Gait & Posture 33 (2011) 147–151

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

ESMAC – Best Paper award 2009 – Runner UP

Botulinum toxin A injections do not improve surface EMG patterns during gait in children with cerebral palsy—A randomized controlled study

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ARTICLE INFO

Article history:
Received 18 February 2010
Received in revised form 3 August 2010
Accepted 30 August 2010

This paper was selected by an ESMAC Reading Committee headed by Professor Maria Grazia Benedetti. The present paper was edited by Tim Theologis.

Keywords:
Cerebral palsy
Multilevel BTX-A
Surface EMG

ABSTRACT

Children with cerebral palsy who walk with knee flexion during midstance are treated with intramuscular injections of botulinum toxin A (BTX-A) to prevent them from potential deterioration and to improve their mobility. The present study evaluates the effect of this treatment on the muscle activation patterns of the rectus femoris, medial hamstrings and gastrocnemius medialis during gait. Twenty-two children (aged 4–11 years) with cerebral palsy, who walked with knee flexion, were randomly assigned to an intervention group (multilevel BTX-A injections combined with comprehensive rehabilitation) or a control group (usual care). Sagittal and frontal video recordings were made of gait, together with simultaneous surface electromyography recordings of the rectus femoris, medial hamstring and gastrocnemius medialis muscles, before and six weeks after treatment. Abnormal muscle activation patterns were quantified, after gain-normalisation, according to the root mean square difference (RMSD), which is the difference relative to normal patterns. Six weeks after the treatment the RMSD of the gastrocnemius medialis muscles in the intervention group changed significantly, showing a deterioration ($p < 0.05$). This study demonstrated that BTX-A injections do not result in an improvement in lower limb muscle activation patterns during gait. In spite of this lack of direct effect on muscle activation patterns, the combination of BTX-A injections and comprehensive rehabilitation was effective in improving gait kinematics.

1. Introduction

Cerebral palsy (CP) is a clinical syndrome, characterised by a persistent disorder in motor control and posture, resulting from non-progressive brain damage [1]. The most common type of motor disorder in children with CP is spastic paresis [2], which is characterised by a posture and movement-dependent tone regulation disorder [3].

In children with spastic paresis, three types of symptoms can be distinguished: impairment of muscle activation, impairment of muscle stiffness, and impairment of muscle length [3]. These symptoms cause deviating gait patterns, resulting in movement disabilities in these children [4].

A typical deviating gait pattern in children with CP is knee flexion during midstance [3]. If these children do not receive adequate treatment, the amount of flexion of the knee in midstance may increase during growth [5] and this, in turn, may lead to a deterioration in mobility [6]. It is thought that this flexion pattern is a result of muscle imbalance, caused by a combination of the three earlier mentioned symptoms [3], and increased involuntary muscle activity (a symptom of impaired muscle activation) is considered to be the main contributor. This increase in involuntary muscle activity occurs, in particular, in the following muscles of the lower limb: the medial hamstrings, psoas, rectus femoris and gastrocnemius muscles [7]. One type of treatment that is currently applied to reduce muscle activity is intramuscular injections with botulinum toxin type A (BTX-A) [8]. BTX-A gives a reversible neuromuscular blockade, which results in a local and dose-dependent muscle weakness [9]. It has recently been demonstrated that when BTX-A injections in agonistic muscles are combined with muscle lengthening and/or antagonistic muscle strengthening exercises, this can improve mobility in children with CP, associated with an improvement in knee angle (i.e. decreased flexion) in midstance [7,10].

Muscle activation patterns during gait can be measured with surface electromyography (sEMG) and this makes it possible to

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0966-6362
doi:10.1016/j.gaitpost.2010.11.001

measure the increase in involuntary muscle activity [11–14], for instance, by assessing the abnormalities in amplitude or abnormalities in the sEMG pattern. However, the sEMG amplitude depends on various factors, for example the thickness of the subcutaneous tissue and the placement of the electrodes [15]. Therefore, in order to compare sEMG patterns (which are determined by the combination of timing and amplitude), inter- and intra-individual normalisation of the amplitude is needed. Hof et al. [16] described a method that can be used to normalise sEMG amplitudes by determining a gain factor and normalising the sEMG with this gain factor. This normalised sEMG profile can be identified as normal or abnormal by comparing it with standard sEMG profiles [16].

