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Lecture

Single-event multilevel surgery, but not botulinum toxin injections normalize joint loading in cerebral palsy patients

S. Van Rossom[a,*], H. Kainz[a,e], M. Wesseling[a], E. Papageorgiou[b], F. De Groote[a], A. Van Campenhout[c,d], G. Molenaers[c,d], K. Desloovere[b], I. Jonkers[a]

[a] Human Movement Biomechanics Research Group, Department of Movement Sciences, KU Leuven, Leuven, Belgium
[b] Research Group for Neurorehabilitation, Department of Rehabilitation Sciences, KU Leuven, Belgium
[c] Organ Systems, Department of Development and Regeneration, KU Leuven, Belgium
[d] Department of Orthopedics, University Hospitals Leuven, Leuven, Belgium
[e] University of Vienna Centre for Sport Science and University Sports Department of Biomechanics, Kinesiology and Computer Science, Austria

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ABSTRACT

Background: Many patients with cerebral palsy present a pathologic gait pattern, which presumably induces aberrant musculoskeletal loading that interferes with natural bone growth, causing bone deformations on the long term. Botulinum toxin interventions and single-event multilevel surgeries are used to restore the gait pattern, assuming that a normal gait pattern restores musculoskeletal loading and thus prevents further bone deformation. However, it is unknown if these interventions are able to restore musculoskeletal loading. Hence, we investigated the impact of botulinum toxin injections and single-event multilevel surgery on musculoskeletal loading.

Methods: Gait data collected in 93 children with bilateral cerebral palsy, which included pre- and post multilevel botulinum toxin (49 children) and single-event multilevel surgery (44 children) assessments, and 15 typically developing children were retrospectively processed using a musculoskeletal modelling workflow to calculate joint angles, moments, muscle and joint contact force magnitudes and orientations. Differences from the typically developing waveform were expressed by a root-mean square difference were compared using paired *t*-tests for each intervention separately (alpha < 0.05).

Findings: Botulinum toxin induced significant changes in the joint angles, but did not improve the muscle and joint contact forces. Single-event multilevel surgery induced significant kinematic and kinetic changes, which were associated with improved muscle and joint contact forces.

Interpretation: The present results indicate that botulinum toxin injections were not able to restore normal gait kinematics nor musculoskeletal loading, whereas single-event multilevel surgery did successfully restore both. Therefore, single-event multilevel surgery might be protective against the re-occurrence of bone deformation on the longer term.

1. Introduction

Patients with cerebral palsy (CP) often present a gait pattern that is characterized by abnormalities due to aberrant musculoskeletal geometry, decreased selective motor control and increased muscle tone (Rosenbaum et al., 2007; Wren et al., 2005). At birth, CP patients have normal musculoskeletal geometry, but bony deformities commonly develop during growth(Kerr Graham and Selber, 2003). It is hypothesized that the altered muscle coordination underlying the pathologic gait pattern induces aberrant skeletal loading and therefore interferes with natural bone growth(Bell et al., 2002).

Several surgical and non-surgical interventions are currently used to correct the pathologic gait pattern, aiming to improve the patient's functionality and to correct or to slow down the progression of musculoskeletal impairments (Galey et al., 2017; Narayanan, 2012). It is assumed that a more 'normal' walking pattern, will normalize skeletal loading and may therefore prevent musculoskeletal deformations.

Botulinum toxin injections (BTI) are widely used to decrease muscle

* Corresponding author at: Tervuursevest 101 – box 1501, 3001 Leuven, Belgium.
E-mail addresses: sam.vanrossom@kuleuven.be (S. Van Rossom), hans.kainz@kuleuven.be (H. Kainz), mariska.wesseling@kuleuven.be (M. Wesseling), eirini.papageorgiou@kuleuven.be (E. Papageorgiou), friedl.degroote@kuleuven.be (F. De Groote), anja.vancampenhout@uzleuven.be (A. Van Campenhout), guy.molenaers@uzleuven.be (G. Molenaers), kaat.desloovere@uzleuven.be (K. Desloovere), ilse.jonkers@kuleuven.be (I. Jonkers).

