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The Effects of Botulinum Toxin Type-A on Spasticity and Motor Function in Children with Cerebral Palsy

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Disciplines

Physical Therapy

Critically Appraised Topic

Title: The Effects of Botulinum Toxin Type-A on Spasticity and Motor Function in Children with Cerebral Palsy

Clinical Scenario: The patient who led me to pursue this question is a 7-year-old male with a diagnosis of cerebral palsy (CP) with spastic diplegia and bilateral hip subluxation with acetabular dysplasia and bilateral equinus contractures. Medical treatment to date has included bilateral proximal femur varus derotation osteotomies with blade plate fixation, Dega pelvic acetabuloplasties, and bilateral botulinum toxin A (BTX-A) injections of the gastrocsoleus complex. Problems identified include bilateral hip and knee flexion contractures, bilateral lower extremity strength deficits, decreased bed mobility, decreased transfers, decreased bilateral lower extremity weight bearing tolerance, and decreased ambulation quality and endurance.

Brief introduction: For the purposes of my clinical question, I want to know what the research says about the effects of BTX-A injections on children with CP. BTX-A is a known biological substance that blocks acetylcholine (ACh) release presynaptically at the neuromuscular junction, which causes temporary paralysis of the injected muscles[1]. Since I did my third clinical rotation at a pediatric orthopedic hospital, the patients I worked with often have orthopedic impairments secondary to cerebral palsy including hip dysplasia; hamstring, adductor, and gastrocsoleus muscle contractures; and foot deformities. Many of the patients with CP that I worked with had BTX-A injections often to the hamstrings and gastrocsoleus complex. According to the literature, it has been shown that the benefits of BTX-A treatment include decreased spasticity, improved joint range of motion, improved gait patterns, and improved functional outcomes. However, controversy exists over the effects of BTX-A injections on muscle size and morphology.

My clinical question: Do botulinum toxin A injections in conjunction with physical therapy treatment result in improved muscle spasticity and motor function compared to physical therapy treatment alone in children with CP?

Clinical question PICO:

Population: Children with spastic CP, Gross Motor Function Classification System (GMFCS) level I-IV

Intervention: BTX-A injections plus physical therapy (PT)/exercise therapy

Comparison: Usual PT treatment

Outcome: Muscle spasticity (outcome measures including, but not limited to, the Modified Ashworth Scale) and motor function (outcome measures including GMFM, muscle strength, gait analysis, and/or joint ROM)

Overall Clinical Bottom Line: Due to the significant number of major threats to the internal validity of the Williams *et* al. study, including lack of a well-explained study design that

necessitated many assumptions regarding data analysis, the data from this article will be excluded in this overall clinical bottom line. Based on the results of the outcomes from Scholtes *et al.*, El-Etribi *et al.*, and Reddihough *et al.* with a composite number of 135 subjects, BTX-A injections to select lower extremity muscles in conjunction with a PT program resulted in only modest statistically significant improvements in muscle spasticity and motor function compared to PT alone. The amount of PT hours the intervention groups received ranged from approximately 27.8 hours to approximately 60 hours. The general principles and concepts of the PT programs can readily be applied in the clinical setting. Of the three studies, the greatest improvement in muscle spasticity was 1.04 MAS points and the greatest improvement in ankle dorsiflexion passive ROM with knee flexion was 13.7˚. However, since there is no established MCID for the MAS in children with CP, it is not known whether this change in muscle spasticity was clinically important. The amount of change in ankle dorsiflexion ROM likely exceeds the MDC for a goniometric measurement, so it is reasonable to expect that some individuals experienced a real average increase in ankle dorsiflexion ROM, though whether this was clinically significant was not determined. Since the peak BTX-A effect is typically around 6 weeks post-injection[1], the majority of the assessment time points (~64%) in all of these studies are likely beyond the timeframe of peak BTX-A effect. Another possible reason why these studies did not show better improvements is suboptimal selection of outcome measures, as muscle strength and muscle volume may not have best captured the effects of the BTX-A injections. Last, due to poor data presentation and discussion, major assumptions needed to be made regarding the assessment time points of the control group in the Reddihough *et al*. article, as well as timing of BTX-A injections in relation to initiation of the strength training program and total number of hours of strength training in the Williams *et al*. article. These assumptions significantly threatened the confidence in data interpretation and conclusions drawn from these studies. Only the Reddihough *et al*. study included outcome measures assessing functional improvements (via the GMFM) and parent satisfaction (via the parental questionnaire). For the other studies, it would have been helpful to know if the small improvements in muscle spasticity and ROM allowed the children and/or parents to more easily perform functional ADLs or IADLs. Future studies should include the use of outcome measures that capture participation level activities. Due to the many threats to the internal validity that significantly compromise methodological quality, the results from these studies should be not be extrapolated to a larger patient population.

Search Terms: cerebral palsy, botulinum toxin-A, spasticity, physical therapy, physiotherapy, exercise therapy

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Rationale for chosen articles

I mainly used the PubMed, PEDro, and Web of Science databases to search for my articles using the search terms listed previously. I narrowed down my search to only include randomized

controlled trials. I briefly skimmed the titles and abstracts of relevant articles that compared the use of botulinum toxin A (BTX-A) in conjunction with physical therapy treatment to physical therapy treatment alone specifically in the population of children with cerebral palsy. From there, I chose to pursue the articles, which included the outcome measures I was interested in, which were spasticity and motor function. I initially sought articles that used the Gross Motor Function Measure (GMFM) as the method of quantifying motor function. However, it soon became apparent that few articles included both spasticity and the GMFM as outcome measures. I realized I had to broaden my outcome measure of interest, so I searched for articles including some method of quantifying motor function as outcome measures. I found additional articles that utilized outcome measures such as muscle morphology and strength, lower extremity joint range of motion, and aspects of muscle function through gait analyses. I finally chose the four articles with the highest PEDro scores and most detailed study designs.

1) Scholtes VA, Dallmeijer AJ, Knol DL, *et al*. Effect of multi-level botulinum toxin A and comprehensive rehabilitation on gait in cerebral palsy. *Pediatr Neurol* 2007; 36:30-39.
    - PEDro score: 5/10
    - **P**opulation: 46 children with spastic hemiplegic or diplegic CP who walk with flexed knees, GMFCS levels I through IV, age 4-11.5 years
    - **I**ntervention: Multi-level BTX-A injections and comprehensive rehabilitation
    - **C**omparison: Usual physiotherapy
    - **O**utcome measures of interest: Lower extremity muscle spasticity, lower extremity muscle length, lower extremity ROM during gait
2) El-Etribi MA, Salem MA, El-Shakankiry HM, *et al*. The effect of botulinum toxin type A injection on spasticity, range of motion and gait patterns in children with spastic diplegic cerebral palsy: an Egyptian study. *Int J Rehabil Res* 2004; 27:275-81.
    - PEDro score: 4/10
    - **P**opulation: 40 children with spastic diplegic CP, GMFCS levels unspecified, age 2-6 years
    - **I**ntervention: BTX-A injections and physiotherapy for 3 months
    - **C**omparison: Physiotherapy only for 3 months
    - **O**utcome measures of interest: MAS, passive ankle dorsiflexion ROM, dynamic gait patterns
3) Reddihough DS, King JA, Coleman GJ, *et al.* Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. *Dev Med Child Neurol* 2002; 44:820-7.
    - PEDro score: 3/10
    - **P**opulation: 49 children with spastic diplegic CP or mild to moderate spastic quadriplegic CP, GMFCS levels I through IV, age 1 year 10 months to 6 years 8 months
    - **I**ntervention: BTX-A injections and physiotherapy for 6 months
    - **C**omparison: Physiotherapy only for 6 months
    - **O**utcome measures of interest: Modified Ashworth Scale (MAS), Gross Motor Function Measure (GMFM), lower extremity joint range of movement (ROM), parental perception questionnaire, and Vulpe Assessment Battery (VAB)

4) Williams SA, Elliot C, Valentine J, *et al*. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength. *Disability & Rehabilitation* 2013; 35(7): 596-605.
    - PEDro score: 4/10
    - **P**opulation: 8 children (mean age 8 years, 3 months) with spastic diplegic CP, GMFCS level I through II
    - **I**ntervention: BTX-A injections and strength training for 10 weeks
    - **C**omparison: BTX-A injections and normal care for 6 months
    - **O**utcome measures of interest: MAS, muscle strength (via Biodex dynamometer and hand held dynamometer), muscle volume (via Magnetic Resonance Imaging), Goal Attainment Scale (GAS), and voluntary motor control (via the Selective Control Assessment of the Lower Extremity)

Table 1: Comparison of Article PEDro Scores

	Scholtes *et al.**	El-Etribi *et al.*	Reddihough *et al.*	Williams *et al.*
Random	✓	✓	✓	
Concealed allocation				
Baseline comparability	✓			
Blind Subjects				
Blind Therapists				
Blind Assessors				✓
Adequate Follow-up	✓	✓		✓
Intention-to-Treat		✓	✓	
Between Group	✓			✓
Point Estimates and Variability	✓	✓	✓	✓
Total Score	5/10	4/10	3/10	4/10

The asterisk (*) indicates the PEDro score was obtained from the PEDro database and was verified by myself. The PEDro scores for the remaining three articles were ranked by myself using the PEDro criteria.

Based on the above comparisons, I have chosen to write this critically appraised paper on the articles by Scholtes *et al*., El-Etribi *et al.*, Reddihough *et al*., and Williams *et al.*

Article: Scholtes VA, Dallmeijer AJ, Knol DL, *et al*. Effect of multi-level botulinum toxin A and comprehensive rehabilitation on gait in cerebral palsy. *Pediatr Neurol* 2007; 36:30-39.

