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Research

Efficacy of Multilevel Botulinum Toxin Type A Injections Applied to the Lower Limb in a Single Session for Children with Spastic Cerebral Palsy

Spastik Serebral Palsili Çocuklarda Alt Ekstremiteye Tek Seansta Uygulanan Çok Düzeyli Botulinum Toksin Tip A Enjeksiyonlarının Etkinliği

Kubilay Beng[1], Evren Akpınar[2], Sebahat Aydil[3], İlhan A. Bayhan[2], Kutalmış Albayrak[2], Mehmet Fırat Yağmurlu[2]

[1]Bahçeşehir University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital, Clinic of Physical Therapy and Rehabilitation, İstanbul, Türkiye

ABSTRACT

Objective: Dynamic spasticity may develop into static contractures in children with cerebral palsy. The study aimed to evaluate the efficacy of multilevel botulinum toxin type A (BtA) in children with spastic cerebral palsy, when combined with casting, followed by physical therapy and orthotics.

Methods: We retrospectively evaluated changes in physical examination and walking in 12 children treated at our institution between January and December 2014 using three-dimensional gait analysis at baseline, and 3 months and 6 months after treatment. We administered BtA 6-8 IU/kg to four points in gastrocnemius and 4-6 IU/kg BtA to two points in the hamstrings. A long-leg cast was applied for 10 days after the injections, after which an ankle-foot orthosis was supplied to all carers and an intensive physical therapy program was undertaken.

Results: Three months after injection, we observed significant improvements in cadence, stride time and velocity, and knee flexion at initial contact and maximum knee extension during the stance phase, but these had returned to baseline by 6 months. However, significant improvements from baseline in ankle plantar flexion at initial contact, maximum ankle dorsiflexion during the stance phase and maximum ankle plantar flexion during the terminal stance phase persisted for 6 months.

Conclusion: A single session of multilevel BtA treatment combined with casting, intensive physical therapy and orthosis use appears to be an effective means of preventing static contractures in children with cerebral palsy for up to 6 months.

Keywords: Botulinum toxin type A, cerebral palsy, kinetic analysis, kinematic analysis, gait analysis

ÖZ

Amaç: Serebral palsili çocuklarda dinamik spastisite statik kontraktürlere dönüşebilir. Çalışmanın amacı, spastik serebral palsili çocuklarda çok seviyeli botulinum toksini tip A (BtA) enjeksiyonu ile birlikte alçı uygulaması ile ardından fizik tedavi ve ortez ile kombine edilen tedavinin etkinliğini değerlendirmektir.

Gereç ve Yöntem: Ocak-Aralık 2014 tarihleri arasında kurumumuzda tedavi edilen 12 çocukta başlangıçta ve tedaviden 3 ay ve 6 ay sonra üç boyutlu yürüme analizi kullanarak fizik muayene ve yürümedeki değişiklikleri geriye dönük olarak değerlendirdik. Gastroknemiusta dört noktaya 6-8 IU/kg BtA, hamstringlerde iki noktaya 4-6 IU/kg BtA uyguladık. Enjeksiyonlardan sonra 10 gün boyunca uzun bacak alçı uygulandı, ardından tüm hastalara ayak bileği ortezi ve yoğun bir fizik tedavi programı uygulandı.

Address for Correspondence: Kubilay Beng, Bahçeşehir University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Türkiye
E-mail: kubilaybeng@yahoo.com ORCID ID: orcid.org/0000-0001-8196-6605

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Bulgular: Enjeksiyondan üç ay sonra, duruş fazı sırasında dakikadaki adım sayısı, çift adım süresi, hızı ve ilk temasta diz fleksiyonunda ve maksimum diz ekstansiyonunda önemli iyileşmeler gözlemledik, ancak bunların 6 ayda başlangıç seviyelerine döndüğünü saptadık. Bununla birlikte, ilk temasta ayak bileği plantar fleksiyonunda, basma fazı sırasında maksimum ayak bileği dorsifleksiyonunda ve basma sonu fazı sırasında maksimum ayak bileği plantar fleksiyonunda başlangıca göre önemli gelişmeler 6 ay boyunca devam etti.