Several studies have investigated the effect of intramuscular BTX-A injections on the sEMG patterns of children with CP [17–24]. The children in these studies walked with equinus gait (with or without knee flexion), so their gastrocnemius muscles were treated. In one randomised study [24] no difference in sEMG patterns was found between BTX-A-injected and placebo-injected muscles. Of the other studies, which were either non-randomised [17,20–23] or non-controlled [18,19], four found no differences in sEMG patterns after the injections [17,19,20,23], but two other studies found an improvement in the sEMG patterns [21,22]. One other study investigated the effect of the injections on the amplitude of sEMG activity, instead of the pattern. In that study the hamstring muscles were also injected, a decrease in sEMG activity was found in both the gastrocnemius and the hamstring muscles [18].

When children walk with knee flexion during midstance, multiple muscles might contribute to this gait pattern, and these can all be treated in one single session. This is referred to as multilevel treatment, and usually involves at least the (medial) hamstring muscles, and sometimes also the gastrocnemius medialis, psoas and rectus femoris muscles. The aim of the present study was to evaluate the effect of multilevel BTX-A injections on the sEMG patterns of the rectus femoris, medial hamstring and gastrocnemius medialis muscles during gait. Indication for injection in these muscles is based on activity during an abnormal period of the stride [7]. It was hypothesized that multilevel BTX-A injections would improve and possibly normalise muscle activation patterns.

2. Methods

2.1. Subjects

All the children who were assessed in the present study were participants in a multicenter trial. The inclusion and exclusion criteria for these children are listed in Table 1. For the selection and randomisation procedures of this multicenter trial, see Scholtes et al. [7]. Only those children who were assessed in the Department of Rehabilitation Medicine of the VU University Medical Center in Amsterdam [7,10], and those who were able to walk six strides successfully, participated in the present study ($n = 22$).

Full written informed consent was obtained from the participants' parents and all 12 year-old children before participation, and the study protocol was approved by the Medical Ethics Committee of the VU University Medical Center.

2.2. Measurements

2.2.1. Dynamic video electromyography

The sEMG patterns of the following muscles were bilaterally assessed during gait: the rectus femoris, the medial hamstrings and the gastrocnemius medialis.

The sEMG signal was recorded by two electrodes on each muscle, with an inter-electrode distance of 20 mm (Kendall: Ag/AgCl electrodes; pre-gelled, 10 × 10 mm electrode area), as recommended by the SENIAM project [28]. The reference electrode was placed on the patella or the wrist. All electrodes were connected to the 16-channel pre-amplifier and telemetric transmitter that was carried on the child's back (BioTel99, Glonner electronics GmbH, Krailling, Germany). All sEMG signals were sampled from the receiver at 1000 Hz, using Labview custom-made acquisition software, and high-pass filtered to remove movement artefacts through a third-order Butterworth high-pass filter at 20 Hz. The sEMG signals were displayed on-line for inspection of the signal quality. They were rectified off-line, and smoothed with a 2 Hz second-order Butterworth low-pass filter to obtain the linear envelope.

While the sEMG signals were being recorded, (digital) video-recordings were also made of both the frontal and the sagittal planes, while the child walked barefoot at a comfortable walking speed (with or without walking aid) on a 10-m pathway. The vertical interval time (VIT) coding of video frames [29] as used to identify initial contacts of six completed strides at constant walking velocity from the video-recordings. Using these time-codes, the sEMG envelopes could be processed into a time-normalised sEMG profile per stride (i.e. from 0 to 100% of the stride). These sEMG envelopes were used to calculate the total average sEMG profile.