Clinical Bottom Line: In this randomized controlled trial of 46 children with spastic hemiplegic or diplegic cerebral palsy (CP) who walk with flexed knees, multilevel botulinum toxin A (BTX-A) injections in conjunction with comprehensive rehabilitation improved muscle spasticity (as measured by the joint angle where a "catch" was felt in response to a single passive stretch occurring over less than 1 second), muscle length (as measured by the ROM with a slow passive stretch occurring over more than 3 seconds), and hip rotation during gait (as measured by a digital screen goniometer through video-recorded gait analysis) compared to usual care alone. The intervention group received BTX-A injections and comprehensive rehabilitation, which included intensive physiotherapy, orthoses, and/or serial casting, if necessary. The intensive physiotherapy protocol was 3-5 times per week for 45-60 minutes each session for 12 weeks (total of approximately 60 hours) and included active and passive stretching of the flexor muscles, strengthening of the extensor muscles, functional mobility training, and gait training. The control group did not receive any BTX-A injections and continued with their usual care that was described as low-intensity physiotherapy, 1-2 sessions per week for 30-60 minutes each session for 12 weeks (total number of approximately 18 hours) with some children using orthoses. At six weeks, the intervention group had statistically significant mean improvements in decreased spasticity of the hamstrings, soleus, and gastrocnemius; increased muscle length of the hamstrings and gastrocnemius; and increased hip forward rotation at terminal swing, compared to the control group. By Week 12, there were still statistically significant improvements in the intervention group on: decreased spasticity of the hamstrings, rectus femoris, soleus, and gastrocnemius; and increased muscle length of the hamstrings, soleus, and gastrocnemius. However, by six months, the only remaining statistically improvement in the intervention group versus the control group was increased muscle length of the hamstrings and gastrocnemius. In general, the 95% CIs for muscle spasticity and length at each time point were fairly narrow, which indicates we would expect only slight variability in the data if this experiment were repeated on a larger population fitting these inclusion and exclusion criteria. Also, in general, the low ends of the 95% CIs for muscle spasticity and length likely would not exceed the minimal detectable change (MDC) for a goniometric measurement. Thus, although there were more statistically significant mean improvements in the intervention group versus the control group during the 24-week study period, the majority of the improvements had dissipated by the 6-month time point, which is consistent with the mechanism of action of the BTX-A injections into the targeted muscles. The improvement in the intervention group cannot be attributed to the BTX-A injections alone due to the multimodal treatment the intervention group received, which also included intensive physiotherapy, orthoses, and/or serial casting as compared to the control group which received only usual therapy. The study had fair internal validity (PEDro score 5/10), with two major threats and one minor threat, which were unsuccessful randomization to groups regarding baseline knee flexion at midstance, rater bias of the gait analysis assessor, and inadequate power. The interventions could be readily applied in the clinical setting and the intensive physiotherapy protocol was described well enough to be reproduced. No additional special equipment was required, and the amount of clinical expertise and treatment time are feasible in the outpatient PT setting. Based on this article alone, the treatment benefits of BTX-A plus a comprehensive therapy intervention on decreasing muscle spasticity, increasing muscle length, and improving knee and hip ROM during gait may outweigh the costs of the therapists'

and patients' time. However, it would have been helpful to know if the small improvements in ROM allowed the children and/or parents to more easily perform functional ADLs or IADLs. Future studies should include the use of an outcome measure that captures participation level activities. Due to the fair internal validity, the results of this study should be cautiously extrapolated to a larger population.

Article PICO:

Population: 46 children with spastic hemiplegic or diplegic CP who walk with flexed knees, GMFCS levels I through IV, age 4-11.5 years

Intervention: Multi-level botulinum toxin A (BTX-A) injections and comprehensive rehabilitation

Comparison: Usual physiotherapy

Outcome measures of interest: Lower extremity muscle spasticity, lower extremity muscle length, lower extremity ROM during gait

Blinding: The authors did not indicate that the subjects or therapists were blinded. The study only had partial blinding of the assessors. The assessor scoring the lower extremity ROM measurements through the gait analysis videos was the only one who was blinded only to time of assessment but not treatment group. The other assessors were not blinded, which include those who assessed muscle length and spasticity. The authors felt that the lack of blinding of these assessors was not a significant threat because the assessors were not aware of any previous measurement results, which weakens rater bias. However, since gait analysis is a subjective qualitative analysis, the threat of rater bias increases. Although it is assumed that the subjects were not blinded to treatment group, the potential threat of the Hawthorne effect is negligible because the ability of these subjects to manipulate their gait patterns and muscle spasticity is very limited. Lack of blinding of the therapists is only a minor threat since they were instructed to follow a standardized treatment protocol.

Controls: The control group continued with usual care, as defined by low-intensity physiotherapy, 1-2 sessions per week for 30-60 minutes each session. Some children used orthoses as part of their usual care routine. Within the context of this study, this was an appropriate control group as the objective was to compare multilevel BTX-A injections and comprehensive rehabilitation to usual care. However, within the context of my clinical question, this was not an appropriate control group since the intervention group received multimodal treatment involving BTX-A injections, intensive physiotherapy, orthoses, and serial casting as needed. Any differences found between the control group and intervention group cannot be attributed to BTX-A alone since the intervention group received more treatments other than just BTX-A.

Randomization: The assignment of subjects to groups was randomized, though the authors did not describe how randomization was done, nor was it concealed. While there were no significant baseline differences between the groups including age, weight, gender, diagnosis, and GMFCS

classification, there was a significant increase in knee flexion angle at midstance in the control group. Although the authors provided no raw data on this difference, it appears that this difference was roughly 7 degrees. Thus, analysis of any difference between groups on outcome measures including this variable should not be assessed, as the control group would have to make a much larger improvement than the experimental group to result in a significant change. Therefore, randomization was only partially successful.

Study: This study was a multicenter, randomized controlled trial with 46 total subjects from four Dutch departments of rehabilitative medicine. The study duration was 24 weeks long. Inclusion criteria were as follows: diagnosis of CP, spastic hemiplegia or diplegia, age between 4-12 years, spasticity in two or more lower extremity muscle groups interfering with mobility, ability to walk independently with or without assistive devices, gait characterized by persistent knee flexion of 10˚ or more in midstance, two or more muscle groups in one limb requiring botulinum toxin A injection, ability to carry out instructions, and adequate knowledge of the Dutch language. Exclusion criteria were as follows: BTX-A treatment in lower extremities within 16 weeks before study inclusion, orthopedic surgery within 24 weeks before inclusion, contraindication for BTX-A, contraindication for general anesthesia, orthopedic deformities which have a negative influence on walking, severe fixed contractures, presence of ataxia or dyskinesia, and other problems negatively influencing walking. Children were randomly assigned to either the intervention group or the control group. There were 23 subjects in the intervention group who received multilevel BTX-A injections in conjunction with comprehensive rehabilitation, which included intensive physiotherapy, orthoses, and serial casting, if necessary. The intensive physiotherapy began one week post-BTX-A injections. The children received PT from a physiotherapist 3-5 times per week for 12 weeks total, with each session lasting 45-60 minutes. The treatment protocol included active and passive stretching of the flexor muscles, strengthening the extensor muscles, functional mobility training, and gait training. There were 23 subjects in the control group who continued with their usual care including low-intensity physiotherapy and orthosis use as necessary. The control group was able to receive multilevel BTX-A injections after the control period. The intervention group had assessments at four time points: baseline, 6 weeks, 12 weeks, and 24 weeks post-BTX-A injection. The control group had assessments at two time points: baseline and at an average of 24 weeks. Of note, the intervention group underwent gait analyses only at baseline, 6 weeks, and 24 weeks post-BTX-A injection.

Outcome measures: Lower extremity muscle spasticity was measured by measuring the joint angle where a "catch" was felt in response to one fast passive stretch occurring over less than 1 second. Lower extremity muscle length was measured at baseline, 6 weeks, 12 weeks, and 24 weeks post-BTX-A injections in the intervention group and at baseline and an average of 24 weeks in the control group. Muscle length was assessed over the ROM with a slow passive stretching occurring over more than 3 seconds. This slow passive stretch was done three times and ROM was measured on the third passive stretch. The authors reported that one experienced investigator performed both the muscle spasticity and muscle length measurements, while a second investigator performed the actual joint goniometric measurements. The authors did not cite any intra-rater reliability of these two assessors. The authors stated that they chose to use these passive stretch methods of assessing muscle spasticity and muscle length because of cited studies stating these were comparable to the modified Tardieu Scale and provide a more sensitive

method of detecting subtle intervention effects related to velocity as compared to the Modified Ashworth Scale. The authors cited one study in which the modified Tardieu Scale demonstrated validity in clinical practice for measuring spasticity. While the Tardieu Scale has been tested in the population of individuals with cerebral palsy, there is no established MCID for any population. The third outcome measure of interest is lower extremity ROM during gait. Subjects were video-recorded in the frontal and sagittal planes while walking on a level 10-meter long walkway, barefoot with or without an assistive device. A single blinded assessor measured the joint angles with a digital screen goniometer. The authors reported good intra-observer reliability with an intraclass correlation coefficient (ICC) of 0.90 for knee angle at midstance, 0.88 for ankle angle at midstance, 0.77 for knee angle at terminal swing and 0.74 for hip rotation at terminal swing.

Study losses: The authors reported that only one subject from the control group dropped out of the study after the baseline assessment due to parent request. The data from this child were not used in any of the analyses. This does not appear to be related to the intervention. Since this correlates to a 2% loss, an intention-to-treat analysis was not required and the authors did not perform one. All subjects were analyzed in the groups to which they were randomized and no group cross-over occurred.

Summary of internal validity: I deem the internal validity of this study to be fair (PEDro score = 5/10). There were three threats I identified. Of these, two were major threats and one was a minor threat. Unsuccessful randomization regarding baseline knee flexion at midstance was a major threat since knee angle during gait was an outcome measure in this study. Since the control group began this study with increased knee flexion at midstance, they would have to make greater improvements than the intervention group to show a significant change. The partially blinded assessor of gait is also a major threat since gait analysis is a subjective qualitative analysis. Since the assessor of gait was only blinded to time of assessment and not treatment group, this increases the threat of rater bias. Although the authors did not perform a power analysis in order to determine how many subjects would have been needed in this study to see a significant treatment effect, inadequate power is a minor threat due to the decent sample size in this study of 46 children.

Evidence: The outcome measures related to my clinical question are muscle spasticity, muscle length, and lower extremity joint angle during gait. Table 2 outlines between-group differences in muscle spasticity at week 6, 12, and 24.

Table 2. Between-group differences in muscle spasticity at Week 6, 12, and 24

Muscle	Week 6 Mean change (95% CI) in degrees	Week 12 Mean change (95% CI) in degrees	Week 24 Mean change (95% CI) in degrees
Hamstrings	-11.40 (-17.37 to -5.43)*	-11.68 (-18.50 to -4.87)*	-5.70 (-14.70 to 3.30)
Rectus femoris	11.50 (-0.25 to 23.26)	14.02 (0.59 to 27.45)*	21.98 (4.23 to 39.72)*
Adductors	2.62 (-1.37 to 6.62)	2.92 (-1.63 to 7.48)	3.41 (-2.61 to 9.42)
Soleus	5.45 (0.69 to 10.21)*	8.88 (3.45 to 14.31)*	3.81 (-3.37 to 10.99)
Gastrocnemius	5.69 (1.40 to 9.98)*	10.03 (5.12 to 14.93)*	6.31 (-0.18 to 12.80)

Asterisk (*) indicates statistical significance at $p < 0.05$. Negative values indicate decreased hamstring spasticity. Positive values indicate decreased spasticity on rectus femoris, adductors, soleus and gastrocnemius.

The authors found statistically significant decreases in hamstring, soleus, and gastrocnemius spasticity in the intervention group versus the control group from baseline to week 6, as measured by changes in the joint angles at which a "catch" was assessed. Clinically, this can be interpreted as a decrease in spasticity in these muscle groups at this time point. 95% confidence intervals (CIs), provided by the authors, indicate the range of values in which there is 95% certainty that the true mean value of the population lies within. For example, the 95% CI for hamstring spasticity of -17.37˚ to -5.43˚ indicates that the authors are 95% confident that the true mean change in hamstring spasticity would be between 5.43˚ and 17.37˚. This is a fairly narrow CI of approximately 12˚, which indicates that we could expect only slight variability in the data if this experiment were repeated on a larger population fitting these inclusion and exclusion criteria. Examination of the 95% CIs for the other muscles at week 6 also indicates a narrow 95% CI. While there was an average decrease in muscle spasticity in these muscle groups, we would expect some individuals would not experience a real change in spasticity at this time point, since the low ends of the 95% CIs for most of these muscles likely do not exceed the minimal detectable change (MDC) for a goniometric measurement of 5˚. The authors stated the same assessor performed the muscle spasticity measurements while a second assessor performed the goniometric measurements. Thus, inter-rater reliability is not a concern; however, intra-rater reliability was not cited.