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spasticity and therefore facilitate muscle stretching(Galey et al., 2017; Heinen et al., 2010). During this period of locally induced muscle denervation, improvement in functional ability can be achieved through the interaction of intensive physiotherapy, casting and orthotic management(Molenaers and Fagard, 2013). BTI was found to increase range of motion during passive testing, walking speed and step length (Scholtes et al., 2006, 2007). Two recent literature reviews concluded that BTI is a valuable and effective treatment to improve gait on the short term, but on the long term, the effect of BTI is not sustained (Galey et al., 2017; Nieuwenhuys et al., 2016). Therefore, repeated injections are necessary to sustain a more durable effect. As such, BTI could temporarily prevent the development of muscle contractures and bony deformities and could have the potential to decrease the complexity of an orthopedic surgery later in life(Molenaers et al., 2010).

In contrast, orthopedic surgeries aim to prevent bony deformities by lengthening or transferring specific muscles or correcting bone deformations, thereby altering the musculoskeletal biomechanics. Typically, all musculoskeletal deformities are addressed in one single session, therefore limiting the number of surgeries and rehabilitation periods. A single-event multilevel surgery (SEMLS) is typically performed after the age of 8 years when a consistent gait pattern is installed(Narayanan, 2012). In contrast to BTI, SEMLS were found to improve the gait pattern during a longer time period (> 5 years) (Gannotti et al., 2007; Gough et al., 2008; Lamberts et al., 2016; Õunpuu et al., 2015; Thomason et al., 2013). Unfortunately, part of the patients require revision surgery later in life due to unsatisfactory results and the re-occurrence of bony deformities (Filho et al., 2008). This process is potentially caused by the fact that skeletal loading was not fully restored.

However, the effect of BTI and SEMLS on muscle force generation and joint loading is currently unknown. Therefore, the purpose of the present study was twofold. First, we evaluated if the pathologic gait pattern in CP patients indeed imposed an aberrant muscle coordination and skeletal loading. Second, we evaluated if treatment with BTI or SEMLS normalized the walking pattern and the underlying musculoskeletal loading. This is important as it is assumed that altered muscle force balance underlying the pathologic gait pattern affects natural bone growth and, therefore, potentially induces bony deformations.

2. Methods

2.1. Participants

Retrospective data of 93 children with spastic bilateral CP from the database of the Clinical Motion Analysis Laboratory of the University Hospitals Leuven were included in this study. Patients were included if they had bilateral CP, ages between 5 and 18 years, GMFCS levels I and II and pre and post-intervention 3D gait analysis data available. A subgroup of 44 patients were treated with SEMLS and a subgroup of 49 patients were treated with multilevel Botulinum toxin injections (BTI), which consisted typically of multilevel injections in the gastrocnemius, hamstrings and/or psoas, followed by casting(Molenaers and Fagard, 2013). Except for 4 patients, all SEMLS patients had bone deformation correction (e.g. derotation) in combination with soft tissue surgery (e.g. muscle transfer and lengthening). A more extended overview of the injected muscles and surgeries can be found in supplementary material (supplementary table 1–2). Pre-measurements were maximum 3 months prior to the intervention and post-intervention measurements were approximately 8 weeks and 12 months post-intervention for BTI and SEMLS, respectively (Table 1). In addition, 15 typically developing children were included as reference. All procedures were approved by the local ethical committee (S57746).

2.2. Data acquisition

All patients were instructed to walk barefoot and unassisted at self-selected speed. A Vicon system was used to capture three-dimensional marker trajectories (100 Hz, Vicon, Oxford Metrics, Oxford, UK). Markers were placed according to the Plug-in-Gait marker set(Davis et al., 1991). Simultaneously, ground reaction forces were measured using ground-embedded force plates (1000–1500 Hz, AMTI, Watertown, USA). At least two trials with successful force plate contact were retained for each leg for further processing.

Table 1
Demographic overview of the study cohorts, Mean (SD) is given.

	TD	BTI	SEMLS
	Mean (SD)	Mean (SD)	Mean (SD)
Gender (Male/Female)	9/6	29/20	31/13
Weight (Kg)			
Pre-intervention	34.61 (13.33)	25.89 (9.08)	35.68 (14.75)
Post-intervention		26.33 (9.16)	41.15 (15.79)
Height (mm)			
Pre-intervention	1392 (166)	1243 (225)	1407 (158)
Post-intervention		1288 (145)	1476 (149)
Age at intervention (y)	9.86 (2.98)	8.78 (2.32)	11.20 (3.07)
Walking speed (m/s)			
Pre-intervention	1.27 (0.19)	1.06 (0.16)	0.99 (0.18)
Post-intervention		1.07 (0.16)	0.95 (0.19)
Pre-intervention femoral anteversion angle (°)	n.a.	31.79 (6.71)	33.41 (8.00)
Time between intervention and post-op measurement (days)	n.a.	59.10 (16.06)	388.23 (111.93)
Number of previous BTI (count)			
0	n.a.	8	2
1–2	n.a.	24	16
3–4	n.a.	12	13
5 or more	n.a.	5	13
Time between intervention and last botox (months)	n.a.	24.71 (23.85)	33.15 (30.28)

