

Positive effect of the combination of multilevel contracture release and glucocorticoid treatment in Duchenne muscular dystrophy

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Abstract

Purpose In the 1980s the first results of an early multilevel contracture release (MLCR) in patients suffering from progressive Duchenne muscular dystrophy (DMD) showed a positive effect on ambulation. Despite the demonstrated positive effects of prolongation of walking this treatment is not part of current guidelines. The aim of our study was to evaluate the effect of MLCR as well as its combination with glucocorticoid (GC) treatment on ambulation.

Methods Data of all boys (n = 86) with DMD treated in our outpatient department were analyzed regarding the treatment and loss of independent ambulation. In all, 23 were treated with GC only, ten were operated on, 21 received GC and underwent MLCR and 32 received neither of the two treatments.

Results The analysis of the loss of independent ambulation in our cohort showed a comparable extension of the ambulatory period between the GC-treated and MLCR-treated boys (p = 0.008 and p = 0.005, respectively). Furthermore, an additive effect of both therapies was found; patients with DMD who had both treatments were able to walk two years longer than those with only one of the two treatment options (p < 0.001).

Conclusion Standard GC treatment and early MLCR in lower limbs have an independent positive effect on prolongation of

ambulation in patients with DMD. In our cohort, the combination of both therapies is significantly more effective than each therapy alone. We suggest both should be offered to all DMD patients eligible.

Level of evidence: III

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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive inherited neuromuscular disease caused by mutations in the dystrophin gene leading to progressive muscular dystrophy.¹ The first clinical signs are delayed motor development, followed by frequent falling, the Gower's manoeuvre and eventually loss of ambulation.²

To date, no curative therapy is available for most mutations of the dystrophin gene. Different regimens of steroid intakes are currently the main component of drug therapy for DMD.^{1,3} Glucocorticoid (GC) medication for DMD has numerous effects: preserving muscular function, thereby prolonging ambulation, respiratory function and slowing down the development of scoliosis.¹ Contractures and consecutive skeletal deformities have an impact on ambulation at an early stage of the disease.

In 1983, Rideau et al⁴ published results of an early multilevel contracture release (MLCR) in Duchenne patients showing a positive effect on ambulation which was reinforced by Forst and Forst.^{2,5} Despite the proven positive effects of prolongation of walking up to two years after MLCR, the procedure is not part of current international guidelines.^{1,6}

The aim of our study was twofold: to assess the influence of our regime of MLCR on ambulation and to check whether the combination of surgery and GC treatment could enhance the described positive effects.

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Patients and methods

The DMD patient cohort treated in our outpatient clinic between 2013 and 2017 was analyzed retrospectively. Included were all boys with genetically proven DMD who were diagnosed and treated at our institution, thereby ensuring only ambulatory boys were in the cohort. All ambulatory patients were offered steroid treatment (0.9 mg/kg body weight (BW) deflazacort or 0.75 mg/kg BW prednisolone). All patients received non-standardized physiotherapy.

All patients with incipient contractures of the hip, knee and ankle joints and/or shortening of the iliotibial band were offered MLCR if certain prerequisites were met.² These prerequisites were sufficient quadriceps strength defined as a total muscle power of at least 3/5 on the muscle power scale (Medical Research Council, MRC) and being able to rise from a supine position to standing in less than 5 seconds.² The MLCR includes a release of the spina muscles (sartorius muscle, tensor fasciae latae muscle, both heads of the rectus femoris muscle), resection of the gluteal fascia, complete aponeurectomy of the iliotibial band, tenotomy of the medial hamstrings, chevron-like fasciotomy of the lateral hamstrings, lengthening of the Achilles tendon and transfer of the tibialis muscle posterior if necessary.²

Postoperatively, below-knee soft casts were applied for two weeks. The boys were mobilized out of bed on the

first postoperative day. They received intensive inpatient or outpatient physiotherapy for four to six weeks. None of them was treated with splints or orthoses after surgery.

The patient cohort was divided in four groups with regard to the treatment: 23 boys had been treated with GC medication (GC only group), in ten patients a MLCR had been performed (MLCR group), 21 boys had been treated with GC medication and MLCR (MLCR+GC group) and in 32 both treatments were declined (no treatment). As soon as the diagnosis is confirmed the parents are acquainted with the treatment options in an interdisciplinary clinic (paediatric neurologist, paediatric orthopaedic surgeon, physiotherapist, social worker). The individual therapy regime was decided by the parents after a detailed consultation with the paediatric neurologist as well as the paediatric orthopaedic surgeon.