From baseline to week 12, the authors found statistically significant decreases in hamstring, rectus femoris, soleus, and gastrocnemius spasticity in the intervention group versus the control group, indicating that these four muscle groups had decreased spasticity. While the four muscles experienced an average decrease in spasticity, we would expect some individuals would not experience a real change in spasticity at this time point, since the low ends of the 95% CIs for all of these muscles likely do not exceed the minimal detectable change for a goniometric measurement. The 95% CI for hamstring spasticity is approximately 14˚, which also indicates more expected variability in the data compared to the 95% CI for hamstring spasticity measured at week 6. The upper end of the CI of 18.50˚ at week 12 is greater than the upper end of the CI of 17.37˚ at week 6, though it likely does not reflect a real expected difference because 1.13˚ likely does not exceed the MDC with this outcome measure.

From baseline to week 24, the authors found a statistically significant decrease only in rectus femoris spasticity in the intervention group versus the control group. Although there was an average decrease in spasticity, we would expect some individuals would not experience a real change in spasticity at this time point, since the low end of the 95% CI (4.23˚) likely does not

exceed the MDC for a goniometric measurement. The 95% CI for rectus femoris spasticity is approximately 35˚. This fairly wide CI indicates more expected variability in the data compared to the 95% CI for rectus femoris spasticity measured at week 6. Effect size could not be calculated due to insufficient data given by the article authors.

Table 3 outlines between-group differences in muscle length at week 6, 12, and 24.

Table 3: Between-group differences in muscle length at Week 6, 12, and 24

Muscle	Week 6 Mean change (95% CI) in degrees	Week 12 Mean change (95% CI) in degrees	Week 24 Mean change (95% CI) in degrees
Hamstrings	-8.87 (-12.87 to -4.88)*	-9.68 (-14.24 to -5.12)*	-10.10 (-16.12 to -4.08)*
Rectus femoris	4.26 (-0.63 to 9.15)	3.71 (-1.83 to 9.29)	6.19 (-1.16 to 13.54)
Adductors	3.10 (-0.05 to 6.25)	1.34 (-2.25 to 4.94)	2.94 (-1.80 to 7.69)
Soleus	2.28 (-0.79 to 5.36)	3.82 (0.30 to 7.33)*	0.94 (-3.71 to 5.59)
Gastrocnemius	4.76 (2.04 to 7.47)*	3.57 (0.47 to 6.67)*	4.66 (0.57 to 8.75)*

Asterisk (*) indicates statistical significance at $p < 0.05$. Negative values indicate increased hamstring muscle length. Positive values indicate increased rectus femoris, adductor, soleus, and gastrocnemius muscle length.

The authors found statistically significant increases in hamstring and gastrocnemius length in the intervention group versus the control group from baseline to week 6, as measured by changes in the joint angles with a slow passive stretch occurring over more than 3 seconds. Clinically, this can be interpreted as an increase in length in these muscle groups at this time point. The 95% CI for hamstring length is -12.87˚ to -4.88˚ indicates that the authors are 95% confident that the true mean change in hamstring length would be between 4.88˚ and 12.87˚. This narrow CI of approximately 8˚ indicates that we could expect only slight variability in the data if this experiment were repeated on a larger population fitting these inclusion and exclusion criteria. Examination of the 95% CI for the other muscle (gastrocnemius) found to have a statistically significant increase in length also indicates a very narrow 95% CI. While these two muscles experienced an average increase in length, we would expect some individuals would not experience a real change in length at this time point, since the low ends of the 95% CIs for these muscles likely do not exceed the MDC for a goniometric measurement of 5˚.

From baseline to week 12, the authors found statistically significant increases in hamstring, soleus, and gastrocnemius length in the intervention group versus the control group, indicating that these three muscles had increased length. While the three muscles experienced an average increase in length, we would expect some individuals would not experience a real change in length at this time point, since the low ends of the 95% CIs for all these muscles likely do not exceed the MDC for a goniometric measurement. The 95% CI for hamstring length is approximately 9˚, which also indicates more expected variability in the data compared to the 95% CI for hamstring length measured at week 6. The upper end of the 95% CI of 14.24˚ at week 12 is greater than the upper end of the 95% CI of 12.87˚ at week 6, though it likely does not reflect a real expected difference because 1.37˚ likely does not exceed the MDC with this outcome measure.

From baseline to week 24, the authors found statistically significant increases in hamstring and gastrocnemius length in the intervention group versus the control group, indicating that these two muscles had increased length. However, the low ends of the 95% CIs for these muscles likely do not exceed the MDC for a goniometric measurement. The 95% CI for hamstring length is approximately12˚, which also indicates more expected variability in the data compared to the 95% CI for hamstring length at week 12. The upper end of the 95% CI of 16.12˚ at week 24 is greater than the upper end of the 95% CI of 14.24˚ at week 12, though it likely does not reflect a real expected difference because 1.88˚ likely does not exceed the MDC.

Table 4 outlines between-group differences in gait parameters at week 6 and 24.

Table 4. Between-group differences in gait parameters at Week 6 and 24

Gait Parameter (˚)	**Week 6 Mean Change (95% CI) in Degrees**	**Week 24 Mean Change (95% CI) in Degrees**
Knee angle at midstance	7.03 (3.76 to 10.30)*	3.62 (-1.01 to 8.24)
Knee angle at terminal swing	5.15 (1.91 to 8.38)*	4.44 (-0.14 to 9.01)
Hip rotation at terminal swing	3.63 (0.58 to 6.67)*	4.18 (-0.12 to 8.48)
Ankle dorsiflexion at midstance	2.08 (-1.63 to 5.80)	2.40 (-2.85 to 7.62)

Asterisk (*) indicates statistical significance at $p < 0.05$.

From baseline to week 6, the authors found statistically significant increases in the intervention group versus the control group in knee angle at midstance, knee angle at terminal swing, and hip rotation at terminal swing as measured by changes in joint angle during video-recorded gait analysis with a digital screen goniometer. However, knee angle at midstance and knee angle at terminal swing should not be analyzed due to the fact that there was a significant increase in knee flexion angle at midstance in the control group at baseline. The 95% CI for hip rotation at terminal swing is 0.58˚ to 6.67˚, which indicates that the authors are 95% confident that the true mean change in hip rotation at terminal swing would be between 0.58˚ and 6.67˚. This narrow CI of approximately 6˚ indicates we could expect only slight variability in the data if this experiment were repeated on a larger population fitting these inclusion and exclusion criteria. While hip rotation at terminal swing experienced an average increase, we would expect some individuals would not experience a real change in length at this time point, since both the low and high ends of the 95% CI likely do not exceed the MDC for a goniometric measurement.

The authors found no statistically significant differences between the intervention group and control group from baseline to week 24 on any of the gait parameters. Effect size could not be calculated due to insufficient data given by the authors.

Applicability of Study Results:

Benefits vs. Costs: At Week 6, there were statistically significant improvements in the intervention group on: decreased spasticity of the hamstrings, soleus, and gastrocnemius; increased muscle length of the hamstrings and gastrocnemius; and increased hip forward rotation at terminal swing. At Week 12, there were still statistically significant improvements in the intervention group on: decreased spasticity of the hamstrings, rectus femoris, soleus, and

gastrocnemius; and increased muscle length of the hamstrings, soleus and gastrocnemius. At Week 24, the only remaining statistically significant improvement in the intervention group versus the control group was on increased muscle length of the hamstrings and gastrocnemius. Thus, there were more statistically significant improvements in the intervention group versus the control group during the 24-week study period, but the majority of the improvements had dissipated by the 6-month time point, which is consistent with the mechanism of action of the BTX-A injections into the targeted muscles. The improvement in the intervention group cannot be attributed to the BTX-A injections alone due to the multimodal treatment the intervention group received, which also included intensive physiotherapy, orthoses, and/or serial casting as compared to the control group which received usual therapy. If the cost of the BTX-A injections and physical therapy sessions are covered by insurance, the cost is minimized for the patient. According to the outline of the physiotherapy protocol used in this study, no special equipment or additional training for the therapists are needed. No adverse events due to any of the interventions were reported. The 12-week intervention period is a feasible duration for outpatient PT treatment. However, the frequency of the PT sessions at 3-5 times per week may be a financial and/or time burden on some patients and parents. It may be more feasible to have the frequency of PT sessions at 1-2 times per week with the addition of a home exercise program consisting of stretching of the flexor muscles assigned to facilitate gains made in PT. Based on this article alone, the treatment benefits of BTX-A plus a comprehensive therapy intervention on decreasing muscle spasticity, increasing muscle length, and improving knee and hip ROM during gait strongly outweigh the costs of the therapists' and patients' time.

Feasibility of treatment: The interventions presented in this study can be readily applied in the clinical setting. The intensive physiotherapy protocol was described well enough to be reproduced. No additional special equipment was required, and the amount of clinical expertise and treatment time are feasible in the outpatient PT setting. The number of weekly PT sessions was a little high, but the duration of each PT session (45-60 minutes) and the PT intervention period (12 weeks) are likely within what may be allowed by insurance companies. The treatment appears feasible for patients. The authors did not mention the assignment of any home exercise program during this study. There were no adverse events due to treatment.

Summary of external validity: The subject sample from this study appears to be very similar to patients treated at the facility I am working at in terms of age, diagnosis, and GMFCS levels. There were two major threats and one minor threat to internal validity, which compromise the ability to generalize these results to a larger patient population. I would not feel comfortable with extrapolating these results outside the scope of this study.

Article: El-Etribi MA, Salem MA, El-Shakankiry HM, *et al*. The effect of botulinum toxin type A injection on spasticity, range of motion and gait patterns in children with spastic diplegic cerebral palsy: an Egyptian study. *Int J Rehabil Res* 2004; 27:275-81.