2.3. Musculoskeletal modelling

A standard musculoskeletal modelling workflow implemented in OpenSim 3.3(Delp et al., 2007) was used: A generic musculoskeletal model (gait23992) was scaled to match the patients' anthropometrics. In addition, the maximal isometric muscle force was scaled to body mass to the power 2/3, to better represent the pediatric force generating capacities (Van Der Krogt et al., 2016). Joint angles were calculated using the Kalman smoother algorithm (De Groote et al., 2008) and external joint moments using OpenSim's Inverse Dynamics Tool. Muscle forces required to balance the external moments were calculated using a static optimization procedure in which the sum of the muscle activations squared was minimized. Lastly, lower limb joint contact forces were calculated using the vector sum of the estimated muscle forces and joint reaction forces(Steele et al., 2012). The resultant contact force magnitude and inclination were calculated in Matlab 2016b (Mathworks Inc.). The definition of the contact force inclinations is shown in Fig. 1.

2.4. Data analysis

For each participant, the average kinematic, kinetic, muscle force, contact force magnitude and inclination waveform was calculated. All variables, except the contact force inclination, were analyzed over the whole gait cycle, whereas the latter was only analyzed over the stance phase. Muscle forces were grouped according to function. Joint moments were normalized to body mass, muscle and contact forces to body weight. Since all patients were bilaterally involved data of individual legs was included separately in the statistical analysis.

Similar to the movement-analysis-profile and muscle-force-profile,

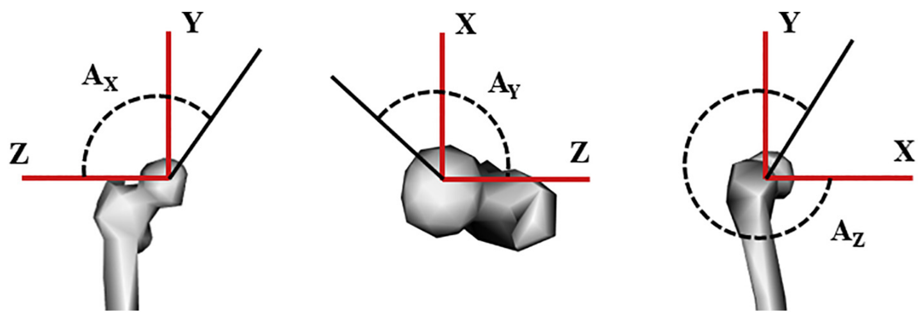

Fig. 1. Definition of the inclination angles of the resultant contact forces.

the average difference between each studied parameter waveform and the average TD pattern was expressed by a root-mean square difference (RMSD) (Baker et al., 2009; Kainz et al., 2019). In addition, the overall deviation from the TD pattern was calculated for the kinematics, kinetics, muscle and contact forces and contact force inclinations as the average RMSD over all joints. Firstly, to compare pre-intervention differences between TD and CP patients, data from both CP groups were combined and waveforms from both groups were compared using independent SPM *t*-tests. The difference between the waveforms in both CP groups was evaluated using independent SPM t-tests(Nieuwenhuys et al., 2017; Pataky, 2010; Robinson et al., 2015). Secondly, the pre- and post-intervention RMSD were compared using a paired t-test for each intervention separately. Thirdly, pre- and post-intervention RMSD values were compared to the RMS value in the TD-group (RMS_{TD}). Alpha level was set at 0.05, with bonferonni-correction to adjust for multiple testing if needed. Patient characteristics were compared using unpaired t-tests.

3. Results

A more extensive description and the figures presenting the results of the SPM analysis are reported in supplementary material.

3.1. Participants

60 male and 33 female CP patients were included (table I). Mean age at surgery was 9.92 years (SD 2.97y). BTI patients were significantly younger at the time of intervention compared to SEMLS patients (Table 1). A more extended overview of the patient's functionality (i.e. passive range of motion, spasticity and strength) can be found in supplementary table 3–5.

