Botulinum A toxin for treatment of lower limb spasticity in cerebral palsy

Gait analysis in 49 patients

Anastasios S Papadonikolakis, Marios D Vekris, Anastasios V Korompilias, John P Kostas, Stavros E Ristanis and Panayotis N Soucacos

Department of Orthopaedic Surgery, University of Athens, School of Medicine, GR-145 61 Athens, Greece
Correspondence: soukakos@panafonet.gr
Submitted 02-09-16. Accepted 03-03-06

Background **Injection of botulinum type A toxin is a new treatment for spasticity.**

Patients and methods **We evaluated the effect of botulinum A toxin (BTX-A) in the lower limb muscles of patients having cerebral palsy. We tested 49 patients before and, on average, 4 (2–9) months after giving the toxin. The evaluation included 3-dimensional computerized gait analysis, changes in mobility level, using the Gillette Functional Assessment Questionnaire, and gastrocnemius muscle bulk, using ultrasonographic measurements.**

Results **The patients were divided into 3 groups, according to the site of BTX-A administration (hamstrings, gastrocnemius and multilevel). Those who were injected in the hamstrings showed a significant improvement in only the maximum knee extension angle during the gait cycle. Those with spastic equinus who were injected in the gastrocnemius muscle responded better than the other groups. The ankle angle on the initial contact, terminal stance and preswing, maximum dorsiflexion, ankle range of motion, per cent of single support and gait velocity improved significantly. Overall, the patients showed significant improvements in motor skill performance and functional health.**

Interpretation **Our findings indicate that botulinum type A toxin can be given as an adjuvant to conservative treatment of patients with cerebral palsy.**

Botulinum type A (BTX-A) toxin has emerged during the last decade as a new treatment for the management of spasticity. The pharmacologic effect of BTX-A is obtained after about 3–6 months (Corry et al. 1998, Koman et al. 2001). The drug is well tolerated and has only minor side effects. When injected intramuscularly, BTX-A inhibits the release of acetylcholine in the neuromuscular junction, which causes partial chemodenervation of the injected muscle (Kao et al. 1976).

Since the first therapeutic application of BTX-A in cerebral palsy (CP) by Koman et al. (1993), several authors have evaluated its effectiveness in the management of spastic equinus (Corry et al. 1998, Eames et al. 1999, Boyd et al. 2000, Koman et al. 2001, Metaxiotis et al. 2002). However, most of them used subjective measures, like observational gait analysis in the form of the Physician Rating Scale and evaluation of spasticity with the Ashworth scale, which may be affected by the caregivers or clinicians (Arens et al. 1998, Goldberg 2000). Only a few studies have used objective measures, such as 3-dimensional computerized gait analysis. Therefore, more evidence-based studies are needed to evaluate changes in functional health, as suggested by Goldberg (2000).

We prospectively assessed the effect of BTX-A treatment on the motor skills and functional health of CP patients who received either multilevel injections or administration of the toxin in selected muscle groups.

Patients and methods

We studied 49 patients with cerebral palsy (33 spas-

tic diplegia, 8 quadriplegia, 8 spastic hemiplegia) of whom 33 were independent ambulators and 16 dependent ambulators. The inclusion criteria were: ability to walk (assisted or unassisted), no previous surgery or previous surgery at least 1 year before (Chambers et al. 1998, DeLuca et al. 1998), no fixed contractures, no other treatment (casting or orthoses), no significant difference in length (> 5 cm) between the right and left legs and no previous BTX-A treatment. The patients in this study followed a standard program of physiotherapy 4–5 times weekly after the injections. As reported by the physiotherapists, the program (stretching, etc.) was influenced positively by a reduction in spasticity.

The mean age of the patients was 11 (2–23) years. On each visit, they underwent a physical examination involving passive range of motion and 3-dimensional computerized gait analysis with 6 cameras, including videotaping (Peak Performance Technologies, Colorado, USA). The data on gait were collected, using Corry et al.'s method (1998). We recorded at least 6 walks on a 10-meter walkway and selected three "typical" walks for analysis. We also documented changes in mobility status noted by parents/caregivers, using the Gillette Functional Assessment Questionnaire (FAQ) (Novacheck et al. 2000). The FAQ is a 10-level, parent report; its walking scale encompasses walking ability ranging from nonambulatory to ambulatory.