Clinical Bottom Line: In this randomized controlled trial of 40 children with spastic diplegic cerebral palsy (CP), botulinum toxin A (BTX-A) injections in conjunction with a physiotherapy program improved muscle spasticity (as measured by the Modified Ashworth Scale), passive ankle dorsiflexion ROM (as measured by a standard goniometer), and dynamic gait pattern (assessed by the Physician Rating Scale) compared to physiotherapy alone. The intervention group received BTX-A injections and physiotherapy. The physiotherapy program was 3 times per week for 65 minutes each session for 3 months (total of approximately 39 hours) and included active assisted exercises for the first two months followed by active resisted exercises with variable weights in the third month. The authors reported these exercises were applied to the antagonist muscle group and stretching exercises were applied to the calf muscle. The control group received only the physiotherapy program (total of approximately 39 hours). At 3 months, the intervention group's mean improvements were: 1.04 in MAS score; 13.7˚ and 10.9˚ in ankle dorsiflexion ROM with the knee flexed and extended, respectively; and 4.13 in PRS composite score. In general, the 95% CIs for muscle spasticity, passive ankle dorsiflexion ROM, and composite PRS scores at the 3-month time point were fairly narrow. The low ends of the 95% CIs for passive ankle dorsiflexion ROM in the intervention group (9.6˚ and 7.33˚, for the knee flexed and extended, respectively) likely exceed the minimal detectable change (MDC) for a goniometric measurement, which indicates that most individuals would experience a real increase in passive ankle dorsiflexion ROM with this intervention. In contrast, passive ankle dorsiflexion ROM measurements at 3 months were the only outcome measures in the control group that the authors found to be statistically significant. The improvements in the intervention group can be attributed to the BTX-A injections since this was the only variable different between the two groups. The study had fair internal validity (PEDro score = 4/10), with one major threat and two minor threats, which were lack of blinding of assessors, unsuccessful randomization regarding baseline passive ankle dorsiflexion ROM, and inadequate power. The interventions could be readily applied to the clinical setting and the physiotherapy protocol, although generalized and vague, could be reproduced using the same principles. No additional special equipment was required, and the amount of clinical expertise and treatment time are feasible in the outpatient PT setting. Based on this article alone, the treatment benefits of BTX-A plus a physiotherapy program on decreasing muscle spasticity, increasing passive ankle dorsiflexion ROM, and improving aspects of the gait pattern may outweigh the costs of the therapists' and patients' time. Due to the fair internal validity, the results of this study should be cautiously extrapolated to a larger population.

Article PICO:

Population: 40 children with spastic diplegic CP, GMFCS levels unspecified, age 2-6 years

Intervention: BTX-A injections and physiotherapy for 3 months

Comparison: Physiotherapy only for 3 months

Outcome measures of interest: Modified Ashworth Scale, passive ankle dorsiflexion ROM, dynamic gait pattern

Blinding: The authors did not report that the subjects, therapists, or assessors were blinded in this study, so it is assumed that no blinding was done. However, the potential threat of the Hawthorne effect is negligible because the ability of these subjects to manipulate their muscle spasticity, joint ROM, and gait pattern is very limited. Lack of blinding of the therapists is only a minor threat since they were instructed to follow a general physiotherapy program, which was consistent between treatment groups. The authors did not report on the number of assessors. Therefore, lack of blinding of the assessors is a major threat since the interpretation of assessment results could have been affected by rater bias.

Controls: The control group received a physiotherapy program 3 times per week for 65 minutes each session for 3 months (total number of approximately 39 hours). This program was described as including active assisted exercises for the first 2 months and active resisted exercises with weights in the third month. These exercises involved the antagonist muscle group and included stretching of the gastrocsoleus complex. This was an appropriate control group since the only difference between the control group and intervention group was that the intervention group received BTX-A injections in conjunction with the physiotherapy program. The differences between groups can be attributed to the intervention of BTX-A injections.

Randomization: The assignment of subjects to groups was randomized, though the authors did not describe how randomization was done, or whether it was concealed. While there were no significant baseline differences between the groups including age, IQ, and diagnosis, the authors did not report on baseline comparability of muscle spasticity scores (as assessed by the Modified Ashworth Scale), passive ankle dorsiflexion ROM (as measured by a standard goniometer), or PRS scores. Upon visual inspection of the data, it appears the two group means were similar at baseline regarding MAS scores (approximately 1.93 for the intervention group and 1.78 for the control group). However, it appears there were baseline group mean differences for passive ankle dorsiflexion and PRS scores. Mean passive ankle dorsiflexion ROM was approximately 7 degrees less in the intervention group. Thus, because the intervention group had more limited passive ankle dorsiflexion ROM than the control group, the intervention group could have had more potential room for improvement. The mean baseline PRS scores appeared significantly different between groups, with the control group appearing to have more normalized gait patterns on all components of the PRS versus the intervention group. The differences at baseline on these two outcome measures would be a significant threat to between-group comparisons; however, the authors did not perform any between-group comparisons. Thus, the threat of baseline differences only relates to the absolute amount of change that each group could expect (i.e., a ceiling effect).

Study: This study was a randomized controlled trial involving 40 children. The study duration was 3 months. Inclusion criteria were: diagnosis of spastic diplegic CP, between the ages of 2 and 6 years, and mobile equinus deformity. Exclusion criteria were: severe or profound mental retardation according to ICD-10, fixed contractures, leg muscle atrophy, or had previous alcohol or phenol injections in the muscles. Children were randomly assigned to either the intervention

group or the control group. There were 20 subjects in the intervention group who received BTX-A injections to appropriate muscles in conjunction with a standard physiotherapy program 3 times per week for 65 minutes each session for 3 months. The physiotherapy program included active assisted exercises for the first 2 months and active resisted exercises in the third month. The exercises involved the antagonist muscle group and stretching exercises involved the gastrocsoleus complex. There were 20 subjects in the control group who received the same standard physiotherapy program as outlined previously. Children with scissoring gait and hip adductor spasticity received BTX-A injections to the hip adductor muscles; children who walked with crouch gait and knee flexor spasticity received injections to the knee flexors. The outcome measures of the MAS, passive ankle dorsiflexion ROM, and dynamic gait patterns were assessed at 1, 2, and 3 months for both treatment groups.

Outcome measures: Muscle spasticity was assessed using the MAS. Passive ankle dorsiflexion ROM with the knee flexed and extended was measured using a standard goniometer. The authors described the protocol for measuring passive ankle dorsiflexion ROM as holding the knee flexed to 90˚ while maintaining the foot in a supinated position in order to minimize subtalar motion and midfoot dorsiflexion. The same procedure was used with the knee in full extension. Dynamic gait patterns were assessed through visual observation using the Physician Rating Scale (PRS), which assesses six components during active walking. These outcome measures were assessed at 1, 2, and 3 months for both the intervention and control group. The authors did not report how many assessors were used or the reliability or validity of the outcome measures. Intra-rater or inter-rater reliability values were not provided. While the authors did not cite an established MCID for the MAS in children with CP, they defined an increase in PRS score of 2 points or greater from baseline to 3 months as an improvement.

Study losses: The authors did not report any subject losses at any time point. It is assumed that all 40 subjects were followed through study completion. All subjects were analyzed in the groups to which they were randomized and no group cross-over occurred.

Summary of internal validity: I deem the internal validity of this study to be fair (PEDro score = 4/10). There were three threats I identified. Of these, one was a major threat and two were minor threats. Lack of blinding of the assessors is a major threat since the MAS and PRS assessments could have been biased to favor one group over the other; thus, rater bias is a major threat. Unsuccessful randomization regarding baseline passive ankle dorsiflexion ROM is a minor threat since it appears there was a significant decrease in passive ankle dorsiflexion ROM in the intervention group of approximately 7 degrees at baseline. Since the intervention group had more limited passive ankle dorsiflexion ROM versus the control group, the intervention group could have had more potential room for improvement. Although the authors did not perform a power analysis in order to determine how many subjects would have been needed in this study to see a significant treatment effect, inadequate power is a minor threat due to the decent sample size of 40 children.

Evidence: The three outcome measures related to my clinical question are muscle spasticity, passive ankle dorsiflexion ROM, and dynamic gait patterns. These outcome measures were assessed four times: at baseline, 1 month, 2 months, and 3 months. However, the authors

provided only the mean and standard deviation for measurements at baseline and 3 months (before and after treatment) for each group.

Table 5 shows the mean changes in MAS scores, 95% CI, and effect sizes for each of the two groups.

Table 5. MAS score within-group mean differences (95% CI) and effect sizes

	Mean difference (95% CI)	Effect size
Intervention	1.04 (0.75 to 1.33)*	3.85
Control	0.01 (-0.21 to 0.23)	0.03

The asterisk (*) indicates a statistically significant difference ($p \leq 0.001$).

The authors found a statistically significant decrease in muscle spasticity only in the intervention group from baseline to 3 months. The intervention group showed a mean decrease in muscle spasticity of 1.04 MAS points. The 95% CIs surrounding the mean change (calculated by the CAT author) indicate the range of values in which there is 95% certainty that the true mean value of the population lies within. For example, the 95% CI indicates that the authors are 95% confident that the true mean change in spasticity would be between 0.75 and 1.33. This is a fairly narrow CI of approximately one half of an MAS point, which indicates that we could expect only slight variability in the data if the experiment were repeated on a larger population fitting these inclusion and exclusion criteria. Since there is no established MCID for the MAS in children with CP, it is not known whether the change in muscle spasticity was enough to be considered clinically important. I calculated the effect size as 3.85, which is large. The authors found no statistically significant differences in the control group from baseline to 3 months. This is supported by a 95% CI that crosses zero, which indicates that there could be a reversal in results if the experiment was repeated again.

Table 6 shows the changes in passive ankle dorsiflexion ROM, 95% CIs, and effect sizes for each of the two groups.

Table 6. Passive ankle dorsiflexion ROM within-group mean differences (95% CI) and effect sizes

	Dorsiflexion with knee flexion		Dorsiflexion with knee extension	
	Mean difference (95% CI)	Effect size	Mean difference (95% CI)	Effect size
Intervention	13.7˚* (9.6 to 17.8)	2.78	10.9˚* (7.33 to 14.47)	2.33
Control	4.9˚* (-0.22 to 10.02)	0.54	4.5˚* (-0.52 to 9.52)	0.52

The asterisk (*) indicates statistical significance in passive ankle dorsiflexion ROM at $p = 0.001$ for the intervention group and at $p < 0.001$ for the control group.

The authors found statistically significant increases in passive ankle dorsiflexion ROM from baseline to 3 months in both groups, as measured by a standard goniometer. In the intervention group, the mean increase in passive ankle dorsiflexion ROM with the knee flexed from baseline to 3 months was 13.7˚. The 95% CI surrounding the mean change indicates that the authors are 95% confident that the true mean change in dorsiflexion ROM would be between

9.60˚ and 17.80˚. This narrow CI of approximately 8˚ indicates that we could expect only slight variability in the data if this experiment were repeated on a larger population fitting these inclusion and exclusion criteria. The intervention group also experienced an average increase in ankle dorsiflexion ROM with the knee extended. Since the low ends of the 95% CIs for both of these measures likely exceed the MDC for a goniometric measurement, we would expect that most individuals would experience a real change in dorsiflexion ROM at this time point. While the control group also experienced an average increase in ankle dorsiflexion ROM, the 95% CIs cross zero, which indicate that there could be a reversal in results if the experiment was repeated again, with a loss of as much as 0.22˚ or 0.52˚ in dorsiflexion with the knee flexed or extended, respectively. While these values do not exceed the MCD, it appears that, at worst, the control group would have no change in ankle dorsiflexion. The trend for the effect sizes revealed moderate effect sizes in the control group and very strong effect sizes in the intervention group. This indicates that while both measures were found to reach statistical significance, there was a much stronger relationship between the intervention group and increased passive dorsiflexion ROM compared to the control group.