The total average sEMG profile was then gain-normalised according to the method described by Hof et al. [16], after which abnormal muscle activation patterns were quantified according to the root mean square difference (RMSD), which is the difference relative to normal patterns [30]. All signal processing was performed with custom software written in Matlab (Mathworks Inc., Massachusetts, USA, version 5.3). The smaller the RMSD, the closer the sEMG pattern is to normal; an increase in the RMSD implies a deterioration in the sEMG pattern. All measurements were performed by one independent, blinded, research assistant (LH).

2.3. Assessments

After the first (baseline) assessment the children were randomly assigned to the intervention group or the control group. The children in the intervention group had one follow-up assessment six weeks after the treatment; children in the control group had a second baseline assessment (Fig. 1).

2.4. Intervention

The children of the intervention group received multilevel BTX-A injections (BOTOX®, Allergan, Nieuwegein, the Netherlands), followed by comprehensive

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Diagnosis of Cerebral Palsy	BTX-A treatment in lower extremities within 16 weeks before inclusion
Spastic hemiplegia or diplegia[a]	Orthopaedic surgery within 24 weeks before inclusion
Age between 4 and 12 years	Contra-indication for BTX-A
Spasticity in two or more lower extremity muscle groups interfering with mobility	Contra-indication for general anaesthesia
	Orthopaedic deformities which have a bad influence on walking
GMFCS level I to IV	(sub)luxation of the hip with a MI > 50°
Gait characterized by persistent flexion of the knee (≥10°) in mid-stance (barefoot or with ankle-foot-orthoses/shoes)	hip endorotation contracture >15°
	flexion contracture of knee >15°
Two or more muscle groups in one limb needing BTX-A injection	Severe fixed contractures:
	age <8 years
	ankle dorsiflexion with knee extended >−20°
Ability to carry out instructions	popliteal angle >90°
Adequate knowledge of the Dutch language	age ≥8 years
Able to walk six strides successfully[b]	ankle dorsiflexion with knee extended >−15°
Patient evaluated in the Department of Rehabilitation Medicine at the VU University Medical Center in Amsterdam[b]	Popliteal angle >80°
	Presence of ataxia or dyskinesia
	Other problems which have a negative influence on walking

[a] According to Hagberg [25].
[b] Added inclusion criteria for the current study, BTX-A: botulinum toxin A; GMFCS: gross motor function classification system [26]; MI: migration index [27].

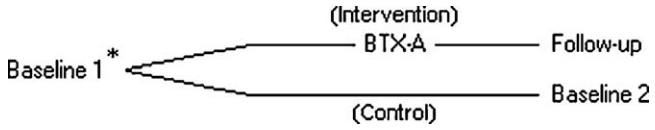

Fig. 1. Schematic design of the moment of assessments. *Randomisation took place after the first baseline assessment.

rehabilitation. The injections were given under general anesthesia, in at least two sites per muscle belly, up to a maximum of 50 Units per site, with a dosage of 4–6 U/kg body weight per muscle group. The maximum total dose was set at 25 U/kg body weight for children ≤5 years, and 30 U/kg body weight for children >6 years, with a maximum recommended dose of 600 U and a dilution of 50 U in 1 ml 0.9% NaCl solution. The injection sites were determined by palpation of the muscle belly, and placement of the needle was verified by stretching of the muscle, controlled for needle movement. Target muscles were identified according to the principles described in Scholtes et al. [7]

The comprehensive rehabilitation consisted of intensive physiotherapy for 12 weeks, three–five times a week, serial casting and/or orthoses. For further details concerning the comprehensive rehabilitation plan, see Scholtes et al. [7,10].

The children of the control group continued with usual care. After the control period, they also received multilevel BTX-A injections, followed by comprehensive rehabilitation.

2.5. Statistical analyses

Six weeks after the treatment the change in the RMSD of the injected muscles in the intervention group was compared with the change in the RMSD of the muscles with treatment indication in the control group. The change in the RMSD in the intervention group was calculated between baseline and the six-week follow-up; in the control group it was calculated between the first and the second baseline measurements. The differences in effect between the two groups were analysed in a linear mixed model analysis (SPSS 11.5).

3. Results

3.1. Patient demographics

The characteristics of all participating children are presented in Table 2.