Sonuç: Alçı, yoğun fizik tedavi ve ortez kullanımı ile birlikte tek seans çok seviyeli BtA tedavisi, 6 aya kadar serebral palsili çocuklarda statik kontraktürleri önlemenin etkili bir yolu gibi görünmektedir.

Anahtar Kelimeler: Botulinum toksin A, serebral palsi, kinetik analiz, kinematik analiz, yürüme analizi

INTRODUCTION

Cerebral palsy (CP) is characterized by a persistent disorder of motor control and posture because of non-progressive brain injury, and multilevel dynamic spasticity is common in early childhood (1). Equinus gait and excessive knee flexion during the stance phase are the most frequently observed walking disorders in children with CP (2,3).

The injection of botulinum toxin A (BtA), casting, orthotics, and intensive physical treatment are used to manage multilevel spasticity in children with CP (4,5). Boyd and Graham (5) and Molenaers et al. (4) have stressed the importance and objectivity of computed gait analysis for the functional assessment of walking in CP.

The therapeutic benefits of BtA are generally measured by comparing the range of motion or by analyzing gait before and after treatment. Investigators who have used these methods as outcome measures have reported improvements in ankle dorsiflexion of approximately 3 months' duration after injection into gastrocnemius (6-11), but the role of multilevel injections (4,5), including to the hamstring (12), has also been examined. Corry et al. (12) used gait analysis to document a significant improvement in knee extension after BtA therapy that was most evident 2 weeks after injection but was beginning to wear off after 12 weeks. Cosgrove et al. (13) used electrogoniometric measurements of sagittal plane angle kinematics at the hip, knee and ankle to identify significant improvements in ankle and knee positions after BtA treatment that lasted approximately 6 months.

We hypothesized that a single session of multilevel BtA therapy would improve walking function in children with CP-related spasticity in the lower extremities for up to 6 months, when administered as part of a multidisciplinary program that also included casting, physical therapy and orthotics. We undertook a retrospective analysis of spatiotemporal parameters and kinematic data obtained by computed gait analysis performed in a cohort of children with CP affecting the lower limb.

METHODS

Participants

The conduct of the study was approved by the Ethics Committee of Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital (decision no: 23, date: 21.04.2015). Patients with CP attending the pediatric orthopedic clinic of our hospital routinely undergo gait analysis before and after BtA treatment. We retrospectively identified a group who had undergone multilevel BtA injection for preventing spasticity in the lower extremity between January and December 2014. We included those with Gross Motor Function Classification System (GMFCS) level I-III disability, with complete three-dimensional gait analysis records obtained before BtA administration and at 3 months and 6 months afterwards (14). We excluded those with GMFSC level IV or V disability, static equinus deformity or knee flexion contracture, severe athetoid movements in the lower extremities, or who had undergone surgery to the foot, ankle, or leg.

Contracture Prevention Program

All BtA injections were administered in the operating room under general anesthesia and aseptic conditions. BtA 100 IU (Botox, Allergan, Irvine, CA, USA) was reconstituted in sterile 0.9% NaCl solution and injected using an insulin syringe with a 26-G needle. The maximum dose per muscle was 50 IU and the maximum total dose was 20 IU/kg. Injections were administered to three points in the medial head and one point in the lateral head of gastrocnemius, and two points 2 cm apart in the medial third of the hamstrings in all patients (15), as described by Cosgrove et al. (13) We administered 6-8 IU/kg BtA to gastrocnemius and 4-6 IU/kg to the hamstrings. We also administered BtA to the psoas, tibialis posterior and soleus in three cases, the adductor muscles in six cases and the rectus muscles in four cases.