The patients were divided into 3 groups according to the site of toxin administration. In group A (n = 18), the multilevel injections were given in at least 2 muscle groups (hip flexors (tensor fasciae latae, rectus femoris), hip adductors, hamstrings, gastrocnemius). 14 patients received bilateral lower limb injections, while 4 patients received unilateral injections. In group B (n =14), the toxin was given to 12 patients in the hamstrings bilaterally and to 2 patients unilaterally. In group C (n =17), the gastrocnemius muscle was injected in 15 patients bilaterally and in 2 unilaterally (Table 1).

We evaluated all patients before and, on average, 4 (2–9) months after the intramuscular injection of the toxin. The maximum dosage was based on the patient's body weight and the site of the injection. The dosage of the toxin (BOTOX, Allergan, USA) ranged from 6 to 14 Units per kg of body weight. Some patients were given Dysport (Spreywood, Wrexham, UK). In these patients, the toxin dosage was calculated, using a conversion ratio of 4:1 Units for Dysport and BOTOX, which has been shown to be a good estimate for similar clinical efficacy and tolerability between the two formulations of the drug (Sampaio et al. 1997).

Apart from body weight, the degree of spasticity, determined on the physical examination, and the bulk of the muscles, were also taken into account when calculating the amount of toxin injected. The dosage of the toxin for each muscle and the number of injection sites are shown in Table 1.

Each vial of BTX-A was reconstituted with 3–5 mL of sterile saline (NaCl 0.9%). No sedation was used for injections although the injection sites were numbed with ice spray. The drug was administered via 27-gauge needles and 2.5-mL syringes under sterile conditions in all injections. The patients were discharged from the hospital after observation for 30 minutes.

The amount of gastrocnemius atrophy produced by the chemodenervation effect of the toxin (To et al. 2001) was evaluated in 10 patients from group C, using ultrasonographic muscle bulk measurements. This indicated the pharmacological effect of the toxin. We also determined the intraobserver variation of the ultrasonographic measurements in the present study in 10 normal subjects. The same observer made the measurements twice on 2 different occasions.

Statistics

The statistical analysis of the Functional Assessment Questionnaire scores was done, using the Wilcoxon signed-rank test. We analyzed selected gait parameters and ultrasonographic muscle width measurements, using paired t-tests. The Kruskal-Wallis one-way analysis of variance was used to assess whether there were differences between the 4 groups in the mobility status (FAQ) at baseline ($p > 0.05$). The level of significance was set at 0.05 for the statistical analyses. All results are expressed as mean (SD).

Results

An increase in the passive range of motion was seen only in the gastrocnemius group during the

Table 1. Dosages of botulinum A toxin (BTX-A), sites of injections and characteristics of the patients

	Group A (n=18)	Group B (n=14)	Group C (n=17)
Mean age in years	12 (4–19)	11 (2–17)	11 (7–14)
Dosage of BTX-A/kg of body weight (maximum)	9–14 IU/kg (400IU)	6–8 IU/kg (400IU)	4–6 IU/kg (200IU)
Injected muscles (number of injection sites)	Any combination of: rectus femoris (2–4), tensor fasciae latae (2–3), semitendinosus (2–4), membranosus (2–4), hip adductors (4), gastrocnemius (4)	Semitendinosus (2–4) Semimembranosus (2–4)	Lateral (2) and medial (2) head of the gastrocnemius
Dosage/muscle	Hip adductors 75–200 IU Other muscles similar to other groups	Semitendinosus 100–200 IU Semimembranosus 50–200 IU	Gastrocnemius 50–200 IU
Previous operations (at least 1 year before)	12 patients= (6 bil. add. release + ATL) (1 uni. rectus femoris release + ATL) (2 bil. HS release + ATL) (3 bil. ATL)	12 patients= (5 bil. add. release + ATL) (3 bil. add. release) (2 bil. ATL) (2 uni. ATL)	14 patients= (2 bil. add. release + ATL) (2 bil. HS release + ATL) (2 bil. HS release) (4 bil. ATL), (3 uni. ATL) (1 bil. HS release + ATL)
Independent ambulators (patients)	12	9	12

Bil bilateral, Uni unilateral, Add adductor, HS hamstrings, ATL Achilles tendon lengthening. Dosages are in IU of Botox.

physical examination. The maximum ankle dorsiflexion was 14 (11) degrees before the injection and 20 (10) degrees after it.