3.2. Pre-intervention TD – CP

3.2.1. Kinematics

Pre-intervention RMSDs were significantly higher for all joints for both CP groups than RMS_{TD}, indicating a deviating kinematic pattern (Fig. 2A and 3A). Compared to TD, CP patients present with decreased anterior pelvis tilt and external hip rotation and increased hip and knee flexion for the major part of the gait cycle, while ankle dorsiflexion was significantly increased during initial stance (supplementary fig. 1). Between SEMLS and BTI, no differences in joint kinematics were observed, except for hip extension in terminal stance, which was significantly lower in SEMLS compared to BTI (supplementary fig. 6).

3.2.2. Kinetics

Pre-intervention RMSDs of all joint moments were significantly higher for both CP groups than RMS_{TD} (Fig. 2B and 3B). Compared to TD, CP patients had higher hip flexion moment during stance and higher hip extension moment during swing, lower hip abduction moment during midstance and during terminal stance, lower knee extension moment during terminal stance and lower knee extension moment during terminal swing. Ankle dorsiflexion moment was higher during first half of stance but lower during terminal stance and swing compared to TD (supplementary fig. 2). No differences in joint kinetics between SEMLS and BTI were observed, only the hip extension moment during the initial part of the swing phase was significantly higher in SEMLS compared to BTI (supplementary fig. 7).

3.2.3. Muscle forces

Pre-intervention RMSDs were significantly higher for all muscle forces for both CP groups than RMS_{TD} (Fig. 2C and 3C). Compared to TD, CP patients had significantly higher gluteus maximus, medial and lateral hamstrings, adductor, vasti and soleus muscle force production during initial stance and significantly lower gluteus medius, lateral hamstrings, rectus femoris and gastrocnemius muscle force during mid and terminal stance. Dorsiflexor muscle force was significantly lower during initial stance. Gluteus medius and medial hamstrings muscle force was significantly lower during terminal swing (Supplementary fig. 3). No differences in muscle forces were observed between BTI and SEMLS, apart from the higher adductor muscle force during initial stance in the SEMLS group (supplementary fig. 8).

3.2.4. Contact forces

Pre-intervention RMSDs were significantly higher for all joint contact force magnitudes for both CP groups than RMS_{TD} (Fig. 2D and 3D). Compared to TD, hip, knee and ankle contact forces were significantly higher during initial stance in CP patients, whereas hip, knee and ankle contact forces were significantly lower during terminal stance and during swing for CP patients (supplementary fig. 4). Between CP groups, the hip contact force was significantly higher in SEMLS compared to BTI during initial swing and the knee contact force was significantly higher in SEMLS compared to BTI during terminal stance (supplementary fig. 9).

Pre-intervention RMSD in contact force inclination were significantly higher for all joints and directions for both CP groups compared to the RMS_{TD} before the intervention (Fig. 2E-G and 3E-G). Compared to TD, the hip contact force was oriented less vertically in the frontal plane (Ax) during terminal stance, the knee contact force was oriented less vertically in the frontal and sagittal planes throughout the major part of the stance phase and less anteriorly in the transverse plane throughout the whole gait cycle. The ankle contact force was oriented less vertically in the frontal and sagittal planes throughout the whole gait cycle and more anteriorly during initial stance (supplementary fig. 5). No differences in joint contact force inclination were observed between CP groups except for the less vertical knee contact force in the sagittal plane in the SEMLS than in BTI (Supplementary fig. 10).

3.3. Effect of BTI intervention

Pre- en post-intervention waveforms are reported in supplementary figs. 12–16.