Table 7 shows the changes in PRS scores, 95% CI, and effect sizes for each of the two groups.

Table 7. Within-group differences in PRS composite scores at baseline and 3 months

	Baseline mean	3-month mean	Mean difference (95% CI)	Effect size
Intervention	7.6	11.73*	4.13 (2.73 to 5.53)	1.95
Control	8.93	8.93	0 (-1.13 to 1.13)	0.00

The asterisk (*) indicates statistical significance in PRS composite score at $p < 0.001$.

The authors found a statistically significant increase in composite PRS scores only in the intervention group from baseline to 3 months. The intervention group showed a mean increase in composite PRS score of 4.13 points, which exceeds the minimum increase of at least two points signifying improvement as stated by the authors. The 95% CI surrounding the mean change indicates that the authors are 95% confident that the true mean change in PRS composite scores would be between 2.73 and 5.53. Since the low end of the 95% CI exceeds the authors' stated MCID of 2 points, we would expect that most individuals would experience a clinically meaningful change in PRS scores at this time point. I calculated the effect size as 1.95, which is large. The authors reported the mean composite PRS score remained unchanged in the control group from baseline to 3 months.

Applicability of study results:

Benefits vs. Costs: At 3 months, there were statistically significant improvements in the intervention group on decreased muscle spasticity, increased passive dorsiflexion ROM with the knee flexed and extended, and increased composite PRS score. At 3 months, there also were statistically significant improvements in the control group on increased passive dorsiflexion ROM with the knee flexed and extended. Thus, there were more statistically significant

improvements in the intervention group versus the control group during the 3-month study period. The improvement in the intervention group can be attributed to the BTX-A injections since that was the only difference in treatment that the intervention group received compared to the control group. If the cost of the BTX-A injections and physiotherapy sessions are covered by insurance, the cost is minimized for the patient. Although the outline of the physiotherapy protocol used in this study was generalized and vague, it appears that no special equipment or additional training for the therapists was needed. No adverse events due to any of the interventions were reported. The frequency of 3 sessions per week at 65 minutes per session and the duration of a 3-month intervention period appear feasible for outpatient PT treatment. Based on this article alone, the treatment benefits of BTX-A plus a physiotherapy program on decreasing muscle spasticity and increasing passive ankle dorsiflexion ROM strongly outweigh the costs of the therapists' and patients' time.

Feasibility of treatment: The interventions presented can be readily applied in the clinical setting. The physiotherapy program was not described well enough to be reproduced; however, a physical therapist should be able to synthesize a treatment plan based on the brief descriptions provided. No additional special equipment was required, and the amount of clinical expertise and treatment time are feasible in the outpatient PT setting. The number of weekly PT sessions (3 per week), duration of each PT session (65 minutes), and the PT intervention period (3 months) are likely within what may be allowed by insurance companies. The treatment appears feasible for patients. The authors did not mention the assignment of any home exercise program during this study. No adverse events due to any of the interventions were reported.

Summary of external validity: The subject sample appears to be similar to patients treated at the facility I did my third clinical rotation at in terms of age and diagnosis. However, the authors did not report any GMFCS scores, so it is difficult to determine the level of physical functioning of the children in this study. There was one major threat and two minor threats to internal validity, which compromise the ability to generalize these results to a larger patient population. I would not feel comfortable with extrapolating these results outside the scope of this study.

Article: Reddihough DS, King JA, Coleman GJ, *et al.* Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. *Dev Med Child Neurol* 2002; 44:820-7.

Clinical Bottom Line: In this randomized controlled cross-over design of 49 children with spastic diplegic cerebral palsy (CP) or mild to moderate spastic quadriplegic CP, botulinum toxin A (BTX-A) injections in conjunction with a physiotherapy program statistically improved muscle spasticity (as measured by the Modified Ashworth Scale) in limited muscle groups on one side, ankle dorsiflexion ROM (as measured by a standard goniometer) in limited muscle groups on the other side, and parental self-reported satisfaction (as measured by the parental perception questionnaire) compared to physiotherapy alone. The authors found no statistically significant differences in either group 3 months and 6 months post-BTX-A injections on any GMFM variable. After baseline assessments, subjects were either randomly assigned to one of two groups or allocated to a corresponding group if they could be matched to an existing subject based on age and CP severity. Group 1 (n=22) received BTX-A injections within 3 weeks of baseline assessment and continued with their usual physiotherapy program. Group 2 continued with physiotherapy alone. At the end of 6 months, Group 1 continued with physiotherapy alone, while Group 2 (n=27) received BTX-A injections with their usual physiotherapy program. All subjects underwent both a control phase of physiotherapy alone and an intervention phase of BTX-A injections with physiotherapy. The physiotherapy program included advice and treatment for improving function and mobility, as well as provision of orthotics and walking aids. The average number of hours of therapy was 27.8 and 20.9, for the intervention phase and control phase, respectively. Thus, the BTX-A group received 33% more physiotherapy than the control group. At 3 months post-BTX-A injection, the BTX-A group showed a mean improvement of 1.36˚ in right ankle dorsiflexion ROM with the knee extended. At 6 months post-BTX-A injection, the BTX-A group's mean improvements were: 0.09 in MAS score in the left calf, 0.63 in MAS score in the left hip adductors, and 5.44˚ right ankle dorsiflexion ROM with the knee extended. It is important to note that decreased muscle spasticity did not result in improved ROM in these muscle groups, which is not typical. According to the parental perception questionnaire, at 3 months and 6 months post-injection, 77% and 84% of parents, respectively, reported they felt their child benefited from the BTX-A injections. The improvements in the BTX-A group may not only be attributed to the BTX-A injections since the BTX-A group also received 33% more physiotherapy time than the control group. The study had poor internal validity (PEDro score = 3/10), with three major threats (partially successful randomization, lack of a true control group, partial blinding of assessors), two moderate threats (lack of adequate follow-up, lack of consistency between groups regarding physiotherapy hours), and one minor threat (inadequate power). The physiotherapy program was not described well enough to be reproduced. The amount of clinical expertise and treatment time are likely feasible in an outpatient setting. Based on this article alone, the treatment benefits of BTX- injections plus a physiotherapy program on improving muscle spasticity, ankle dorsiflexion ROM, and parental satisfaction do not outweigh the costs of the therapists' and patients' time. Due to poor internal validity, the results of this study should not be extrapolated to a larger population.

Article PICO:

Population: 49 children with spastic diplegic CP or mild to moderate spastic quadriplegic CP, GMFCS levels I through IV, age 1 year 10 months to 6 years 8 months

Intervention: BTX-A injections and physiotherapy for 6 months

Comparison: Physiotherapy only for 6 months

Outcomes: Modified Ashworth Scale (MAS), Gross Motor Function Measure (GMFM), lower extremity joint range of movement (ROM), parental perception questionnaire, and Vulpe Assessment Battery (VAB)

Blinding: The authors did not report that the subjects or therapists were blinded. The potential threat of the Hawthorne effect on my outcome measures of interest is negligible because the ability of these subjects to manipulate their muscle spasticity, joint ROM, and functional movements is very limited. Lack of blinding of the therapists is a minor threat since they were instructed to follow a general physiotherapy program, which was consistent between treatment groups. The only blinding that the authors indicated was blinding of the assessors (unknown number) to treatment group with administration of the Gross Motor Function Measure (GMFM). The authors did not report on the number of assessors. Therefore, lack of blinding of the assessors is a major threat since the interpretation of the assessment results could have been affected by rater bias on the MAS and joint ROM measurements.

Controls: This study utilized a randomized cross-over design over a 12-month period in which all subjects went through a control phase of 6 months of only physiotherapy treatment (average of approximately 20.9 hours) to which their assessments with BTX-A in conjunction with physiotherapy treatment (average of approximately 27.8 hours) were compared. The physiotherapy program included advice and treatment for improving function and mobility, as well as the provision of orthotics and walking aids. The physiotherapy approaches were based on principles of neurodevelopmental therapy, conductive education, and hydrotherapy. This was not a perfect comparison group since the BTX-A group received 33% more physiotherapy time than the control group.

Randomization: Subjects were randomly assigned to one of two groups in age- and GMFCS-level matched pairs, although the authors did not describe how randomization was done, or whether it was concealed. The randomization was not successful as the authors state that they were unable to obtain complete subject matching on all participants. The authors report only within-group mean differences from baseline to 3 months or 6 months, so baseline comparability between groups cannot be evaluated.

Study: This study utilized a randomized, cross-over design in which all participants received one episode of BTX-A treatment over the 12-month study duration. Children were recruited from CP clinics at the Royal Children's Hospital in Victoria, Australia. Exclusion criteria were: spastic quadriplegia, orthopedic surgery to the lower limb within previous 12 months, BTX-A therapy or inhibitory plasters applied within previous 6 months, tone-reducing interventions such as intrathecal baclofen, receiving controversial therapies, and fixed lower extremity contractures. Inclusion criteria were: spastic diplegia or mild to moderate spastic quadriplegia. Children were first classified using the Gross Motor Function Classification System (GMFCS) and were matched according to GMFCS level and age at the first assessment. After the baseline

assessment, they were either randomly assigned to one of two groups or were allocated to a corresponding group if they could be matched to an existing subject based on age and severity. Group 1 (n=22) received BTX-A injections within 3 weeks of their baseline assessment and continued with their usual physiotherapy program. Group 2 (n=27) continued with physiotherapy alone. At the end of 6 months, Group 1 continued with physiotherapy alone, while Group 2 received BTX-A injections with their usual physiotherapy program. Thus, all subjects underwent both a control phase of physiotherapy alone and an intervention phase of BTX-A injections with physiotherapy. For the intervention phase, target muscles for BTX-A injections were identified by examination and were discussed with parents, therapists, and an orthopedic surgeon. Common injection sites included the hamstrings, calves, and adductor muscles. All children received injection in at least two muscle groups, and most received injections into four sites.

Outcome measures: The four outcome measures related to my clinical question are muscle spasticity, lower extremity joint ROM, GMFM, and parental perception questionnaire. Muscle spasticity was assessed using the MAS. Hip abduction, popliteal angle, ankle dorsiflexion with knee flexion and ankle dorsiflexion with knee extension were measured using a standard goniometer using standard positions. The GMFM was administered by a single physiotherapist and assessed through videotaped recordings by an unknown number of blinded physiotherapists. The authors stated that both the assessing and rating physiotherapists "had met the acceptable criterion level for reliable use of the GMFM tool." The authors reported an inter-rater correlation coefficient of 0.9 between the administering physiotherapist and blind raters' scores on 47/49 (96%) of the correlations. Although the authors did not report on the validity or reliability of the GMFM, it has been reported as the "gold standard" for measuring gross motor function in children with CP.[2,3] The parental perception questionnaire was synthesized by the authors specifically for this study and consisted of 12 questions addressing the effects of BTX-A injections on such aspects as pain at injection sites and timing of benefits. This questionnaire was given to parents at 3 and 6 months post-BTX-A injections. The authors did not report reliability or validity of this questionnaire. The time points at which the muscle spasticity, lower extremity joint ROM, and GMFM outcome measures were assessed is unclear. The authors stated that, at study commencement, it was decided that assessments would be taken three times in the intervention period (BTX-A and physiotherapy) at baseline, 3 months post-BTX-A injections, 6-months post-BTX-A injections, and in the control period (physiotherapy alone) only twice, at baseline and 6 months. The authors reported that the assessment frequency was changed at some point during the study to assess children at the mid-point of 3 months in the control period. They reported that 19 children underwent five assessments and 30 children underwent four assessments. However, since Group 1 consisted of 22 subjects while Group 2 consisted of 27 subjects, it is unclear at what time point the assessment frequency was changed.