Once injections were complete, stretching plaster of Paris casts were applied for 10 days to maintain the ankle joint in a neutral position and the knee in semi-flexion (5°-10°). After that, carers were provided with a non-articulated ankle-foot orthosis to be used in the shoe when walking. Patients also underwent 60-minute intensive physical therapy sessions

three times a week after cast removal (8), focused on active and passive stretching of the flexor muscles, strengthening of the extensors, functional mobility and gait training.

Outcome Measures

All patients underwent physical examination at baseline and 3 months and 6 months after injection. We recorded the Modified Ashworth scale (MAS) (16), hip extension, popliteal angle and ankle dorsiflexion using standard procedures (4,5,12,17). All examinations were conducted by the same physical therapist.

Gait Analysis

Three-dimensional gait analysis was performed before BtA injection, and 3 months and 6 months after injection. Walking was analyzed using the Vicon Bonita System (Oxford Metrics, Oxford, UK) using eight 100 Hz infrared cameras and two Bertec power platforms (Bertec, Columbus, OH, USA). Sixteen retroreflective markers were positioned at anatomic points according to the Modified Helen Hayes model (18-20). Patients were instructed to walk barefoot along a 9-m walkway at a normal speed. Data were processed using the Vicon Nexus 1.8.2 program. (Vicon Motion Systems, Oxford, UK) Time-distance parameters and kinematic graphs were obtained using Polygon 4.0.1 software (Vicon Motion Systems). Walking cycles when both feet were placed fully on the pressure plates one after the other, were accepted as normal. We recorded data for two to four walking cycles from each affected extremity. The most representative cycle was selected and used for statistical assessment.

Time-distance variables recorded were step width, stride length, stride time, cadence and walking speed, kinematic variables recorded were pelvic tilt, pelvic rotation, pelvic obliquity, hip abduction, maximum hip flexion at initial contact (H1), maximum hip extension during the stance phase (H2), maximum hip flexion during the swing stage (H3), knee flexion at initial contact (K1), maximum knee extension during the stance phase (K2), maximum knee flexion during the swing phase (K3), ankle plantar flexion after initial contact (A1), maximum ankle dorsiflexion during the stance phase (A2) and maximum ankle plantar flexion during the terminal and pre-swing phases (A3).

Statistical Analysis

Data are presented as the mean (± standard deviation) or the median (range). Data from one limb were subject to analysis, the right limb in diplegic children and the affected limb in hemiplegic children. The distribution of variables was assessed using the Kolmogorov-Smirnov test. Repeated measures analysis of variance (ANOVA) and the least significant difference (LSD) was used for pairwise comparisons of parametric data, and the Friedman and Wilcoxon tests were used for pairwise comparison of non-parametric data. The significance level for ANOVA and the Friedman test was $p<0.05$. Pairwise comparisons using the LSD and Wilcoxon tests were subject to the Bonferroni correction; for these analyses, the significance level was $p<0.016$. We used the SPSS statistical program for all analyses (version 22.0; IBM, Armonk, NY, USA).

RESULTS

Patient Cohort

Twelve patients met the inclusion criteria, four girls and eight boys. Their mean age was 6 years 3 months (range 4 years 7 months to 9 years 2 months); seven were diplegic and five hemiplegic. A physical examination identified dynamic gastrocnemius and hamstring spasticity in all cases at baseline.

Physical Examination

Statistically significant improvements in all parameters were identified after multilevel BtA injection (Table 1). Passive hip extension and hamstring and ankle MAS were found to have improved significantly at 3 months, but although they had deteriorated by 6 months were still significantly superior to the baseline. Popliteal angles had also improved significantly by 3 months, but had deteriorated to the extent that they were not significantly different from baseline by 6 months. Significant improvements in ankle dorsiflexion were maintained throughout the 6-month follow-up period.

