as most of the items in the distal domain assessing very distal activities such as different pinches were still present even in the older untreated boys.

One of the limitations of this study is that the results in the non-ambulant cohort were part of a larger study also including ambulant boys, and the study was not prospectively designed with a randomized approach to establish the value of different regimens of GC. Even if patients were not prospectively randomized, however, there were no obvious differences in age between the two main groups. The mean ages of the patients who were still on steroids and those who stopped at loss of ambulation were similar, or if anything the latter were even slightly older. The ages when they stopped ambulation were also similar.

Our data provide for the first time evidence that continuing GC after loss of ambulation had a beneficial effect on upper limb function even if most patients were on an intermittent regime and on a relatively low dose as after loss of ambulation the dose is often not adapted to the weight.

The effect of GC was more obvious in the patients between 12 and 18 years and at shoulder and elbow levels. This issue is highly relevant if we consider that the activities assessed at middle domain include activities that are essential for functional activities such as self-feeding or ability to perform positional transfers. Maintaining these activities or slowing the progression leading to their loss is therefore likely to have a significant impact on their activities of daily living and on their overall quality of life. Further studies, using a more systematic prospective approach, will help to clarify the possible effects of different regime steroids or dosage or weight that were not systematically explored in our study.

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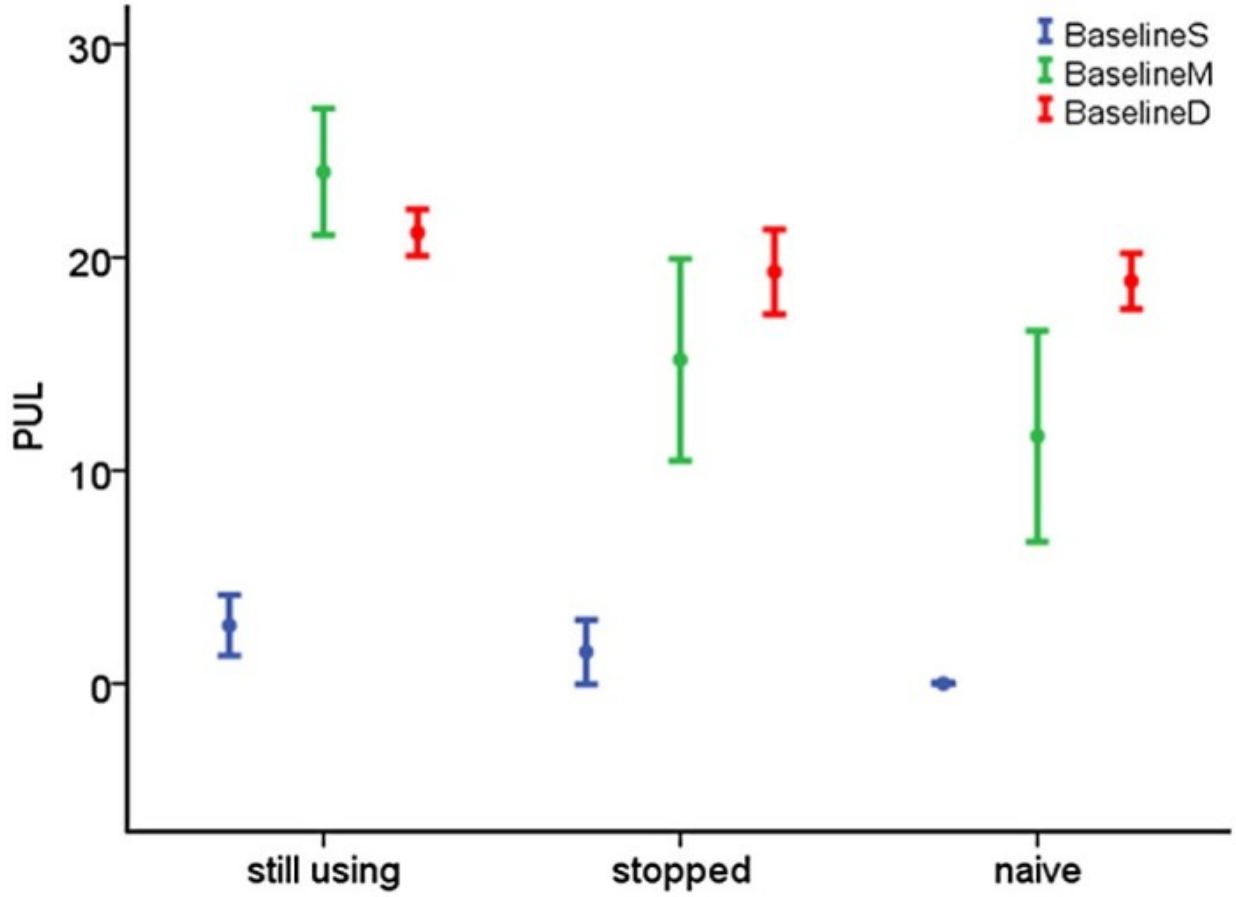
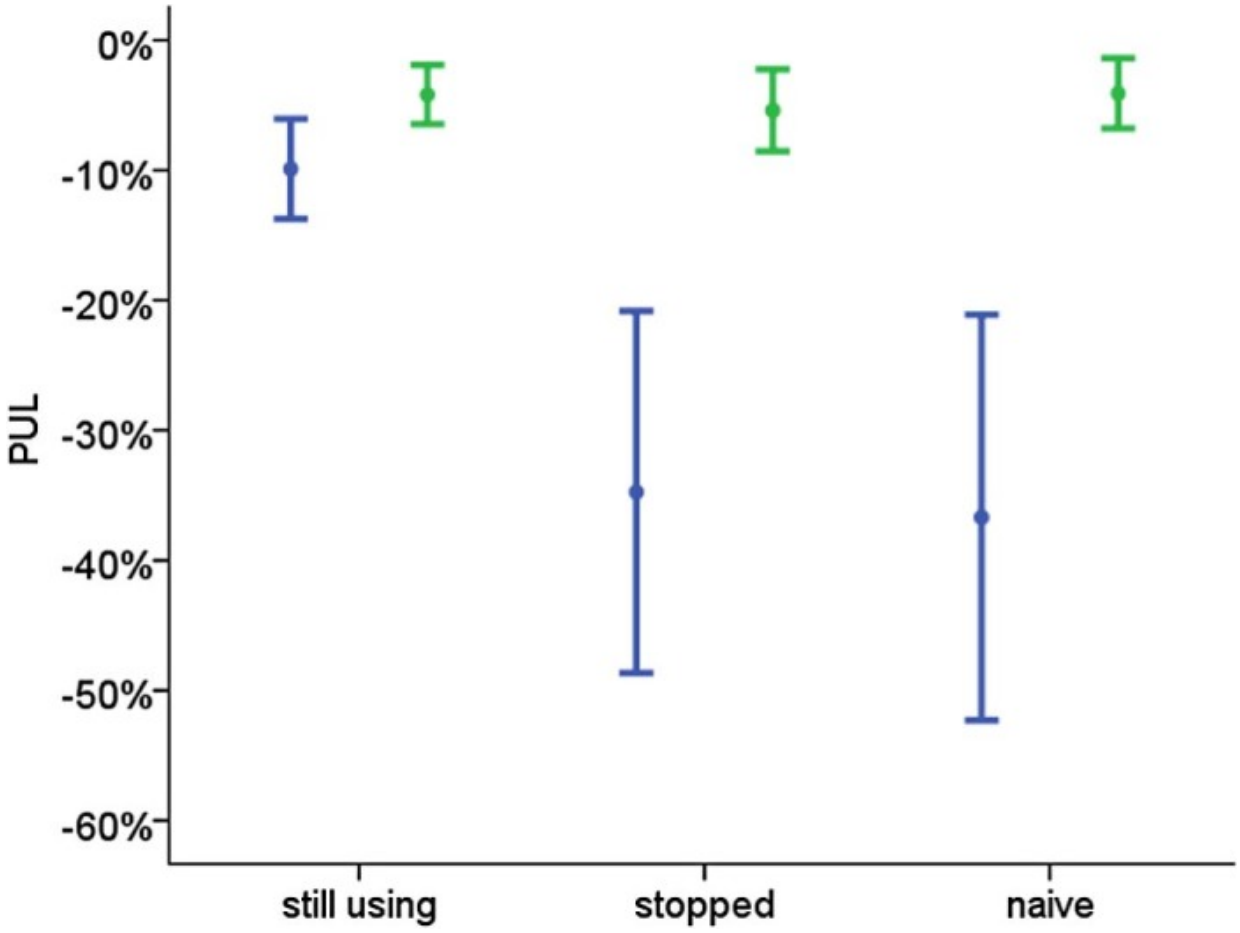
Figures and Tables

Fig. 1



Baseline PUL scores in the shoulder (S), middle (M) and distal (D) domains, according to GC exposure.