Study losses: The authors stated that 61 children were originally recruited. Twelve subjects did not complete the study: 7 required surgery during the study period and were withdrawn, and 5 left due to being unable to continue with the assessment protocol. It was not stated at what time points these 12 subjects left the study nor which groups they were from. Although this correlates to a 19.5% attrition rate, which would merit an intention-to-treat analysis, the authors did not perform one. The authors chose to exclude the data from the subjects who dropped out of the

study, and only used the data from the remaining 49 children for statistical analyses. All subjects were analyzed in the groups to which they were randomized.

Summary of internal validity: I deem the internal validity of this study to be poor (PEDro score = 3/10). There were six threats I identified. Of these, three were major threats, two were moderate threats, and one was a minor threat. Partially successful randomization is a major threat since it is assumed that the subjects were not similar at baseline. The only baseline values the authors reported were GMFCS levels of subjects in both groups, and it appears that each group was comprised of a roughly equal number of subjects from each GMFCS level. Lack of a true control group is a major threat since the study duration was over one year, subjects could have improved on outcome measures such as the GMFM through natural developmental maturation regardless of intervention. Since each subject underwent both a control phase and an intervention phase, and the time points at which each group was considered to be in the control phase were considerably different (approximately a 6-month time difference), this weakens their ability as a true control group. Lack of blinding of the assessors on MAS assessments and lower extremity ROM measurements could have been biased to favor one group over the other; thus, rater bias is a major threat. Lack of adequate follow-up is a moderate threat since the authors did not provide any flow diagram, it is difficult to determine which subjects were assessed at each time point. Lack of consistency between groups regarding amount of physiotherapy is a moderate threat since the BTX-A group received 33% more physiotherapy time than the control group. Unequal amount of physiotherapy time could have potentially facilitated better outcomes in the BTX-A group. Although the authors did not perform a power analysis in order to determine how many subjects would have been needed in this study to see a significant treatment effect, it appears that they pooled the results from both groups during their respective control and intervention periods. This may have been done to increase the power of their study. Therefore, inadequate power is a minor threat due to the decent pooled sample size of 49 children.

Evidence: The four outcome measures related to my clinical question are muscle spasticity, lower extremity joint ROM, GMFM, and parental perception questionnaire. These outcome measures were assessed three times during the intervention period: at baseline, 3 months, and 6 months. The outcome measures were also assessed either two or three times during the control period: at baseline, 3 months, and 6 months. All of the subjects were injected into at least 2 muscle groups and 63% of the subjects were injected in 4 sites. Table 8 shows only the mean changes in MAS scores (SD) that were statistically significant ($p< 0.05$) because these are the only data the authors provided.

Table 8. MAS score within-group mean differences (SD) from baseline to 6 months

	n	Mean change (SD) for BTX-A phase	Mean change (SD) for control phase
Left calf	35	-0.09 (0.78)	0.43 (0.81)
Left hip adductors	8	-0.63 (1.06)	1 (0.76)

The authors only found statistically significant decreases in muscle spasticity in the BTX-A group in the left calf and left hip adductors from baseline to 6 months, as indicated by mean decreases of 0.09 and 0.63 MAS points, respectively. The SDs surrounding the mean changes are large and indicate significant variability in these data from this study. The range in the SDs

surrounding the mean changes both cross zero, which indicate that some individuals actually experienced an increase in muscle spasticity. Since there is no established MCID for the MAS in children with CP, it is unknown whether the change in muscle spasticity was enough to be considered clinically important. The authors reported that 36 children received BTX-A injections to the left calf, yet only 35 children were reported on. The authors did not report any information regarding the missing data on the single subject. The authors found statistically significant mean increases in muscle spasticity in the left calf and left hip adductors in the control group from baseline to 6 months of 0.43 and 1 MAS point, respectively. The range in the SDs surrounding the mean changes both cross zero, which indicates that some individuals actually experienced in a decrease in muscle spasticity.

Table 9 shows the mean changes in lower extremity joint ROM (SD) that were statistically significant ($p < 0.05$ at 3 months and $p < 0.01$ at 6 months) because these are the only data the authors provided.

Table 9. LE joint ROM within-group mean differences (SD) from baseline to 3 and 6 months

	n	Mean change (SD) in degrees for BTX-A phase	Mean change (SD) in degrees for control phase
Right ankle dorsiflexion with knee extended at 3 months	11	1.36 (7.45)	-7.27 (7.86)
Right ankle dorsiflexion with knee flexed at 6 months	34	5.44 (9.16)	-3.09 (11.74)

The authors found statistically significant increases in right ankle dorsiflexion ROM with the knee extended from baseline to 3 months and in right ankle dorsiflexion ROM with the knee flexed from baseline to 6 months in the BTX-A group, as measured by a standard goniometer. The mean increase in right ankle dorsiflexion ROM with the knee extended from baseline to 3 months was 1.36˚. This likely does not exceed the MDC for a goniometric measurement, which indicates that, on average, the subjects did not experience a real change in ROM due to the intervention. Although the SD surrounding the mean change is fairly narrow, the range in SD crosses zero, which indicates that some individuals actually experienced a decrease in ankle ROM during this intervention. The mean change of right ankle dorsiflexion ROM with the knee flexed from baseline to 6 months was 5.44˚. This likely minimally exceeds the MDC for a goniometric measurement, which indicates that, on average, the subjects may have experienced a small, but real change in ROM due to the intervention. The SD surrounding the mean change is moderate and crosses zero, which also indicates that some individuals experienced a decrease in ankle ROM. In the control group, there was a statistically significant mean decrease in right ankle ROM with the knee extended and flexed in the control group from baseline to 3 months and baseline to 6 months, respectively. The range in the SDs surrounding the mean changes both cross zero, which indicates that some individuals actually experienced in an improvement in ankle ROM during the control phase. It is interesting to note that while the subjects demonstrated improvements in muscle spasticity in a limited number of muscle groups on the left side, this did not correspond to an improvement in ROM in the same muscle groups; instead, improvements in ROM were seen on the right side. This is not what would typically be expected. It is possible that

the subjects started out with better average ankle dorsiflexion ROM on the right side or that the subjects started out with better MAS scores on average on the left side at study initiation, which may have resulted in greater average improvements at each assessment time point. Also, due to the minimally significant improvements in both outcome measures, the results could have been affected by rater bias or instrumentation error in favor of the BTX-A group. However, since the authors did not provide any raw data, it is difficult to determine the reasons why improvements in MAS scores did not correlate with improvements in ROM.

For the GMFM, the authors found no statistically significant differences in either the BTX-A group or the control group at 3 months and 6 months post-BTX-A injection in any GMFM variables. At 3 months and 6 months, the BTX-A group showed higher mean scores (i.e., improvements) in four of the eight variables while the control group showed higher mean scores in the other four variables. At 3 months, the BTX-A group showed a higher mean change in scores for the variables of sitting, sitting with aids, standing with aids, and walking with aids. The control group showed a higher mean change in scores for the variables of lying and rolling, crawling and kneeling, standing, and walking. Thus, there was no clear emerging trend in the data at 3 months post-BTX-A injections. At 6 months, the BTX-A group showed a higher mean change in scores for the variables of sitting, sitting with aids, standing with aids, and walking. The control group showed higher mean scores for the variables of lying and rolling, crawling and kneeling, standing, and walking with aids. Thus, there was no clear emerging trend in the data at 6 months post-BTX-A injections. While reference curves have been created for the GMFM-66 by age and GMFCS level[4], it is impossible to compare the data from this study to these normative interpretations since the authors did not provide any raw data. The subjects in this study ranged in age from 1 year and 10 months to 6 years and 8 months, and ranged in GMFCS level from I through IV. Since the authors reported that all 49 subjects were able to perform six out of eight GMFM variables by 6 months, it appears that the authors pooled data from both groups during their respective BTX-A phase and control phase. Nineteen subjects were able to perform lying and rolling at 3 months, while all 49 subjects were able to perform this variable at 6 months regardless of group allocation. This may indicate that the majority of subjects improved their overall outcome scores primarily through natural developmental maturation.

Parents were given a questionnaire asking about the effects of BTX-A injections on their child at 3 and 6 months post-BTX-A injections. The authors reported that there were "significantly more positive responses" at 3 and 6 months post-BTX-A injection in response to being asked if the parents thought their child's ability benefited from the BTX-A injections. The authors reported that, of the parents who considered the BTX-A injections to be beneficial, 36 out of 47 parents (77%) and 35 out of 43 parents (84%) rated the benefits as good, very good, or excellent at 3 months and 6 months, respectively. The authors reported that 3 months post-injection, 26 out of 33 parents (79%) reported they perceived the maximum benefit of the BTX-A occurred by 6 weeks post-BTX-A injection. The remaining seven out of 33 parents (21%) reported they believed the maximum benefit occurred between 6 and 12 weeks post-BTX-A injection. At 6 months post-injection, 23 out of 35 parents (66%) reported maximum benefits occurred between 1 to 2 months post-BTX-A injection. The authors found that 4 out of 21 (19%) and 6 out of 23 parents (26%) at 3 months and 6 months, respectively, reported their child experienced complications or negative side effects from the injections including incontinence (n=4), muscle weakness (n=4), and less specific complaints (n=2). Although the authors did not report the exact questions on the questionnaire or the reliability and validity of the questionnaire, the majority of parents reported that the peak beneficial effects appeared to be within the first 6

weeks of BTX-A injection and a minority of parents reported adverse effects to BTX-A injections.