Spatiotemporal Parameters

There were significant changes in cadence, stride time and walking speed after multilevel BtA injection (Table 2). Cadence had fallen significantly by 3 months, but had returned to baseline levels by 6 months. Stride time was significantly higher than the baseline at 3 months, but had returned to baseline by 6 months. Walking speed had fallen significantly from baseline by 3 months, but had returned to baseline by 6 months. There were no significant changes in any other spatiotemporal parameter.

Kinematics

There were no significant changes in the kinematic parameters measured in the pelvis or hip (Table 3, Figure 1 A-B), but there were significant improvements in knee flexion and extension (K1 and K2), and ankle plantar and dorsiflexion (A1, A2, and A3), throughout the walking cycle (Table 3, Figure 1 C-D). The significant improvements in knee kinematics observed at 3 months had returned to baseline by 6 months, but were still evident in the ankle at 6 months (A1, A2, and A3).

Table 1. Changes in physical examination variables before and after a single session of multilevel botulinum toxin type A injection

		Mean ± SD	Median	Range	p*
Hip extension (°)*	Pre BtA	14.6±6.2	15	0-20	0.042
	Post BtA 3 months	19.6±2.6	20	15-25	
	Post BtA 6 months	18.3±3.9	20	10-20	
Popliteal angle (°)*	Pre BtA	60.0±10.9	57.5	45-80	0.005
	Post BtA 3 months	50.0±6.0	50	40-60	
	Post BtA 6 months	54.2±7.9	55	35-65	
Ankle dorsiflexion (°)*	Pre BtA	-2.5±10.3	0	-25-5	0.001
	Post BtA 3 months	6.6±9.6	7.5	-10-25	
	Post BtA 6 months	5.4±12.5	10	-20-20	
Hamstring MAS†	Pre BtA	-	2	1-3	0.018
	Post BtA 3 months	-	1	0-2	
	Post BtA 6 months	-	1	0-3	
Ankle MAS†	Pre BtA	-	2	1-3	<0.001
	Post BtA 3 months	-	1	0-2	
	Post BtA 6 months	-	1	0-3	

SD: Standard deviation, BtA: Botulinum toxin type A, MAS: Modified Ashworth scale
*ANOVA test, †Friedman test; p<0.05 was considered statistically significant

DISCUSSION

We found that a single session of multilevel BtA treatment combined with casting, physical therapy and use of an orthosis was an effective treatment strategy for childhood lower limb spasticity in CP, improving various gait parameters for at least 3 months, and ankle movements for at least 6 months. These findings chimed with those of other investigators (4,6,7,9,21). An integrated approach to the treatment of dynamic spasticity is critical to success and should be timed correctly; patients should be selected for treatment according to objective measurement methods, appropriate doses of BtA should be administered at multiple levels, casting, orthoses and intensive physical therapy should be provided, and outcomes should be monitored regularly and objectively (4,5). Using this approach, we could achieve positive therapeutic outcomes for the patients in our cohort for up to 6 months, by which time the pharmacologic effects of BtA would likely have waned.

Gage et al. (2) described normal walking as having adequate stability during the stance phase, proper lifting of the foot away from the ground in the swing phase, proper positioning of the foot for initial contact at the end of the swing phase, and provision of adequate step length. Corry et al. (12) reported that cadence and walking speed had increased 2 weeks after BtA treatment, and although both had fallen by 12 weeks, they had not returned to baseline. We found that cadence and walking speed had decreased and stride time had increased 3 months after BtA treatment, but these changes were no longer evident 6 months after treatment. We interpret the changes that we observed at 3 months as an improvement in walking function, when taken together with a decrease in maximum knee flexion at initial contact (which depends on longitudinal extension of the hamstrings). In our opinion, the deterioration of spatiotemporal parameters seen 6 months after treatment was a consequence of knee function returning to baseline levels.