Fig. 2



Middle and distal 12-month PUL change decrease (%) according to GC exposure in the middle domain (in green) and in the distal domain (in blue).

Table 1

Baseline values according to age and GC exposure for total PUL score and the three domains.

			AGE	Baseline S	Baseline M	Baseline D	Baseline T
	Still using	Mean	16.98	2.73	24.02	21.17	47.92
	(n = 48)	SD	3.873	4.911	10.245	3.738	16.240
All	Stopped	Mean	16.21	1.48	15.20	19.32	36.00
	(n = 25)	SD	3.060	3.664	11.475	4.828	18.118
	Naïve	Mean	18.03	.00	11.61	18.89	30.50
	(n = 18)	SD	3.050	.000	9.971	2.632	11.927
	Total	Mean	16.98	1.85	19.14	20.21	41.20
	(n = 91)	SD	3.532	4.160	11.707	3.985	17.510
	Still using	Mean	14.77	3.88	25.61	21.61	51.09
	(n = 33)	SD	1.652	5.550	9.083	3.122	15.277
<18 yrs	Stopped	Mean	14.94	1.95	18.68	20.68	41.32
	(n = 19)	SD	1.898	4.116	10.630	3.728	16.783
	Naïve	Mean	15.43	.00	15.11	20.00	35.11
	(n = 9)	SD	1.590	.000	11.152	2.121	12.494
	Total	Mean	14.92	2.70	21.90	21.08	45.69
	(n = 61)	SD	1.710	4.852	10.594	3.216	16.392
	Still using	Mean	21.84	.20	20.53	20.20	40.93
	(n = 15)	SD	2.703	.775	12.035	4.814	16.611
>18 yrs	Stopped	Mean	20.21	.00	4.17	15.00	19.17
	(n = 6)	SD	2.577	.000	5.742	5.692	10.685
	Naïve	Mean	20.64	.00	8.11	17.78	25.89
	(n = 9)	SD	1.402	.000	7.705	2.728	9.918
	Total	Mean	21.16	.10	13.53	18.43	32.07
	(n = 30)	SD	2.393	.548	12.025	4.797	16.339

Table 2

12-month changes according to age and GC exposure for total PUL score and the three domains.

			AGE	12-month changes S	12-month changes M	12-month changes D	12-month changes T
	Still using	Mean	16.98	−1	−2.06	−0.73	−3.79
	(n = 48)	SD	3.873	2.51	3.04	1.63	3.71
All	Stopped	Mean	16.21	−0.08	−4.60	−0.84	−5.52
	(n = 25)	SD	3.060	1.25	6.30	1.40	7.08
	Naïve	Mean	18.03	0	−3.83	−0.61	−4.44
	(n = 18)	SD	3.050	0	4.16	1.37	4.63
	Total	Mean	16.98	−0.55	−3.11	−0.74	−4.4
	(n = 91)	SD	3.532	1.99	4.47	1.51	5
	Still using	Mean	14.77	−1.36	−2.09	−0.64	−4.09

			AGE	12-month changes S	12-month changes M	12-month changes D	12-month changes T
	(n = 33)	SD	1.652	2.93	2.91	1.49	3.76
<18	Stopped	Mean	14.94	−0.11	−5.84	−1.00	−6.95
	(n = 19)	SD	1.898	1.44	6.74	1.41	7.38
	Naïve	Mean	15.43	.00	−4.11	−0.89	−5
	(n = 9)	SD	1.590	.000	4.42	1.83	4.71
	Total	Mean	14.92	−0.77	−3.56	−0.79	−5.11
	(n = 61)	SD	1.710	2.37	4.86	1.50	5.34
	Still using	Mean	21.84	−2.20	−2.00	−0.93	−3.13
	(n = 15)	SD	2.703	0.77	3.42	1.94	3.66
>18	Stopped	Mean	20.21	.00	−0.67	-0.33	−1.00
	(n = 6)	SD	2.577	.000	1.63	1.36	2.96
	Naïve	Mean	20.64	.00	−3.50	−0.10	−3.60
	(n = 9)	SD	1.402	.000	3.89	0.99	4.57
	Total (n = 30)	Mean	21.16	−0.10	−2.23	−0.55	−2.87
		SD	2.393	0.53	3.39	1.58	3.86