The overall mean mobility level (FAQ) in all patients improved significantly during the follow-up ($p < 0.001$) (Figure 1). 16 patients had a 1-level improvement, 5 a 2-level improvement and 28 patients had no change.

Gait parameters

In group A (Table 2), the maximum hip extension was 6 (10) degrees of flexion before the injection and 0 (12) degrees of extension at follow-up ($p = 0.03$). We also found improvements in the ankle angle on initial contact ($p = 0.02$) and terminal stance ($p = 0.03$), while the maximum ankle dorsiflexion during the gait cycle had also improved ($p = 0.03$). The time and distance parameters showed no significant improvement in this group, apart from the gait velocity (pre: 0.6 (0.3) m/sec; post: 0.8 (0.2) m/sec; $p = 0.02$).

We found minor changes in group B. The maximum knee extension during the gait cycle had improved (pre: 14 (9) degrees; post: 10 (9) degrees; $p = 0.04$) as also had the stride length on both sides. However, no significant difference was found in the gait velocity.

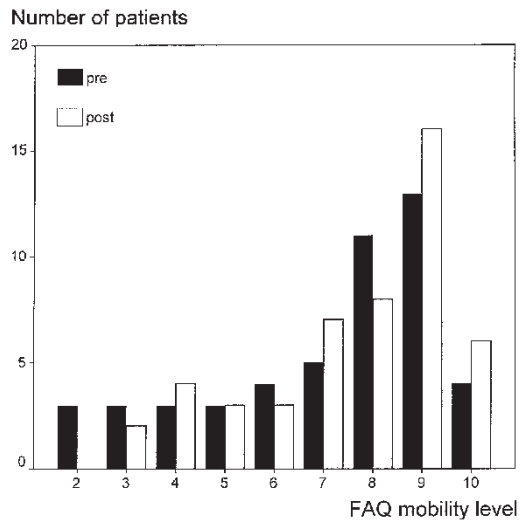

Figure 1. FAQ mobility level before and after intramuscular injection of BTX-A.

The patients in group C who received the toxin only in the gastrocnemius muscles showed a better response than the other 2 groups. Almost all sagittal plane ankle kinematic variables (ankle

Table 2. Mean kinematic and time distance parameters with standard deviation (SD) in all groups of patients before and after treatment

Gait parameters	(A) Multilevel (n=18) Pre	(A) Multilevel (n=18) Post	(B) Hamstrings (n=14) Pre	(B) Hamstrings (n=14) Post	(C) Gastrocnemius (n=17) Pre	(C) Gastrocnemius (n=17) Post
Hip flexion (initial contact)	42 (15)	37 (14)	46 (34)	40 (5)	39 (13)	42 (7)
Hip flexion (terminal stance)	9 (9)	7 (17)	12 (4)	10 (6)	21 (5)	23 (6)
Max hip flexion [a]	49 (13)	44 (14)	49 (4)	46 (5)	38 (8)	43 (5)
Min hip flexion [a]	6 (10)	0 (12) [b]	17 (16)	16 (11)	–3 (12)	3 (11)
Hip range of motion [a]	43 (12)	44 (10)	32 (11)	30 (10)	41 (9)	40 (10)
Max hip abduction [a]	1 (8)	–3 (4)	–2 (3)	1 (6)	4 (6)	4 (5)
Max hip adduction [a]	–16 (4)	17 (7)	–14 (4)	12 (3)	–11 (7)	–12 (4)
Knee flexion (initial contact)	18 (16)	17 (13)	19 (4)	17 (8)	14 (12)	15 (8)
Knee flexion (loading response)	9 (12)	5 (11)	22 (6)	21 (9)	11 (13)	13 (11)
Knee flexion (terminal stance)	10 (13)	8 (10)	18 (12)	13 (9)	8 (12)	7 (8)
Knee flexion (preswing)	17 (11)	14 (11)	24 (18)	26 (18)	26 (17)	20 (12)
Max knee flexion (during swing)	41 (13)	40 (10)	50 (10)	49 (13)	52 (10)	51 (13)
Min knee flexion (during stance)	0 (10)	0 (8)	14 (9)	10 (9) [b]	0 (9)	3 (9)
Knee range of motion [a]	41 (15)	40 (12)	35 (9)	38 (14)	52 (11)	48 (16)
Ankle dorsiflexion (initial contact)	–9 (7)	4 (9) [c]	10 (8)	7 (9)	–4 (6)	2 (5) [d]
Ankle dorsiflexion (terminal stance)	3 (6)	7 (4) [b]	5 (6)	1 (4)	–4 (5)	0 (3) [c]
Ankle dorsiflexion (preswing)	–2 (10)	3 (9)	8 (7)	6 (9)	0 (7)	8 (5) [d]
Max ankle dorsiflexion [a]	7 (5)	11 (5) [b]	13 (10)	15 (8)	5 (5)	10 (4) [c]
Min ankle dorsiflexion [a]	–22 (12)	–19 (12)	–10 (4)	–12 (4)	–22 (10)	25 (5)
Ankle range of motion [a]	30 (13)	31 (12)	23 (12)	27 (6)	27 (9)	36 (6) [b]
Right double support %	38 (17)	32 (12)	44 (7.7)	41 (7.6)	44 (17)	36 (17)
Left double support %	38 (13)	30 (2.7)	41 (5.7)	40 (8.5)	40 (14)	30 (14) [c]
Right single support %	30 (11)	34 (9.8)	30 (10)	29 (12)	30 (9.7)	34 (9.5) [c]
Left single support %	31 (8.5)	31 (4.8)	30 (3.3)	29 (4.2)	29 (7.9)	32 (9.1)
Right stride length (m)	0.80 (0.3)	0.80 (0.2)	0.63 (0.1)	0.75 (0.2) [b]	0.76 (0.2)	0.85 (0.2)
Left stride length (m)	0.70 (0.2)	0.80 (0.2)	0.70 (0.1)	0.76 (0.2) [b]	0.76 (0.3)	0.76 (0.2)
Cadence (steps/min)	92 (19)	99 (21)	88 (27)	93 (17)	100 (35)	119 (46)
Gait velocity (m/sec)	0.60 (0.3)	0.80 (0.2) [c]	0.57 (0.21)	0.59 (0.20)	0.68 (0.34)	0.91 (0.39) [b]