Few investigators have used objective outcome measures to evaluate the therapeutic effects of BtA injection on the proximal muscles of the lower extremities. Molenaers et al. (4) used gait analysis alone to examine the influence of BtA treatment in CP and reported improvements in pelvic stability, especially in the frontal and transverse planes, but found no changes in kinematic hip parameters. We found no significant changes in any pelvis or hip movements on gait analysis, despite improvements in hip extension detected on physical examination. Walking is a dynamic activity, and weakness in the trunk muscles combined with spasticity in the ankle and knee likely affects the hip joint and overloads the pelvis.

Table 2. Changes in spatiotemporal parameters before and after multilevel botulinum toxin A injection

		Mean ± SD	Median	Range	p*
Cadence (/min)	Pre BtA	141.3±21.2	144.5	99.0-185.0	0.006
	Post BtA 3 months	123.6±18.7	128.0	80.0-146.0	
	Post BtA 6 months	139.7±22.3	141.5	87.6-169.0	
Stride time (s)	Pre BtA	0.87±0.14	0.85	0.65-1.21	0.032
	Post BtA 3 months	0.99±0.18	0.94	0.82-1.50	
	Post BtA 6 months	0.89±0.17	0.85	0.71-1.37	
Single support	Pre BtA	0.36±0.06	0.36	0.28-0.50	0.218
	Post BtA 3 months	0.40±0.09	0.36	0.31-0.63	
	Post BtA 6 months	0.37±0.08	0.36	0.26-0.59	
Double support	Pre BtA	0.16±0.71	0.16	0.03-0.30	0.141
	Post BtA 3 months	0.20±0.06	0.20	0.11-0.35	
	Post BtA 6 months	0.21±0.19	0.16	0.07-0.82	
Stride length (m)	Pre BtA	0.85±0.092	0.82	0.75-1.04	0.438
	Post BtA 3 months	0.81±0.15	0.80	0.54-1.03	
	Post BtA 6 months	0.84±0.10	0.84	0.72-1.07	
Step width (m)	Pre BtA	0.15±0.12	0.12	0.01-0.53	0.742
	Post BtA 3 months	0.12±0.07	0.11	0.03-0.27	
	Post BtA 6 months	0.12±0.06	0.11	0.05-0.29	
Walking speed (m/s)	Pre BtA	0.99±0.14	1.01	0.72-1.21	0.019
	Post BtA 3 months	0.81±0.22	0.86	0.4-1.22	
	Post BtA 6 months	0.97±0.15	0.99	0.58-1.15	

SD: Standard deviation, BtA: Botulinum toxin type A, *ANOVA test, $p<0.05$ was considered statistically significant

BtA is the most effective in patients with dynamic contractures. Dynamic spasticity may develop into static contractures at older ages (6). Addressing spasticity between the ages of 1 and 6 years reportedly prevents the onset of contracture and delays the age at which surgery is required (7,21). Computerized gait analysis has some limitations in children. The proximity of the retroreflective markers makes analysis unreliable and children must be cooperative; consequently, the minimum height for gait analysis in our laboratory is 1 m and the minimum age is 4 years (22). We assessed gait in children aged <4 years visually and by physical examination. Consequently, we cannot generalize our findings to younger children, and the age of our cohort may have contributed to the limited changes in hip and pelvic parameters that we observed.

The specific goal of BtA injection is to increase stability during walking. To achieve this, foot contact during the stance phase must be optimized, along with proper positioning of the knee and ankle at the end of the swing phase for initial contact (2,4). We found that BtA injection combined with an integrated treatment strategy in children with multilevel spasticity-improved foot position at initial contact, and that the subsequent improvement in gait stability persisted for up to 6 months. However, although the knee extension at initial contact (K1) had improved statistically after 3 months, we found that the knee was still more flexed compared with reference data (23). Full knee extension could only be achieved in the mid-stance phase (K2), and improvements in knee movements had subsided to baseline by 6 months. Corry et al. (12) reported that improvements in hamstring function seen 2 weeks after BtA injection had subsided by 12 weeks, although not to baseline levels. Desloovere et al. (22) found no significant difference in the knee angle at initial contact between baseline and 3 months. Nevertheless, we observed a significant improvement in knee flexion at initial contact, possibly because we used an above-knee cast; Corry et al. (24) did not apply casts to their patients, and Desloovere et al. (22) used a below-knee cast. The short-term efficacy of BtA treatment to gastrocnemius is well recognized (6,7,9,11): Corry et al. (12) observed continuing