All the children received multilevel injections in at least one of their limbs, and the sEMG of the rectus femoris, the medial hamstrings and the gastrocnemius medialis were analysed in the present study. The total number of injected muscles can also be found in Table 2. The most frequently injected muscles were the medial hamstrings (86%) and the gastrocnemius medialis (64%): the rectus femoris was only injected in a few children (20%).

3.2. Baseline differences

There was no difference between the two groups with regard to personal characteristics, as summarized in Table 2.

3.3. Effects of BTX-A injections on sEMG patterns of injected muscles

The effects of BTX-A injections on the sEMG patterns of the injected muscles are presented in Table 3. Six weeks after the BTX-A treatment there was no significant improvement or deterioration in the sEMG patterns of the rectus femoris (RMSD −1.03, $p = 0.73$) or the medial hamstrings (RMSD 3.74, $p = 0.22$), compared to the control group. However, in the sEMG pattern of the gastrocnemius medialis (RMSD 13.98, $p = 0.04$) there was a significant deterioration, compared to the control group (Fig. 2).

4. Discussion

In this study the effect of treatment with multilevel BTX-A injections and comprehensive rehabilitation on sEMG patterns during gait was evaluated in children with CP who walked with flexion of the knee in midstance. Six weeks after the treatment only the gastrocnemius medialis showed a significant increase in RMSD, which indicates a deterioration of the sEMG pattern. The RMSD in the rectus femoris and the medial hamstring muscles remained unchanged. Therefore, we concluded that multilevel BTX-A injections do not result in any improvement in lower limb muscle activation patterns during gait.

Various different normalisation and non-normalisation methods can be used to make the sEMG pattern suitable for research; in the present study we used the normalisation method described by Hof et al. [30] After normalisation we compared the sEMG patterns

Table 2
Characteristics of all participating children and number of injected muscles.

Group (*n*)	Age (yr) Mean (S.D.) [range]	Weight (kg) Mean (S.D.) [range]	Sex (*n*) m:f	Diagnosis (*n*) uni:bi	GMFCS (*n*) I:II:III	ml-BTX-A (U/kg) Mean (S.D.) [range]	Injected muscle (N)		
							RF	MH	GAM
Intervention (12)	7.95 (2.34) [4.14–10.84]	26.00 (8.23) [15.0–45.0]	7:5	1:11	6:0:6	17.97 (4.61) [10.97–24.78]	4	21	12
Control (10)	7.17 (1.84) [4.43–10.47]	23.75 (9.50) [13.0–44.0]	7:3	0:10	3:3:4	20.43 (5.54) [12.00–27.14]	5	17	16

n, number of children; S.D., standard deviation; m, male; f, female; uni, unilateral; bi, bilateral; GMFCS, Gross motor function classification system [34]; ml-BTX-A, multilevel botulinum toxin A; U, Units; *N*, number of limbs; RF, rectus femoris; MH, medial hamstrings; GAM, gastrocnemius medialis.
This table shows characteristics of all participation children. After the control period, children of the control group were treated with multilevel botulinum toxin A injections. Their treatment characteristics are also presented in this table, for comparison only.

Table 3
Effect on root mean square difference (RMSD).

Muscle	RMSD of the intervention group			RMSD of the control group			Effect (95% CI) on the RMSD	*p*-Value
	Baseline 1	Follow-up	Δ	Baseline 1	Baseline 2	Δ		
RF	36.00	34.00	−2.00	35.67	34.69	−0.98	−1.03 (−7.39 to 5.34)	0.73
MH	46.56	53.84	7.28	53.00	56.54	3.54	3.74 (−2.25 to 9.72)	0.22
GAM	41.57	56.40	14.83	44.76	45.61	0.85	13.98 (0.65–27.31)	0.04

Δ, change from baseline 1; RF, rectus femoris; MH, medial hamstrings; GAM, gastrocnemius medialis.
RMSD of the intervention group and the control group at different measurement points and effect (mean differences in change between the two groups, corrected for baseline differences) on the RMSD six weeks after treatment with BTX-A.