Kaplan Meier curves were generated for the different groups to evaluate the loss of ambulation. Loss of ambulation was defined as loss of the ability to walk more than 10 metres independently. Differences between the groups were tested for significance using the log rank test. To take into consideration the alpha-error changes due to multiple testing, the Bonferroni-Holm correction was applied.

Results

In total, 86 patients with confirmed DMD were included in this analysis. Their mean age at last follow-up was 16.2

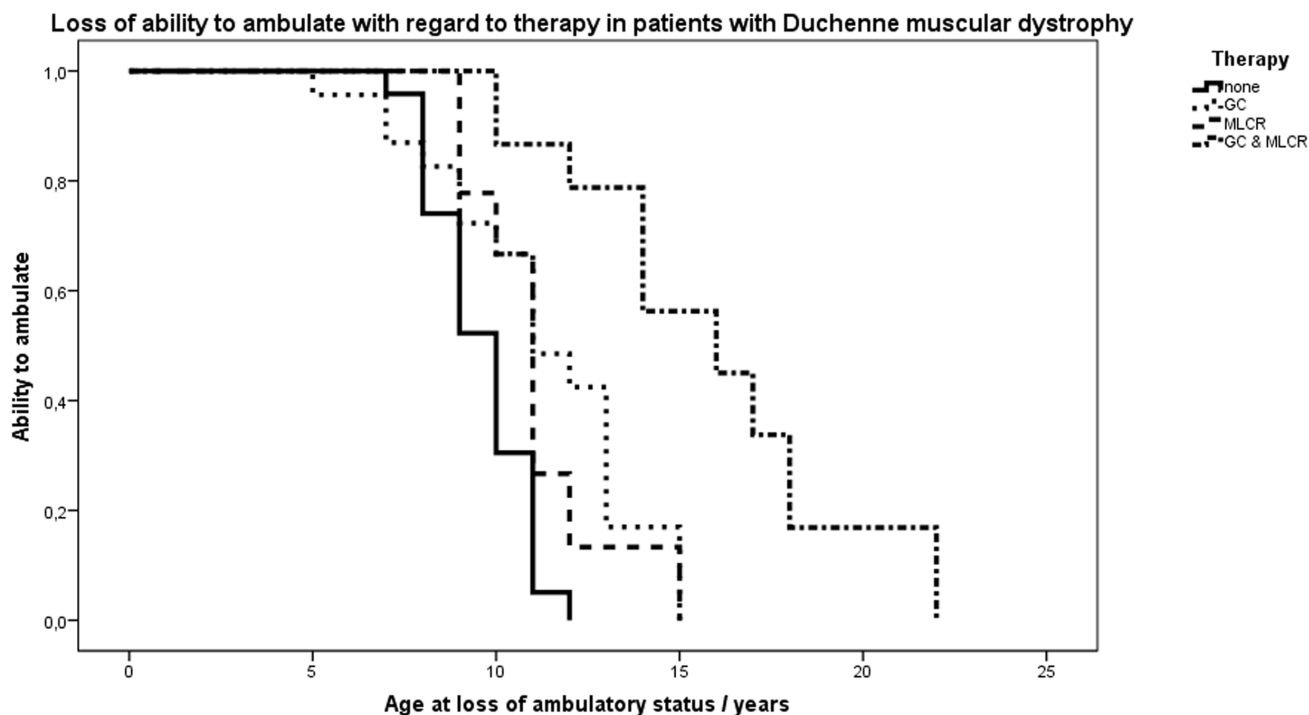


Fig. 1 Loss of the ability to ambulate with regard to therapy in patients with Duchenne muscular dystrophy (GC, glucocorticoid; MLCR, multilevel contracture release).

years (SD 8.4). Out of the 86 boys 23 (27%) had been treated with GC only. Ten patients (12%) had a MLCR according to Rideau^{2,4,5} at a mean age of 7.0 years (SD 1.7). In total, 21 boys (24%) received GC and underwent contracture release, while 32 patients (37%) received neither of the two treatments. The Kaplan-Meier survival curves are shown in Figure 1.