[a] During the entire gait cycle
Significant differences at the [b] 0.05, [c] 0.02 and [d] 0.01 level. Positive values indicate ankle dorsiflexion, knee flexion, hip flexion and hip abduction, while negative values indicate ankle plantarflexion, knee hyperextension, hip extension and hip abduction.

angle on initial contact, terminal stance, preswing, maximum dorsiflexion and ankle range of motion) had significantly improved. The percent period of double support for the left limb had become significantly lower (pre: 40 (14); post: 30 (14); $p = 0.02$) and these patients showed a significant improvement in gait velocity (pre: 0.68 (0.34) m/sec; post: 0.91 (0.39) m/sec; $p = 0.04$) (Table 2).

Ultrasonographic measurements

The intraclass correlation coefficient (ICC) for the ultrasonographic measurements in 10 normal subjects was 0.89. In 10 group C patients, the ultrasonographic gastrocnemius muscle belly measurements showed that the toxin significantly reduced the size of the lateral and medial heads of the muscle. The width of the medial head of the gastrocnemius had decreased from 12.6 (2.8) mm to 10.6 (2.8) mm ($p < 0.001$), while the lateral head had decreased from 12.1 (2.8) mm to 9.7 (2.0) mm ($p < 0.001$). However, the muscle belly atrophy did not correlate with the improvement in the ankle kinematic variables.

Adverse effects

No serious adverse reactions were observed. 4 patients complained of muscle weakness and imbalance, but recovered about 2 weeks after the injection. Pain at the injection site was the commonest adverse effect, the rarest complication being a transient autonomic nervous system dysfunction. This has also been reported previously (Papadonikolakis et al. 2002).

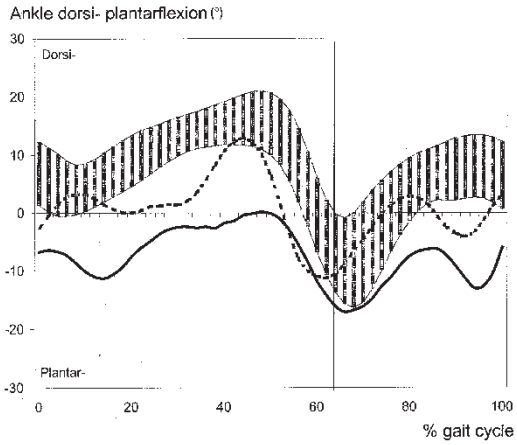

Figure 2. 9-year-old male with spastic equinus of the foot. Dynamic left ankle dorsi- plantarflexion curves before (solid line) and after BTX-A injections into the gastrocnemius muscle (dotted line). Normal curves are shown for comparison.