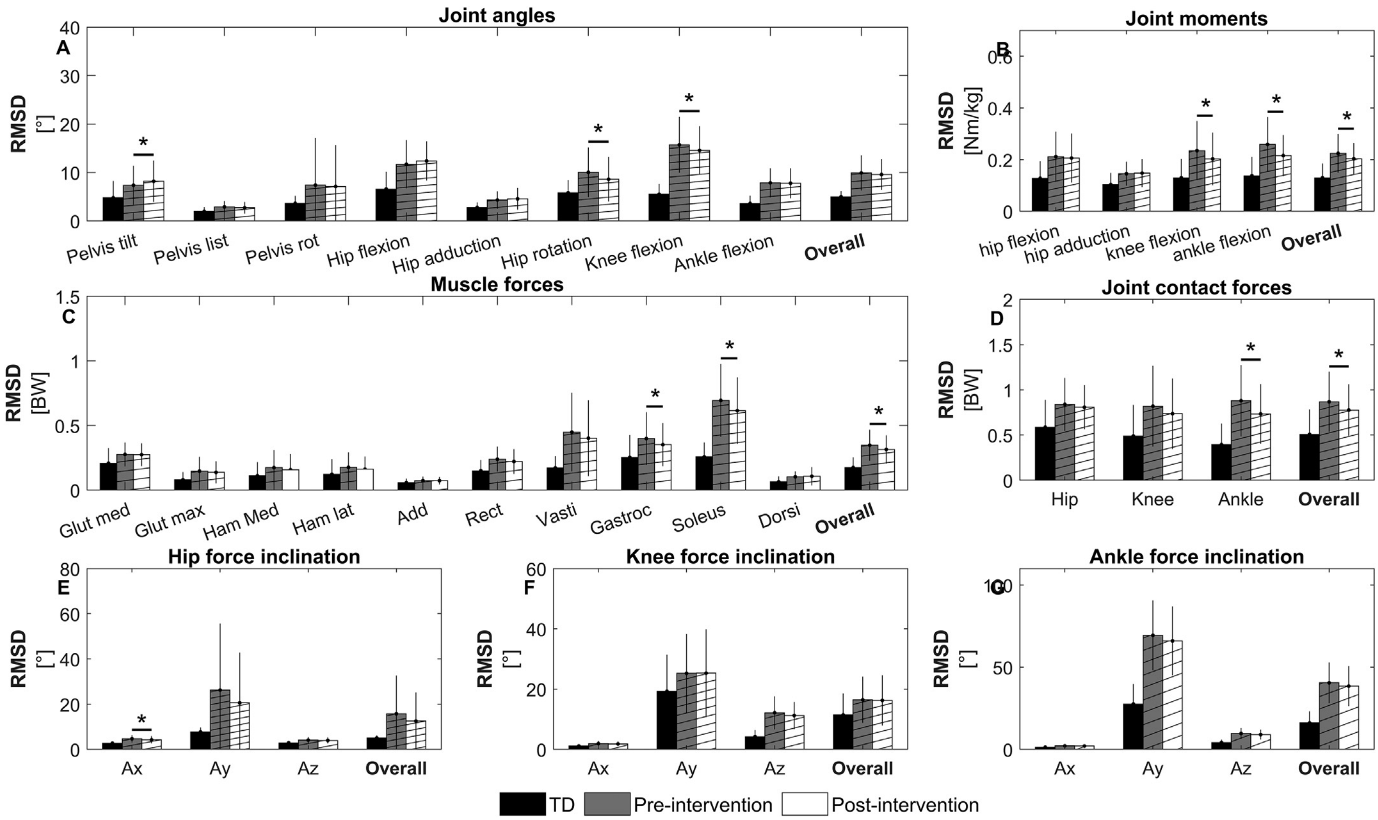

Fig. 2. Root mean square differences between BTI and TD for A) kinematics; B) joint moments; C) Muscle forces; D) Contact force magnitude; E) Hip contact force inclination; F) Knee contact force inclination; G) Ankle contact force inclination. *indicates a significant difference between the pre and post BTI RMSD value. Dashed bars indicate a significant difference between the pre/post RMSD and TD RMS value. The overall RSM value was calculated as the average RMSD over all joints.

3.3.1. Kinematics

The overall kinematic RMSD was not affected by BTI, but hip rotation and knee flexion RMSD significantly decreased, whereas pelvic tilt RMSD significantly increased (Fig. 2A). However, post-intervention RMSDs were still significantly higher than RMS_{TD} for all joint angles.

3.3.2. Kinetics

The overall joint moment RMSD significantly decreased after BTI, with sagittal plane knee and ankle moment RMSD being significantly decreased (Fig. 2B). However, post-intervention RMSDs were still significantly higher than RMS_{TD} for all joint moments.

3.3.3. Muscle forces

The overall muscle force RMSD significantly decreased after BTI, with specifically gastrocnemius and soleus muscle force RMSDs being significantly decreased (Fig. 2C). Post-intervention RMSDs of the medial and lateral hamstrings were no longer significantly different from the RMS_{TD}, but RMSDs of the other muscles remained significantly higher than RMS_{TD}.

3.3.4. Contact forces

The overall contact force magnitude RMSD significantly decreased, with ankle contact force RMSD being significantly decreased after BTI (Fig. 2E). However, post-intervention RMSDs were still significantly higher than RMS_{TD} for all joints.