Application of study results:

Benefit vs. Costs: At 3 months, there were statistically significant improvements in the BTX-A group on increased right ankle dorsiflexion ROM with the knee extended. At 6 months, there were statistically significant improvements in the BTX-A group on decreased muscle spasticity of the left calf and increased right ankle dorsiflexion ROM with the knee flexed. At 6 months, there also were statistically significant improvements in the control group on decreased muscle spasticity of the left hip adductors. Thus, there were more statistically significant improvements in the BTX-A group versus the control group during the 12-month study period. However, since there is no established MCID for the MAS in children with CP, it is not known whether the change in muscle spasticity was enough to be considered clinically important. Also, the mean changes in ankle dorsiflexion ROM were between 1˚ and 5˚ in the BTX-A group likely do not exceed the MDC for a goniometric measurement, which indicates that, on average, the subjects did not experience a real change in ROM due to the intervention. However, according to the parental perception questionnaire, 77% of parents at 3 months and 84% of parents at 6 months post-BTX-A injections reported that their child benefited from the BTX-A injections. If the cost of the BTX-A injections and physiotherapy sessions are covered by insurance, the direct financial cost is minimized for the patient. The only reported adverse reactions related to the intervention came from the parental perception questionnaire. 19% and 26% of parents at 3 months and 6 months, respectively, reported their child experienced complications or negative side effects from the injections including incontinence (n=4), muscle weakness (n=4), and less specific complaints (n=2). Seven children were withdrawn during the study period due to requiring surgery, but the authors did not report the indications for the surgeries. The average number of physiotherapy hours of 27.8 and 20.9, for the intervention phase and control phase, respectively, is feasible for outpatient PT treatment. Based on this article alone, the treatment benefits of BTX-A plus a physiotherapy program on improving muscle spasticity, ankle dorsiflexion ROM, and parental satisfaction do not appear to outweigh the costs of the therapists' and patients' time.

Feasibility of treatment: The physiotherapy program was not described well enough to be reproduced in the clinical setting. It was unclear if special equipment was required. However, the amount of clinical expertise and treatment time are feasible in the outpatient PT setting. The total number of physiotherapy hours (averaging between 20 and 28 hours) and the PT intervention period (6 months) are likely within what may be allowed by insurance companies. The treatment appears feasible for most patients. The authors did not mention the assignment of any home exercise program during this study. However, 12 subjects left the study and several parents reported that their child experienced complications or negative side effects from the BTX-A injections at 3 months and 6 months post-injections through the parental perception questionnaire.

Summary of external validity: The study sample appears to be similar to patients treated at the facility I did my third clinical rotation at in terms of age, diagnosis, and GMFCS level. There were three major threats, two moderate threats, and one minor threat to internal validity, which

compromise the ability to generalize these results to a larger patient population. I would not feel comfortable with extrapolating these results outside the scope of this study.

Article: Williams SA, Elliot C, Valentine J, *et al*. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength. *Disability & Rehabilitation* 2013; 35(7): 596-605.

Clinical Bottom Line: In this non-randomized cross-over design trial of eight children with spastic diplegic cerebral palsy (CP), botulinum toxin A (BTX-A) injections into select lower extremity muscles in conjunction with a 10-week strength training program initiated immediately after the BTX-A injections statistically improved mean isometric peak torque of the knee extensors (as measured by a Biodex System-3 dynamometer) by 63.99 Nm/kg and decreased gastrocnemius isometric strength (as measured by a hand-held dynamometer) by 6.4 kg compared to BTX-A injections alone. Eight children were selected through an unknown method to serve as the subjects for the 6-month control period in which they received one bout of BTX-A injections to lower extremity muscles half way through the control period at approximately three months. During the control period, subjects continued with their normal care routines, including standard clinical care. At the end of the 6-month control period, these same subjects entered the 6-month intervention period. At three months into the intervention period, the subjects received another bout of BTX-A injections. Since the authors did not report at what time point the 10-week strength training program occurred, it is assumed that it was initiated immediately after the BTX-A injections. The strength training program was a home-based program, which occurred three times per week for 10 weeks. The program was coordinated and progressed every two weeks by a visiting exercise physiologist. Each training session included manual and passive stretching to the lower extremity muscle groups. Since the authors did not report on the duration of each session, it is assumed that each session was one hour in duration. Although the strength training program was a home-based program, no compliance was reported. From the control period to the intervention period, there was a statistically significant mean improvement of 63.99 Nm/kg in isometric knee extensor peak torque and a statistically significant mean decrease of 6.4 kg in isometric gastrocnemius strength. The majority of the 95% CIs (excluding gastrocnemius isometric strength) were large and crossed zero, which indicates that there could be a reversal of results if this experiment were repeated again with individuals meeting the same inclusion criteria. Since the authors performed multiple t-tests to analyze their data, this could have resulted in data appearing to be significant when the result was actually due to chance, which appears to be the case in this specific measure. The study had poor internal validity (PEDro score = 4/10), with four major threats (lack of well-explained study design that necessitated many assumptions regarding data analysis, lack of randomization, lack of reported compliance to the strength training program, and inadequate power), one moderate threat (lack of a true control group), and one minor threat (lack of appropriate utilization of statistical tests). Although the authors did not report on functional improvements, increased knee extensor strength and decreased gastrocnemius strength could facilitate improvements in sit-to-stand transfers and gait. Additionally, decreased gastrocnemius strength in this specific population could be beneficial in order to facilitate more normalized foot and ankle positioning for improved functional mobility. The time points at which the subjects were assessed was appropriate to see effects from the interventions based on the physiological responses to BTX-A injections; however, some early effects may have been missed since each assessment was at three-month intervals (which is likely the tail end of the drug's efficacy). The strength training program, although generalized and vague, could be reproduced using the same principles and concepts and readily applied to the clinical setting. The equipment used (ankle weights,

resistance bands, Fit balls, and Duradiscs) are common items typically available in a PT clinic. Seeing a patient for one-hour PT sessions once every other week for 10 weeks is feasible in the outpatient PT setting. Based on this article alone, the benefits of BTX-A plus a strength training program on improving mean knee extensor isometric peak torque and decreasing mean gastrocnemius isometric strength minimally outweigh the costs of the therapists' and patients' time compared to BTX-A alone. It would have been helpful to know if the improvements in isometric muscle strength correlated with improved functional mobility and gait. Future studies should include the use of an outcome measure that captures participation level activities. Due to the poor internal validity, the results of this study should not be extrapolated to a larger population.

Article PICO:

Population: 8 children (mean age 8 years, 3 months) with spastic diplegic CP, GMFCS level I through II

Intervention: BTX-A injections and strength training for 10 weeks

Comparison: BTX-A injections and normal care for 6 months

Outcome measures of interest: Modified Ashworth Scale (MAS), muscle strength (via Biodex dynamometer and hand-held dynamometer), muscle volume (via Magnetic Resonance Imaging), Goal Achievement Scale (GAS), and voluntary motor control (via the Selective Control Assessment of the Lower Extremity)

Blinding: The authors did not report that the subjects or therapists were blinded. The potential threat of the Hawthorne effect on my outcome measures of interest, specifically muscle strength, is minor because subjects may have exerted more effort with strength assessments because they may have been aware that there was an expectation that they would achieve better strength measurements. Lack of blinding of the therapists is a minor threat since they were instructed to follow a general physiotherapy program. A single assessor who conducted all of the assessments was blinded to group allocation. Additionally, the occupational therapist (OT) that inputted and rated the GAS was blinded to group allocation.

Controls: This study utilized a repeated measures cross-comparison design including a 6-month pre-intervention baseline period, which served as the control period. Subjects were block randomized by age, gender, and GMFCS level into a PRE or POST BTX-A strength training group. It is important to note that eight children served as the control group and received BTX-A injections once during the 6-month control period. They were instructed to continue with their normal care routine including standard clinical care. For the purposes of my clinical question and this critically appraised paper, this analysis will focus only on this group of eight children, and only the data from these eight subjects will be analyzed.

Randomization: Although the authors reported that subjects were block randomized by age, gender, and GMFCS level into a PRE or POST BTX-A strength training group, they did not report how the eight children who served as the control group were selected.

Study: This study utilized a repeated measures cross-comparison design including a 6-month pre-intervention baseline period, which served as the control period. Children were recruited from the Cerebral Palsy Mobility Service at Princess Margaret Hospital in Perth, Australia. Inclusion criteria were: spastic diplegia, GMFCS level I through II, and currently receiving BTX-A treatment for spasticity management in bilateral lower extremities. The authors reported that no child had undergone serial casting within previous 6 months or had a history of lower limb surgery. Subjects were assessed at five time points: baseline (B), Assessment 1 (A1) approximately 12 weeks prior to BTX-A injection, Assessment 2 (A2) ~2 weeks prior to BTX-A injection, Assessment 3 (A3) ~5 weeks post-injection, and Assessment 4 (A4) ~14 weeks post-injection. The eight children who served as the control group had a mean age of 8 years and 3 months, and six were classified as GMFCS level I, and two were classified as GMFCS level II. Assessments of this group were performed at the time points A1 and A4 scheduled around their BTX-A injections. All 15 children received BTX-A injections to bilateral medial gastrocnemius muscles, 5 subjects received BTX-A to bilateral medial hamstrings. Other injected muscles were: soleus (4 legs), adductors (2 legs), rectus femoris (2 legs), and tibialis posterior (1 leg). No child had more than three injections per leg. The authors did not report which muscle groups received BTX-A injections in the eight children who served as the control group. The strength training program was a home-based program, which occurred three times per week for 10 weeks. The program was coordinated and progressed every two weeks by a visiting exercise physiologist. Each training session included manual and passive stretching to the lower extremity muscle groups. Each subject's strength training program was based on the child's strength assessment at evaluation and their functional goals. Strengthening exercises progressed in repetitions and loading levels as the subject's strength improved and were in accordance with the American College of Sports Medicine guidelines. The program focused on motor control initially through utilization of manual resistance, resistance bands, and ankle weights with increasing repetitions and then increasing loads. The program then progressed to more complex movements and functional tasks specific to the child's goals. Special equipment included ankle weights, resistance bands, Fit balls, and Duradiscs. Since the authors did not report what time points the strength training for the control group occurred, it is assumed that the strength training occurred immediately after the BTX-A injections during their intervention phase, which was approximately three months into the intervention period.

Outcome measures: The outcome measure related to my clinical question is isometric muscle strength of the knee flexors, knee extensors, gastrocnemius, and tibialis anterior. Though I am interested in the effects of BTX-A on spasticity, I did not analyze the MAS data because it was not measured in the group of eight children, which is the focus of this analysis. Isometric muscle strength of the knee flexors and extensors was assessed using the Biodex System-3 dynamometer. Subjects performed three maximum isometric contractions of bilateral knee flexors and knee extensors. Test side was randomized. Isometric measurements assessed muscle peak torque normalized to body weight in a static position with the knee flexed to 90˚. Maximal isometric strength of the gastrocnemius and tibialis anterior was assessed in standardized positions using a hand-held dynamometer by a trained physiotherapist. The authors did not report any validity or reliability of these outcome assessment methods. According to Drouin et al. (2004), the interclass correlation coefficient (ICC) is 0.99 for both reliability and validity of isometric torque[5]. Although the authors also assessed isokinetic muscle strength and muscle

volume for this group, these outcome measures do not necessarily correlate with functional improvements in mobility or gait. Isokinetic strength is not a functional measurement because natural, functional human movement does not occur only at a single fixed speed. Muscle volume is not a functional measurement because, although it can be assumed that improvements in strength correlate to muscle hypertrophy, which would mean an increase in muscle volume, this is not always the case since other factors, such as neuromuscular recruitment and training, are involved in improvements of strength.

Study losses: The authors did not report any subject losses at any time point. It is assumed that all 15 subjects were followed through study completion, including the eight control subjects. Although the authors did not report if the eight subjects were analyzed in the groups to which they were randomized, it is likely that they were since all eight subjects received the interventions at the same time points.