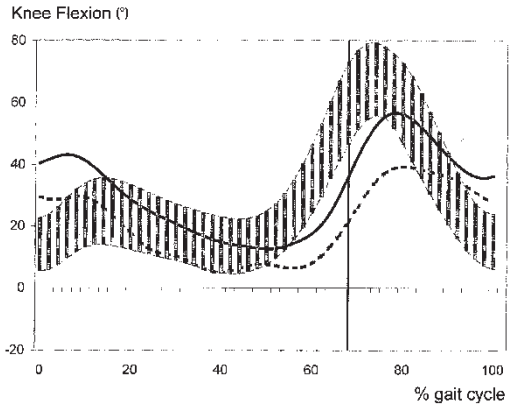

Figure 3. 13-year-old female with bilateral crouch knee gait due to hamstring spasticity. Right knee flexion extension during a gait cycle. Solid line represents knee kinematics before the BTX-A injection. Initial foot contact with 40 degrees of knee flexion. After the BTX-A treatment, initial foot contact with 30 degrees of flexion (dotted line). Normal findings are shown for comparison.

Discussion

Only patients who were injected in the gastrocnemius muscle for the treatment of spastic equinus showed an improvement in the passive range of motion during physical examination. However, since a passive range of motion is a subjective measure, we did not analyze the data statistically (McMulkin et al. 2000). Moreover, it should be emphasized that the range of motion recorded during gait analysis and the passive range of motion measured on physical examination are not necessarily related (Corry et al. 1998).

Computerized gait analysis is generally recognized as an objective measure of changes in ambulation after therapeutic intervention (Gage et al. 1996). In this series, patients with spastic equinus who were injected in the calf muscles showed improvement in a greater number of kinematic variables than the other groups. Patients with spastic equinus had significant improvement in ankle angular kinematics (Figure 2).

Other authors (Cosgrove et al. 1994, Sampaio et al. 1997, Corry et al. 1998, 1999, Eames et al. 1999, Sutherland et al. 1999, Wissel et al. 1999, Koman et al. 2000, Ubhi et al. 2000), using observational video analysis in the form of the Physician Rating Scale or computerized gait analysis have reported a significant improvement in the range of motion. Eames et al. (1999) found that the toxin improves gait function and contributes to the delay in gastrocnemius shortening. They used 3-dimensional gait analysis and mathematical muscle modeling. Evidence of improvement in the kinetics of the ankle has also been noted (Boyd et al. 2000). Sutherland et al. (1999) studied 10 patients with dynamic spastic equinus who were injected in the calf muscles and reported improvement in the ankle angle on initial foot contact and maximum dorsiflexion in stance at 2 and 12 weeks after injection.

We evaluated muscle belly atrophy produced by the partial chemodenervation effect of the toxin after calf injections, using ultrasonographic measurements in 10 group C patients. Ultrasonography has been reported to be a reliable and valid method for assessing muscle size (Bemben 2002). A significant reduction was found, on average, 5 months after the injections. Similarly, To et al. (2001), using ultrasonography, reported a peak reduction of 30% 3 months after BTX-A injection in the masseteric muscle. The differences in the amount of atrophy may have been due to differences in the distribution and concentration of the motor end plates together with differences in size between the gastrocnemius and masseteric muscles. We regarded muscle belly atrophy as an indication of the response to the toxin. However, we found no correlation between the degree of the response (atrophy) and the dynamic component (gain in range of motion during gait).

Eames et al. (1999), using mathematical modeling, also reported that no correlation exists between these two parameters.

Although the mean age of our patients exceeded that in other reports (Corry et al. 1998, Koman et al. 2000, Metaxiotis et al. 2002), we observed significant improvements following BTX-A treatment. Our findings support the view of Koman et al. (2000) that if patients are carefully chosen, BTX treatment can improve function, even in older children. However, Cosgrove et al. (1994) reported that only the gastrocnemius muscle was characterized by an inadequate response in older patients, while the response of the hamstrings was not affected by the patients' age. Our data do not confirm the limited response of the gastrocnemius muscle in older patients.