Table 3. Changes in kinematic parameters before and after multilevel botulinum toxin A injection

		Mean ± SD	Median	Range	p*
Pelvic tilt	Pre BtA	17.18±5.65	17.60	9.15-25.50	0.685
	Post BtA 3 months	16.26±6.60	15.60	6.73-27.70	
	Post BtA 6 months	16.34±5.71	14.95	8.31-28.30	
Pelvic rotation	Pre BtA	-1.28±6.70	-2.50	-8.54-12.20	0.150
	Post BtA 3 months	-1.57±5.52	-2.39	-9.11-9.04	
	Post BtA 6 months	0.97±5.97	3.64	-10.1-8.78	
Pelvic obliquity	Pre BtA	0.90±3.51	1.05	-5.49-7.29	0.194
	Post BtA 3 months	1.62±3.42	1.94	-3.01-7.64	
	Post BtA 6 months	2.48±2.51	2.20	-1.83-8.67	
Hip abduction	Pre BtA	3.51±4.19	3.65	-2.23-10.50	0.704
	Post BtA 3 months	4.53±4.69	4.59	-2.70-11.60	
	Post BtA 6 months	4.42±3.70	4.84	-0.37-9.17	
H1	Pre BtA	40.79±6.46	41.10	30.06-52.90	0.937
	Post BtA 3 months	40.83±5.84	38.95	34.40-55.00	
	Post BtA 6 months	41.25±7.39	42.30	26.80-53.30	
H2	Pre BtA	-3.06±3.05	-3.16	-8.19-2.59	0.062
	Post BtA 3 months	-4.96±6.09	-4.69	-17.80-7.09	
	Post BtA 6 months	-0.83±7.17	-1.42	-14.20-8.23	
H3	Pre BtA	48.38±8.88	48.45	34.10-59.70	0.176
	Post BtA 3 months	46.15±9.52	43.20	35.0-63.90	
	Post BtA 6 months	49.14±10.60	49.25	34.10-73.90	
K1	Pre BtA	28.74±7.16	29.35	19.60-41.10	0.003
	Post BtA 3 months	23.68±8.14	23.85	9.12-34.20	
	Post BtA 6 months	26.71±11.78	28.00	9.82-52.10	
K2	Pre BtA	6.01±7.42	7.52	-8.87-19.00	0.012
	Post BtA 3 months	-0.46±4.98	-0.69	-7.04-8.45	
	Post BtA 6 months	4.33±8.34	1.83	-6.89-24.20	
K3	Pre BtA	59.04±8.94	60.15	46.50-73.30	0.665
	Post BtA 3 months	60.15±9.46	58.40	45.50-77.20	
	Post BtA 6 months	61.67±8.98	62.50	43.90-72.10	
A1	Pre BtA	-8.17±9.77	-5.88	-26.70-3.98	0.018
	Post BtA 3 months	0.37±6.34	1.12	-14.50-7.83	
	Post BtA 6 months	1.64±4.46	1.35	-5.31-9.17	
A2	Pre BtA	-5.72±19.33	-2.32	-60.90-16.90	0.006
	Post BtA 3 months	10.15±15.71	13.60	-28.10-27.20	
	Post BtA 6 months	3.51±19.22	10.90	-53.90-19.10	
A3	Pre BtA	-34.92±24.58	-34.25	-81.90 - -1.03	0.002
	Post BtA 3 months	-19.33±24.66	-11.60	-76.60-4.40	
	Post BtA 6 months	-16.37±20.37	-11.15	-75.30 - -0.27	