The overall contact force inclination RMSDs were not affected after BTI, although the frontal plane hip contact force inclination (Ax) RMSD significantly decreased. However, post-intervention RMSDs were still significantly higher than RMS_{TD} for all contact force inclinations resulting in a more horizontally aligned contact force. (Fig. 2E).

3.4. Effect of SEMLS intervention

Pre- en post-intervention waveforms are reported in supplementary figs. 17–21.

3.4.1. Kinematics

The overall kinematic RMSD significantly decreased with pelvis tilt, hip flexion, hip rotation, knee flexion and ankle flexion RMSDs being significantly decreased (Fig. 3A). After SEMLS, only the RMSD of the pelvic tilt was not significantly different from RMS_{TD}, whereas the others remained significantly higher.

3.4.2. Kinetics

The overall joint moment RMSD significantly decreased, with sagittal plane hip, knee and ankle moment RMSDs being significantly decreased (Fig. 3B). After SEMLS, all RMSDs remained significantly higher than RMS_{TD}.

3.4.3. Muscle forces

The overall muscle force RMSD significantly decreased with specifically gluteus maximus, medial and lateral hamstrings, rectus femoris, vasti, gastrocnemius and soleus RMSDs being significantly decreased (Fig. 3C). After SEMLS, gluteus maximus as well as medial and lateral hamstrings RMSD were no longer significantly different from RMS_{TD}.

3.4.4. Contact forces

The overall contact force magnitude RMSD significantly decreased as well as the hip, knee and ankle contact force RMSDs (Fig. 3D). After SEMLS, the knee contact force RMSD was significantly decreased and not significantly different from RMS_{TD}.

The overall hip contact force inclination RMSD significantly decreased, as well as in all three planes individually (Fig. 3E). The overall