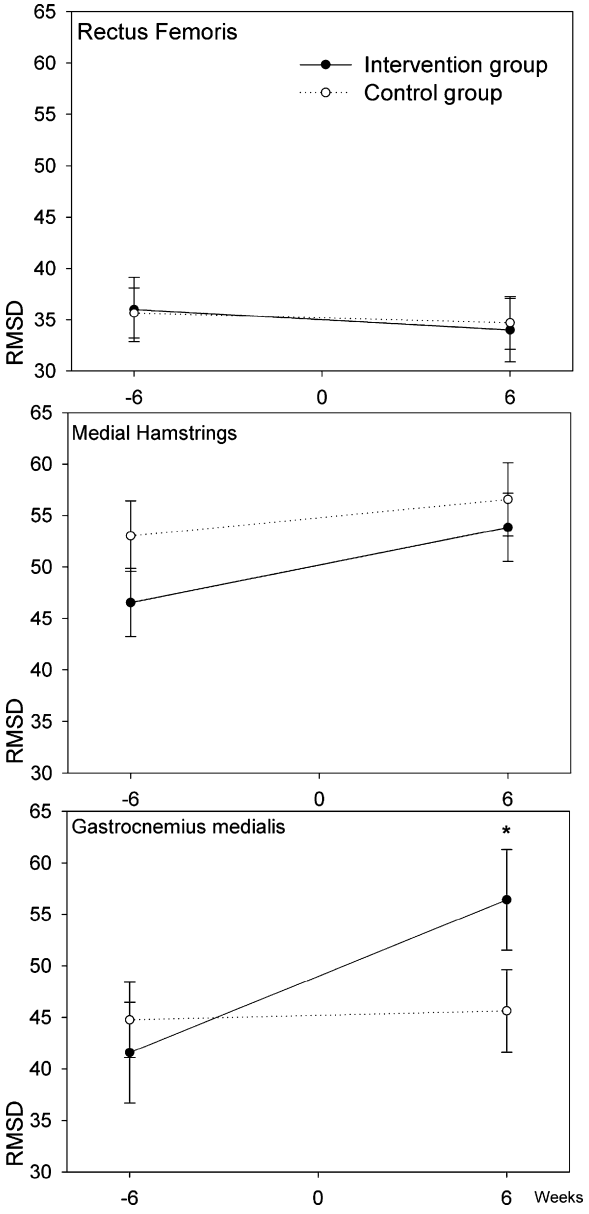

Fig. 2. Estimated mean values in root mean square difference (RMSD) of the rectus femoris, medial hamstrings and gastrocnemius medialis in the intervention group and the control group. *A significant difference in change from baseline between the two groups. On the horizontal axis: weeks before/after botulinum toxin A injections in the intervention group. On the vertical axis: RMSD. The smaller the RMSD, the closer the sEMG pattern is to normal.

with those of normal healthy adults, as also described by Hof et al. [30]. The RMSD describes the amount of sEMG deviation from the reference sEMG pattern, derived from normal gait. This means that the RMSD should be interpreted with care, because it is calculated from a complete sEMG pattern. An unchanged RMSD does not mean that the sEMG pattern gets closer to normal and this does not imply that changes did not occur. Changes in the opposite direction in different parts of the gait cycle (i.e. a decrease in one part, and an increase in another) might cancel each other out when the RMSD is calculated. Thus, it would be interesting to investigate the effect on certain points during the stride, in which involuntary muscle activity is specifically increased. However, whether it is possible to define such points during the stride is, as yet, unknown. They probably need to be determined for each separate muscle and for each different type of gait, because a certain amount of muscle activity can be regarded as gait-specific; abnormal muscle activity cannot be regarded per definition as 'involuntary' muscle activity [31].