SD: Standard deviation, BtA: Botulinum toxin type A, H1: Maximum hip flexion at initial contact, H2: Maximum hip extension during the stance phase, H3: Maximum hip flexion during the swing stage, K1: knee flexion at initial contact, K2: Maximum knee extension during the stance phase, K3: Maximum knee flexion during the swing phase, A1: Ankle plantar flexion after initial contact, A2: Maximum ankle dorsiflexion during the stance phase, A3: Maximum ankle plantar flexion during the terminal and pre-swing phases, *ANOVA test; $p<0.05$ was considered statistically significant

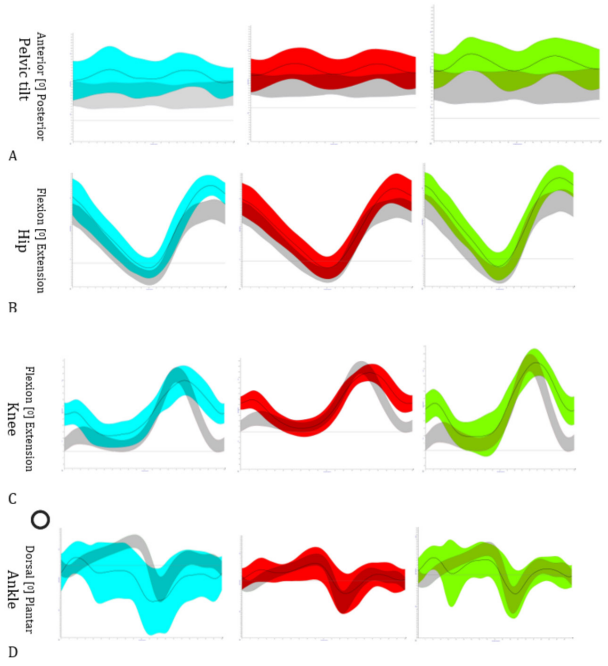

Figure 1. Mean sagittal plane kinematic mass graphs are shown for (A) pelvic tilt, (B) hip flexion, (C) knee flexion and (D) ankle dorsiflexion and plantar flexion for all patients at baseline (blue line), 3 months (red line) and 6 months (green line) after botulinum toxin type A injection, and for an age-matched control group of 19 subjects (gray area, ±1 standard deviation). Positive values indicate anterior pelvic tilt, hip flexion, knee flexion and ankle dorsiflexion

benefits at 12 weeks; Choi et al. (11) reported a therapeutic effect at 4 months; whereas we found that some benefits persisted for 6 months.

To enhance the statistical power of our study, we only analyzed data from one limb of each patient (the affected limb of in hemiplegic children and the right limb of diplegic children). Although our small sample size could be considered a limitation, it should be deemed a beta error; we used posteriori power analysis to ensure that the study had reached adequate statistical power.

CONCLUSION

We found that multilevel BtA treatment administered in a single session is an effective treatment for lower limb spasticity in children with CP. When combined with casting, intensive physical therapy and use of an orthosis, the most significant improvements were seen at the ankle joint, an effect that lasted 6 months. This is the first study to use computed gait analysis as an objective outcome measure over a 6-month follow-up period. We saw more short-lived improvements at the knee joint, but no improvements were observed in hip or pelvic locomotor function.

ETHICS

Ethics Committee Approval: The conduct of the study was approved by the Ethics Committee of Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital (decision no: 23, date: 21.04.2015).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: K.B., E.A., S.A., İ.A.B., K.A., M.F.Y., Concept: K.B., S.A., İ.A.B., K.A., M.F.Y., Design: K.B., E.A., İ.A.B., K.A., M.F.Y., Data Collection or Processing: K.B., E.A., S.A., K.A., M.F.Y., Analysis or Interpretation: K.B., E.A., S.A., İ.A.B., K.A., M.F.Y., Literature Search: K.B., E.A., S.A., K.A., Writing: K.B., İ.A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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