Patients having received neither GC treatment nor MLCR lost ambulation at a mean age of 9.6 years (SD 0.28; 95% confidence interval (CI) 9.0 to 10.1). Patients on GC medication were able to walk up until a mean age of 11.2 years (SD 0.6; 95% CI 10.0 to 12.5) which is significantly longer than without drug or surgical treatment ($p = 0.009$). Patients who received MLCR lost ambulation at a mean age of 11.1 years (SD 0.7; 95% CI 9.8 to 12.4) which is also longer than without any of the two therapies, but not significantly after Bonferroni-Holm alpha-error correction ($p = 0.066$). Patients with the combined treatment of GC medication and surgery were able to walk independently up to an age of 14.9 years (SD 1.2; 95% CI 13.5 to 18.3) which is significantly longer than with no therapy ($p < 0.001$) as with only one of the two (*versus* GC only $p = 0.008$; *versus* MLCR only $p = 0.005$).

Discussion

Our retrospective study of 86 patients with DMD for whom the parents decided about the therapy confirms the positive effect of the combination of MLCR and GC medication on ambulation in DMD patients.^{2,4,5,7-9} Although we were able to include 86 patients in our cohort of this rare disease, the subgroups were small and differed in size. The early appointments at our institution gave the opportunity to counsel parents and carers about the treatment options from the beginning. Nevertheless, the decision making by the parents (proxy) could create bias, which we tried to minimize by offering all treatment options to all patient eligible. It seemed the only kind of allocation given the ethical presumptions by randomization. The end point of the loss of ambulation was chosen because so far there are no uniform recommendations and it seemed feasible.

The analysis of the loss of independent ambulation in our cohort showed a comparable extension of the ambulatory period between the GC-treated and MLCR-treated boys. Interestingly, not only could we replicate both the positive effects of GC treatment and lower limb surgery as single treatments but show an additive effect on ambulation by combining both treatment options. Despite this, the MLCR is regarded with reservations. One concern expressed by some authors is the acceleration of the loss of ambulation following MLCR.^{1,6,10} However, this is less likely to occur if the published functional prerequisites are followed.^{2,4} These are valid criteria to define the early

ambulatory stage. By applying these concise function tests it is possible to avoid the above mentioned negative surgical outcomes in the majority of cases as the analysis of our cohort reveals.

The correct time of surgery is the first step to appraise the results regarding MLCR. The second one is the adherence to all steps of MLCR to prolong the ambulation of DMD patients. The idea of MLCR according to Rideau et al⁴ is to release the antagonists of the antigravity muscles to provide the latter with the possibility to work effectively despite decreasing strength. Hence, it seems quite predictable that this effect cannot be achieved if the muscles have already become too weak or the limb girdle was not addressed in patients with DMD which is well known to start on the pelvic level. Thus, the studies presenting negative results after MLCR either included patients who passed the early stage of ambulation^{6,10,11,12} or did not adhere completely to the pathoanatomical concepts of Rideau et al.^{1,6,10,13}

GC treatment on the other hand is a well-accepted symptomatic therapy for DMD which is included in the major treatment guidelines.^{3,14} This is probably due to the better evidence when compared with MLCR.³ Despite the advantages of the GC medication, the adverse effects – weight gain, hypertonia, behavioural changes and osteopenia¹⁴ – deter quite a few families from this treatment.

Little evidence exists for the positive effects of the ubiquitous stretching therapy as well as orthotics.¹⁵

Thus, there exists a number of more or less validated, non-curative options to supply the families' need for treatment. All of them should be provided to patients and parents until a curative therapy is available.

So far, it could not be proved that patients after MLCR developed less severe contractures than patients who were not operated on. Due to the prolongation of ambulation by GC as well as lower limb surgery according to Rideau et al⁴ it seems feasible to assume that the latter has the potential to have a similar effect. This point, as well as the precise analysis of the functional changes after MLCR, should be the aim of future investigations.

Conclusion

Standard GC treatment and early MLCR in lower limbs have an independent and positive effect on prolongation of ambulation in DMD patients. The combination of both therapies is significantly more effective than each single therapy. To our knowledge, this is the first evidence for a significant positive effect of combining GC treatment with early multilevel contracture release in order to prolong ambulation in DMD patients. Therefore, in our opinion early MLCR should be offered to all DMD patients eligible and its inclusion in the major treatment guidelines should be considered.

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COMPLIANCE WITH ETHICAL STANDARDS

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ETHICAL STATEMENT

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was not needed for individual participants included in the study as per advice by the ethical committee reviewing and approving this retrospective study (EA2/061/18).

ICMJE CONFLICT OF INTEREST STATEMENT

None declared.

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AUTHOR CONTRIBUTIONS

CW: Main author of manuscript, Study design, Data collection and analysis.

CS: Study design, Data collection and analysis.

DB: Data collection.

JF: Data analysis, Manuscript revision.

SL: Interpretation of study material, Manuscript revision, Data analysis, Senior author.

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