As mentioned earlier, we compared the sEMG patterns of children with normal sEMG patterns, based on the sEMG patterns of ten healthy young men (mean age 22 years) [30]. However, it is unlikely that the sEMG patterns of children are identical to the sEMG patterns of adults. Sutherland et al. [32] investigated the sEMG patterns of typically developing children between one and seven years of age. They concluded that with increasing age most sEMG patterns become identical to the sEMG patterns of adults; only the sEMG pattern of the gastrocnemius was found to be identical to that of adults from the early age of two [32]. Furthermore, Berger et al. [33] concluded that the sEMG patterns of children aged six years and older are identical to those of adults. In our study, only five children were under six years of age, and this might have influenced our results. Therefore, more research is needed to investigate whether sEMG patterns of children are comparable with those of adults. Research is also needed to assess the homogeneity of the sEMG patterns of typically developing children, in order to determine whether or not it is possible to conclude that the sEMG patterns of children with CP deviate significantly from the sEMG patterns of typically developing children.

In addition, sEMG patterns strongly depend on walking speed [30]. For children with CP it is not easy to walk at a pre-defined walking speed, so the children in our study were instructed to walk at their own comfortable walking speed. Unfortunately, however, walking speed was not measured in our study, so any negative effects in this respect could not be accounted for.

Other studies [17–24] that have investigated the effect of BTX-A injections on sEMG patterns in children with CP did not use the RMSD method. The children in these studies walked with equines gait, so only the gastrocnemius muscles were injected and evaluated. Only two of these studies [21,22] found an improvement in the sEMG patterns. However, the first study used the area of the burst, which depends on both absolute amplitude (not normalised) and timing [21], and in the second study it remained unclear as to what kind of change the improvement was based on [22]. One other study [18] also injected and evaluated the hamstring muscles and found a decrease in sEMG activity, but because this study evaluated sEMG activity and not sEMG patterns, it is difficult to compare the results with results of our study. Five other studies [17,19,20,23,24] (including one placebo-controlled randomized study) found no differences in sEMG patterns after injection with BTX-A.

Sutherland et al. [23] postulated that there is no reason to expect changes in sEMG patterns of the gastrocnemius muscle, because muscles remain under abnormal central nervous control. Indeed, the fixed upper motor lesion in CP, leading to aberrant supra spinal control, is not likely to be effected by peripheral changes such as chemical denervation of the muscle. However, during gait sEMG patterns do not only directly result from supraspinal control, but they also adapt to changes in the biomechanics of certain gait patterns [31]. So, in order to explain the deterioration of the sEMG pattern of the gastrocnemius medialis, it is necessary to further analyze the sEMG levels for different phases of gait. Such analysis should also include changes in muscle length as a result of changes in gait kinematics [34].

However, despite the lack of change or deterioration in the sEMG patterns of the gastrocnemius medialis, the children in our previous published study showed significant improvements in gait kinematics after treatment with BTX-A [7], as found in other studies [35,36]. Therefore, with respect to the direct effect of muscle denervation on muscle activation patterns, the decrease in deteriorating effects resulting from involuntary contractions might eventually be more beneficial, as opposed to the equal loss

of effective voluntary contractions, to improve gait kinematics. It is thought that gait deviations are the result of muscle imbalance, caused by an impairment not only in muscle activation, but also in muscle stiffness and muscle length [3]. The improvement in gait kinematics might therefore also be explained by decreasing the excessively expression at one side of the balance. This might be the result of multilevel BTX-A injections combined with comprehensive rehabilitation [7,35,36], aimed at (antagonistic) muscle stretching and lengthening. The overall effect of BTX-A injections might therefore also depends on the effectiveness of a comprehensive rehabilitation program at the level of gait kinematics.

In conclusion muscle denervation with BTX-A injections has no effect, or a negative effect on muscle activation patterns, based on root mean square difference analysis. However, evaluation at the level of gait analysis showed that the application of BTX-A and comprehensive rehabilitation as a combined treatment program is still an effective way to improve gait kinematics [7].

Acknowledgements

We are grateful to all the children and their parents for their dedicated and enthusiastic participation in this study. The study was supported by a grant from the Johanna Kinderfonds (2000/0145), the Prinses Beatrix Fonds (PGO01-134) and the Stichting Bio-Kinderrevalidatie in the Netherlands.

Conflict of interest statement

The authors declare that they have no conflict of interests.

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