Patients with a crouch gait who received injections in the hamstrings (group B) showed improvement in their maximum knee extension angle during the gait cycle (Figure 3). Thompson et al. (1998), who examined 10 patients, reported an increase in the maximum knee extension 2 weeks after isolated hamstring injections. They found that both short and adequate length hamstring muscles sustained significant muscle lengthening. Although in our study the stride length showed improvement, gait velocity didnot change significantly in this group. In contrast, gait velocity improved in all other groups.

It is not clear whether multilevel injections of BTX-A have a good effect. We found an improvement in 3 gait variables after multilevel injections. This accords with the findings of Molenaers et al. (2001), who proposed multilevel injections only in young patients, to avoid the development of fixed contractures and bony deformities. Moreover, we believe that if all patients were evaluated during a period of 3-6 months, which is the duration of the chemodenervation effect of BTX-A, the improvement in gait patterns might have been slightly better.

It is also unclear whether treatment of hip flexion contracture deformities with botulinum toxin injections can improve the ambulatory status of CP patients. Willenborg et al. (2002) reported that under ultrasonographic guidance combined with active electromyography it is possible to inject the iliopsoas muscle, which is thought to be primarily responsible for hip flexion contracture deformity (DeLuca et al. 1998). However, more studies are needed to evaluate such an approach.

Since the goals of treatment in CP are to improve function and not only joint motion, supplementary community information is of value in assessing therapeutic interventions (Goldberg 2000). We used the functional assessment questionnaire (FAQ) as a parent-based functional questionnaire to measure physical performance (Novacheck et al. 2000). The FAQ is a reliable tool for between and within raters for the range of community ambulation and it has a good correlation with the WeeFIM and POSNA scales in a variety of functional levels (Novacheck et al. 2000). We noted a 2-level improvement in only 5 patients, a 1-level improvement in 16 and no change in 28 patients. In a group of 118 operated patients, no change was found in about 35 patients (Novacheck 1997). Although 3- and 4-level improvements have been reported in operated patients, there was also a reduction in the mobility level (Novacheck 1997). We found no negative changes in the mobility level.

Some variations in the rates of response to BTX have been reported. Koman et al. (2000) reported a 40–60% response, using the Physician Rating Scale. Ubhi et al. (2000) found a 37% rate of response in a randomized double blind control trial. The overall response to the BTX-A treatment was 43% in this study, according to the FAQ.

Patients injected with BTX-A had no severe adverse effects. Pain at the injection site was the commonest adverse effect and could be reduced by applying ice spray on the injection site before giving BTX-A. Imbalance, fatigue and unstable gait were rare events and usually transient. A case of transient erectile dysfunction was noticed in one patient after hamstring injections (Papadonikolakis et al. 2002). However, very few autonomic nervous system dysfunctions have been reported in the literature after BTX treatment (Boyd et al. 1996). Autonomic dysfunctions are most likely the result of retrograde axoplasmic flow of the toxin to the spinal cord or local spread of the toxin.

Arens L J, Goldschmidt R B, Leary P M. Botulinum toxin treatment in cerebral palsy: intervention with poor evaluation? Dev Med Child Neurol 1998; 40 (11): 785-7.

Bemben M G. Use of diagnostic ultrasound for assessing muscle size. J Strength Cond Res 2002; 16 (1): 103-8.

Boyd R N, Britton T C, Robinson R O, Borzyskowski M. Transient urinary incontinence after botulinum A toxin. Lancet 1996; 348 (9025): 481-2.

Boyd R N, Pliatsios V, Starr R, Wolfe R, Graham H K. Biomechanical transformation of the gastrocnemius-soleus muscle with botulinum toxin A in children with cerebral palsy. Dev Med Child Neurol 2000; 42 (1): 32-41.

Chambers H, Lauer A, Kaufman K, Cardelia J M, Sutherland D. Prediction of outcome after rectus femoris surgery in cerebral palsy: the role of cocontraction of the rectus femoris and vastus lateralis. J Pediatr Orthop 1998; 18 (6): 703-11.

Corry I S, Cosgrove A P, Duffy C M, McNeill S, Taylor T C, Graham H K. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. J Pediatr Orthop 1998; 18 (3): 304-11.

Corry I S, Cosgrove A P, Duffy C M, Taylor T C, Graham H K. Botulinum toxin A in hamstring spasticity. Gait Posture 1999; 10 (3): 206-10.

Cosgrove A P, Corry I S, Graham H K. Botulinum toxin in the management of the lower limb in cerebral palsy. Dev Med Child Neurol 1994; 36 (5): 386-96.