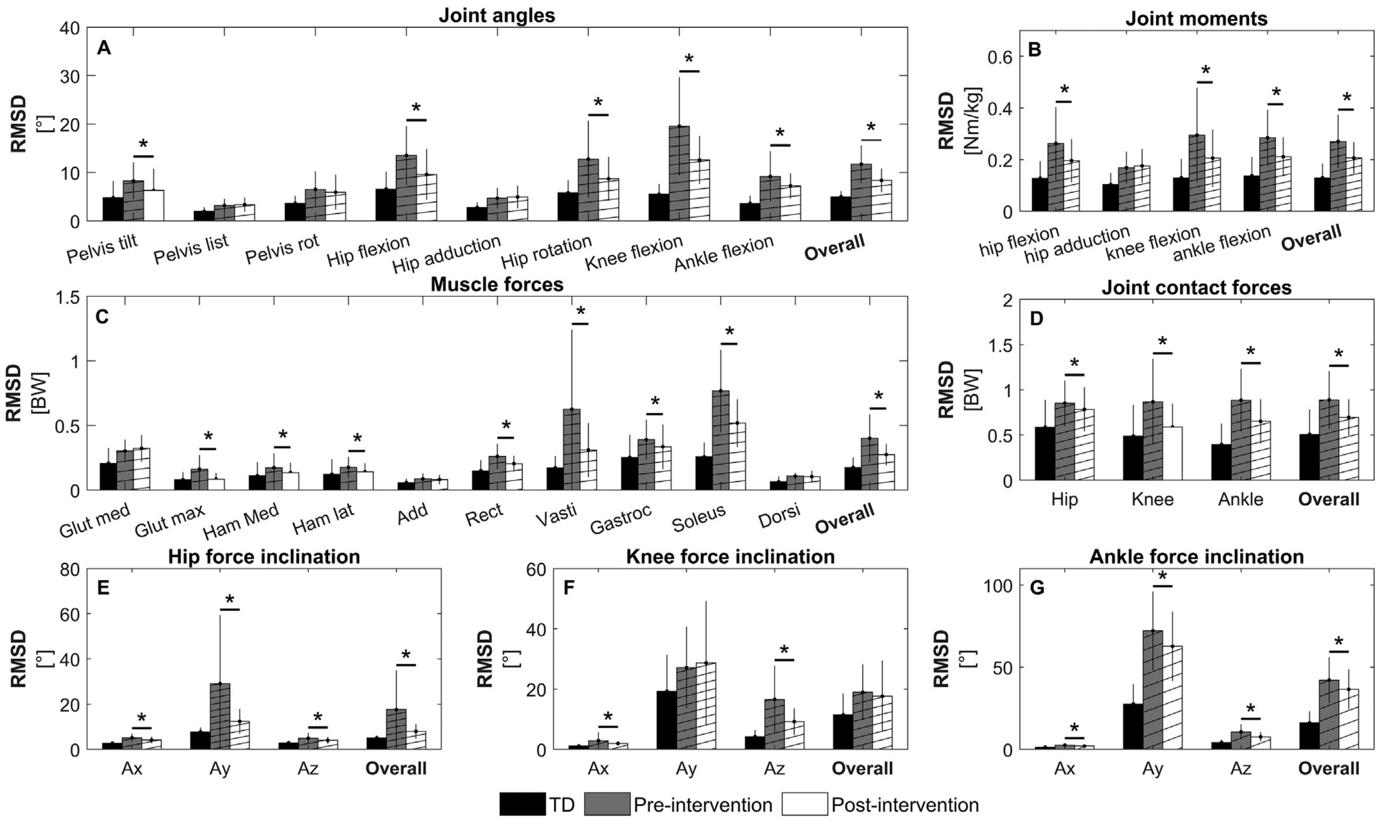

Fig. 3. Root mean square differences between SEMLS and TD for A) kinematics; B) joint moments; C) Muscle forces; D) Contact force magnitude; E) Hip contact force inclination; F) Knee contact force inclination; G) Ankle contact force inclination. *indicates a significant difference between the pre and post SEMLS RMSD value. Dashed bars indicate a significant difference between the pre/post RMSD and TD RMS value. The overall RSM value was calculated as the average RMSD over all joints.

knee contact force inclination RMSD was not affected after SEMLS, but the sagittal and frontal plane RMSDs significantly decreased (Az and Ax, respectively), resulting in a more vertically oriented contact force (Fig. 3F). The overall ankle contact force inclination RMSD significantly decreased as well as in all three planes (Fig. 3G). However, after SEMLS, contact force inclination RMSDs were still significantly higher than $RMS_{TD.}$

4. Discussion

This was the first study that evaluated whether BTI and SEMLS are capable of normalizing the pathologic gait pattern with associated changes in musculoskeletal loading abnormalities in CP patients. After SEMLS, joint loading was improved in all joints, with a normalization of knee joint loading, whereas after BTI only ankle contact forces were improved.

Before the intervention, both treatment cohorts presented an aberrant gait pattern, indicative of flexed knee gait. This pathologic gait pattern required increased muscle force generation of the gluteus maximus, hamstrings, vasti and soleus for propulsion. This altered muscle force balance resulted in significantly increased loading on all joints during the first part of the stance phase and in agreement with previous studies, in slight underloading of the hip joint during the second part of the stance phase(Bosmans et al., 2014). Due to this altered musculoskeletal loading balance, both CP groups presented with a reduced vertically oriented contact force on the hip and knee joint, which has been related to the development of a decreased neck-shaft angle and torsional deformities of the tibia, respectively(Bell et al., 2002; Carriero et al., 2011). When left untreated, this altered joint loading might contribute to progressive bone deformation(Bell et al., 2002; Carriero et al., 2011).

SEMLS resulted in significantly improved joint loading of all lower limb joints. Pelvis tilt, hip flexion, hip rotation, knee flexion and ankle flexion angle were improved, as well as the sagittal plane joint moments one year after SEMLS. These changes in the gait pattern resulted in significantly altered muscle force generation that was closer to the muscle forces observed in the TD group. This altered muscle force balance around each joint resulted in a decreased hip, knee and ankle contact force magnitude during the first part of the stance phase and in a normalized knee contact force. Furthermore, after SEMLS, contact forces were more vertically oriented and might therefore be protective against the development of an increased neck shaft angle.

Multilevel BTI only improved ankle contact force magnitude. In agreement with previous studies that investigated the effect of BTI on the gait pattern, hip rotation and knee flexion angle were improved after BTI(Galey et al., 2017; Nieuwenhuys et al., 2016). However, in the present BTI cohort, no changes in the ankle kinematics were reported, although it was previously observed that the ankle joint was mostly affected by BTI(Galey et al., 2017; Nieuwenhuys et al., 2016). These kinematic changes resulted in closer to normal knee and ankle joint moments, however these changes appeared to be insufficient to normalize the muscle force balance and joint contact forces. Only the muscle forces generated by the gastrocnemius and soleus were significantly decreased during the initial part of the gait cycle, which explains the decreased ankle contact force observed during the first part of the gait cycle.