DeLuca P A, Ounpuu S, Davis R B, Walsh J H. Effect of hamstring and psoas lengthening on pelvic tilt in patients with spastic diplegic cerebral palsy. J Pediatr Orthop 1998; 18 (6): 712-8.

Eames N W, Baker R, Hill N, Graham K, Taylor T, Cosgrove A. The effect of botulinum toxin A on gastrocnemius length: magnitude and duration of response. Dev Med Child Neurol 1999; 41 (4): 226-32.

Gage J R, DeLuca P A, Renshaw T S. Gait analysis: principle and applications with emphasis on its use in cerebral palsy. Instr Course Lect 1996; 45 (10): 491-507.

Goldberg M J. Botulinum toxin type A improved ankle function in children with cerebral palsy and dynamic equinus foot deformity. J Bone Joint Surg (Am) 2000; 82 (6): 874.

Kao I, Drachman D B, Price D L. Botulinum toxin: mechanism of presynaptic blockade. Science 1976; 193 (4259): 1256-8.

Koman L A, Mooney J F, III, Smith B, Goodman A, Mulvaney T. Management of cerebral palsy with botulinum-A toxin: preliminary investigation. J Pediatr Orthop 1993; 13 (4): 489-95.

Koman L A, Mooney J F, III, Smith B P, Walker F, Leon J M. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. BOTOX Study Group. J Pediatr Orthop 2000; 20 (1): 108-15.

Koman L A, Brashear A, Rosenfeld S, et al. Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. Pediatrics 2001; 108 (5): 1062-71.

McMulkin M L, Gulliford J J, Williamson R V, Ferguson R L. Correlation of static to dynamic measures of lower extremity range of motion in cerebral palsy and control populations. J Pediatr Orthop 2000; 20 (3): 366-9.

Metaxiotis D, Siebel A, Doederlein L. Repeated botulinum toxin A injections in the treatment of spastic equinus foot. Clin Orthop 2002; 394: 177-85.

Molenaers G, Desloovere K, De Cat J, et al. Single event multilevel botulinum toxin type A treatment and surgery: similarities and differences. Eur J Neurol (Suppl 5) 2001; 8: 88-97.

Novacheck, T F. Assessing Functional Outcomes. 1997. Connecticut Children's Medical Center, Hartford, Connecticut, U.S.A. Clinical Gait Analysis. A Focus on Interpretation. Course Handout April 24, 1997.

Novacheck T F, Stout J L, Tervo R. Reliability and validity of the Gillette Functional Assessment Questionnaire as an outcome measure in children with walking disabilities. J Pediatr Orthop 2000; 20 (1): 75-81.

Papadonikolakis A S, Vekris M D, Kostas J P, Korompilias A V, Soucacos P N. Transient erectile dysfunction associated with botulinum type A intramuscular injection. J South Orthop Assoc 2002; 11 (2):116-88.

Sampaio C, Ferreira J J, Simoes F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A--Dysport and Botox--assuming a ratio of 4:1. Mov Disord 1997; 12 (6): 1013-8.

Sutherland D H, Kaufman K R, Wyatt M P, Chambers H G, Mubarak S J. Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. Gait Posture 1999; 10 (1): 1-9.

Thompson N S, Baker R J, Cosgrove A P, Corry I S, Graham H K. Musculoskeletal modelling in determining the effect of botulinum toxin on the hamstrings of patients with crouch gait. Dev Med Child Neurol 1998; 40 (9): 622-5.

To E W, Ahuja A T, Ho W S, et al. A prospective study of the effect of botulinum toxin A on masseteric muscle hypertrophy with ultrasonographic and electromyographic measurement. Br J Plast Surg 2001; 54 (3): 197-200.

Ubhi T, Bhakta B B, Ives H L, Allgar V, Roussounis S H. Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. Arch Dis Child 2000; 83 (6): 481-7.

Willenborg M J, Shilt J S, Smith B P, Estrada R L, Castle J A, Koman L A. Technique for iliopsoas ultrasound-guided active electromyography-directed botulinum A toxin injection in cerebral palsy. J. Pediatr Orthop 2002; 22 (2): 165-8.

Wissel J, Heinen F, Schenkel A, et al. Botulinum toxin A in the management of spastic gait disorders in children and young adults with cerebral palsy: a randomized, double-blind study of "high-dose" versus "low-dose" treatment. Neuropediatrics 1999; 30 (3): 120-4.