Based on the present results, we can conclude that SEMLS is an effective treatment for restoring the pathologic gait pattern and to improve joint loading. Consequently, SEMLS might be effective for the prevention of new bone deformation. Furthermore, it was previously found that the kinematic changes after a SEMLS intervention were sustained on the long term and therefore SEMLS might provide effective prevention of bone deformation on the long term(Dreher et al., 2018; Lamberts et al., 2016). Both, contact force magnitude and orientation were restored after SEMLS. This is of utmost importance, as it was reported that they both contribute to the development of bony deformities(Carriero et al., 2011; Shefelbine and Carter, 2004). A deviating force magnitude was found to affect merely the amount of deformation, whereas a deviating orientation merely influences the direction of the deformation (e.g. *endo*- or exotorsion)(Bosmans et al., 2014; Carriero et al., 2011). This is in contrast with BTI, which was found not to restore joint loading and might therefore not be an appropriate intervention to prevent bone deformation. This is in contrast to previous studies which suggested that BTI could be used as an intervention to restore the walking pattern and thus avoid bone deformation. This as a temporary intervention to diminish the amount of bone deformation with the goal to decrease the complexity of an orthopedic intervention later in life(Molenaers et al., 2010). Furthermore, our results showed that multilevel BTI only has an effect on the distal joints, whereas SEMLS resulted in improvements of the whole lower limb kinematics and joint loading.

Musculoskeletal modelling allowed to quantify the effect of BTI and SEMLS on the muscle and contact forces, whereas this is not possible only based on the results obtained during a standard clinical 3D gait assessment. Using the latter, the effect of the intervention on loading is rather indirectly deducted from the changes in the kinematics and kinetics. However, our results showed that changes in the kinematics do not guarantee changes in musculoskeletal loading. For example, in BTI patients, changes in the kinematics and kinetics were found in the pelvis and hip, but these did not result in changes in hip loading. Furthermore, musculoskeletal modelling analysis is needed to further unravel the contribution of muscle coordination during pathologic gait to bone deformation by interfering with normal bone loading.

Some limitations need to be considered when interpreting the findings of this study. Firstly, these patients are likely to have altered musculoskeletal geometry, which contributes to the pathologic gait pattern. However, the present study used generic models that have normal musculoskeletal geometry to isolate the effect of altered gait following the intervention on the muscle forces and joint loading (Carriero et al., 2014). Previously, it was found that hip contact force was slightly underestimated when using a generic model compared to a subject-specific model that accounts for bony deformities(Bosmans et al., 2014). Therefore, the effect of the SEMLS intervention might be underestimated. In addition, femoral anteversion angle before the intervention was comparable between both groups, therefore the effect of using a generic model is similar in both groups (Table 1). Secondly, a generic model including identical musculotendon parameters for both CP cohorts and TD children was used to process the data, although MT-parameters are known to differ between CP patients and TD children. Therefore, the effect of differences in muscle constitution and changes in muscle constitution by the intervention are not accounted for in our results, nevertheless, this approach allows to defer the effect of the altered gait pattern on the musculoskeletal loading. Currently, no approaches are available that allow the non-invasive estimation of the muscle-tendon characteristics that are relevant to the static optimization approach. Thirdly, a static optimization procedure was used to estimate the muscle forces. In this optimization, squared muscle activation was minimized, however, it is possible that this optimization criterion is not representative for CP patients. Nevertheless, a recent study showed that the overall findings and conclusions are similar between static optimization and an electromyography-informed approach (Kainz et al., 2019). Hence, we expect to get similar conclusions when taking the subject-specific motor control into account. In addition, muscle spasticity was not accounted for in the optimization, therefore neglecting the possible effect of co-contraction, which increases joint loading. Fourthly, despite the interdependence of the legs, both legs were treated as independent samples in the statistical analysis. Lastly, our findings might be affected by the fact that the major part of the patients (84%) already had previous BTI injections, even though the observed changes in the gait pattern were not related to the number of pre-intervention BTI treatments (Supplementary fig. 11).

5. Conclusions

In conclusion, BTI did not induce sufficient changes in the pathological gait pattern to restore closer to normal joint loading and may therefore only be appropriate to temporarily alleviate muscle spasticity and hypertonia and prevent muscle contractures. SEMLS, on the other hand, was found to be successful in restoring a closer to normal gait pattern and joint loading and might therefore be protective against the re-occurrence of bone deformation.

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Declaration of Competing Interest

None of the authors have any conflict of interest to disclose

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiomech.2020.105025.

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