Summary of internal validity: I deem the internal validity of this study to be poor (PEDro = 4/10). There were seven threats I identified. Of these, four were major threats, one was a moderate threat, and two were minor threats. Lack of a well-explained study design is a major threat to this study. Since the authors did not provide adequate information about the study design, specifically about the eight children who comprised the control group, many assumptions had to be made, which greatly weakens the confidence in interpreting the results of this study. Although the authors reported that the children were block randomized into either the PRE or POST strength training group, they did not report how the eight children were selected for the control group. Since no baseline raw data were reported, it is assumed that randomization was not performed with this group, which is a major threat. The authors also did not report compliance to the physiotherapy program and did not provide any approximation of mean hours of therapy, which is a major threat. Although the authors performed a post hoc power analysis, which indicated that their total subject sample of 15 children had adequate power to detect a meaningful difference ($\alpha = 0.05$), inadequate power is a major threat because the control group had only eight subjects and these are the focus of the current analysis. Since the eight subjects served as their own controls, lack of a true control group is a moderate threat as improvements in muscle strength could have been due to natural developmental maturation regardless of intervention. Lack of appropriate utilization of statistical tests is a relatively minor threat as the authors performed multiple t-tests to assess the significance of their data, which possibly could have resulted in data appearing to have statistical significance just by chance. Finally, the Hawthorne threat is a minor threat because subjects may have exerted more effort with strength assessments because they may have been aware that there was an expectation that they would achieve better strength measurements.

Evidence: The outcome measure related to my clinical question is isometric muscle strength of the knee flexors, knee extensors, gastrocnemius, and tibialis anterior. This outcome measure was assessed at five time points: baseline, A1, A2, A3, and A4. However, the authors only reported mean changes in muscle strength (SD) from baseline to A1 and from A1 to A4. Table 10 shows the changes in isometric strength and torque. The differences from baseline to A4 address the question of whether strength training improves strength in muscles that were injected with BTX-A immediately before strength training program initiation, which occurred three months into the intervention period.

Table 10. Mean differences in isometric muscle strength and torque (95% CI)

	Mean change (SD) for control period (baseline to A1)	Mean change (SD) for strength training period (A1 to A4)	Difference from baseline to end of strength training period (baseline to A4; 95% CI)	Effect size
Knee flexors isometric peak torque (Nm/kg)	18.60 ± 35.28	28.52 ± 39.68	9.92 (-30.3 to 50.2)	0.26
Knee extensors isometric peak torque (Nm/kg)	4.20 ± 40.37	68.19 ± 76.75	63.99* (-1.77 to 129.75)	0.83
Gastrocnemius isometric strength (kg)	9.53 ± 6.07	3.13 ± 5.74	-6.4* (-12.73 to -0.07)	1.09
Tibialis anterior isometric strength (kg)	3.33 ± 4.69	1.71 ± 1.28	-1.62 (-5.31 to 2.07)	0.54

Asterisk (*) indicates statistical significance at p = 0.05.

The authors found statistically significant differences in isometric knee extensor peak torque and gastrocnemius isometric strength from the control period to the intervention period as measured by a Biodex System-3 dynamometer and hand-held dynamometer, respectively. At the A4 time point (3 months after the BTX-A injections and after initiation of the 10-week strength training intervention), there was a statistically significant improvement in knee extensor peak torque of 63.99 Nm/kg with a very large 95% CI that crosses zero. This indicates a large expected variability in the results ranging from a large gain in peak torque (up to ~130 Nm/kg) to a slight weakening (only by 1.77 Nm/kg) of the knee extensors if the experiment were repeated in a population that fit the inclusion/exclusion criteria. The effect size was calculated by the authors to be 0.83, which is large. Also, at the A4 time point, there was a statistically significant decrease in gastrocnemius isometric strength of -6.4 kg with a large 95% CI. This indicates that all subjects would likely experience real decreases in gastrocnemius isometric strength if this experiment were repeated again in a population that fit the inclusion/exclusion criteria. This decrease in muscle strength following BTX-A injections and a strength training program is not a typical response. This could be due to the fact that, while both groups increased gastrocnemius muscle strength, there was a greater increase in mean strength in the control period (9.53 kg) compared to the intervention period (3.13 kg). The effect size is 1.09, which is large. No minimal detectable change (MDC), minimal clinically important difference (MCID), or normative values have been established for isometric muscle strength in children with cerebral palsy assessed by either a Biodex machine or hand-held dynamometer, so it is difficult to determine if these mean differences in muscle strength would correlate to clinically important changes. However, it appears that 10 weeks of strength training initiated immediately after lower extremity BTX-A injections increased overall knee extensor torque increased and decreased gastrocnemius isometric strength, both of which could facilitate improvements in ADLs such as sit-to-stand transfers and gait. The overall weakening of gastrocnemius strength in this specific population would be beneficial because it could correlate with improved dorsiflexion ROM, which would

result in improved neutral foot and ankle positioning to facilitate transfers and gait. The overall decrease in gastrocnemius strength is appropriate since all subjects received BTX-A injections to bilateral medial gastrocnemius muscles. However, only two legs (of the total 30 legs from the entire study sample) received BTX-A injections to the rectus femoris, so the overall mean improvements in knee extensor peak torque were likely due to the component of the strength training program rather than the actual BTX-A injections. BTX-A is a known biological substance that blocks acetylcholine (ACh) release at the neuromuscular junction, which causes temporary local paralysis of the injected muscles. These effects start to diminish as the nerve terminals begin to regenerate, which is a process that takes approximately three months.[1] Since it is assumed that the 10-week-long strength training period occurred immediately after the BTX-A injections, which were given three months into the intervention period, it is feasible to expect that physiological effects from these injections occurred during this time period. According to the results in the parental perception survey by Reddihough et al. (2002), the majority of parents perceived that the maximum benefits from the BTX-A injections occurred by 6 weeks post-injections. This supports the notion that the muscle weakening as a result of the BTX-A injections was still occurring during the 10-week strength training period of this study. The subjects were assessed at the A4 time point, which was three months after the injections. Thus, the A4 time point likely captured the effects of the injections (increased weakness) as well as the effects of the strength training program (increased strength). However, as indicated by the parental survey mentioned above, some early effects of the BTX-A could have been missed due to the three-month assessment interval.

Application of study results:

Benefits vs. Costs: At the end of the 6-month intervention period which included 10 weeks of strength training and BTX-A injections of select lower extremity muscles, the only statistically significant differences were increased knee extensor peak torque and decreased gastrocnemius isometric strength. However, since there is no established MCID for assessing isometric muscle strength with either a Biodex machine or hand-held dynamometer, it is unknown whether these changes in muscle strength were sufficient to be considered clinically important. If the cost of the BTX-A injections and physiotherapy sessions are covered by insurance, the direct financial cost is minimized for the patient. No adverse reactions related to the intervention or subject losses were reported. The authors did not report the average number of physiotherapy hours. If a one-hour long treatment session is assumed, then the subjects received approximately 30 hours of physiotherapy during the 10-week long strength training period. However, this strength training program was primarily carried out as a home exercise program with the physiotherapist checking in only once every other week to modify and progress the training program. Based on this article alone, the treatment benefits of BTX-A plus a physiotherapy program on improving isometric muscle strength and peak torque do not appear to outweigh the costs of the therapists' or patients' time.

Feasibility of treatment: The interventions presented can be readily applied in the clinical setting. The physiotherapy program was not described well enough to be exactly replicated; however, a physical therapist should be able to synthesize a treatment plan based on the general descriptions and concepts provided. The authors described the physiotherapy program included use of ankle weights, resistance bands, Fit balls and Duradiscs. This equipment should be readily available in

an outpatient clinic setting. Since this strength training program was primarily carried out as a home exercise program with the physiotherapist checking in only once every two weeks, this amount of treatment time is feasible in the outpatient PT setting. However, this also places the majority of the responsibility on the caregiver to carry out the exercises, and one-hour long sessions three times per week may not be realistic or feasible for all individuals. Since the authors did not report any measures of compliance to the strengthening program, it is difficult to determine how many hours of physiotherapy each child actually received. No adverse events due to any intervention were reported.

Summary of external validity: The subject sample appears to be similar to patients treated at the facility I did my third clinical rotation at in terms of age and CP severity. Because on the number of significant threats to the internal validity, I would not feel comfortable with extrapolating these results.

Synthesis/Discussion:
Overall, the four studies analyzed in this Critically Appraised Topic demonstrated that BTX-A injections to select lower extremity muscles plus a physical therapy (PT) or strengthening program resulted in modest statistically significant improvements in muscle spasticity and motor function compared to either PT or BTX-A injections alone. The PT interventions presented in these four studies could readily be applied in the clinical setting. The PT protocol in only one study (Scholtes *et al.*) was described well enough to be reproduced. The protocols in two studies (El-Etribi *et al.* and Williams *et al.*) were vague and generalized, but could be reproduced using the same principles. The protocol in the remaining study (Reddihough *et al*.) was not described well enough to be reproduced. The results from two articles (Scholtes *et al.* and El-Etribi *et al*.) suggest that the treatment benefits of BTX-A injections plus a PT program on decreasing muscle spasticity and improving lower extremity ROM may outweigh the costs of the therapists' and patients' time. However, the results from the other two articles (Reddihough *et al.* and Williams *et al.*) suggest that the treatment benefits of BTX-A injections plus a PT or strengthening program on improving muscle spasticity and ankle dorsiflexion ROM (Reddihough *et al*.) and on improving isometric peak torque and isometric strength for select lower extremity muscles (Williams *et al*.) likely do not outweigh the costs of the therapists' and patients' time. Although the subjects in all four studies appear to be similar to patients I treated in my third clinical rotation at in terms of age, diagnosis, and GMFCS levels, I would not feel comfortable extrapolating the results of any of these studies to a larger patient population due to the poor to fair internal validity of the studies. The following factors outline some of the differences between these studies.

The methodological quality of these four studies was assessed using the PEDro scale. PEDro scores were calculated to be: 5/10 (Scholtes *et al*.), 4/10 (El Etribi *et al*.), 3/10 (Reddihough *et al*.), and 4/10 (Williams *et al.*). In order for PEDro scores to be moderate to high quality, the scores should be greater than or equal to 5/10. Since three studies had PEDro scores that were less than 5/10, the overall methodological quality for these four studies was fair. The common methodological flaws in each of the four studies were lack of concealed allocation, lack of baseline comparability, and lack of blinded subjects and therapists. All four of the studies were randomized controlled trials. However, for the purposes of this critical analysis for my clinical question, the way in which I needed to analyze the data from the Williams *et al*. article focused on a specific group subset of subjects that was not randomized. This was the only study in which all of the assessors were blinded to group allocation. The Scholtes *et al*. and Reddihough *et al*. studies demonstrated partial blinding of assessors, while the El Etribi *et al*. study indicated no blinding of assessors. Although the duration of the intervention and follow-up periods were sufficient to see improvements due to the interventions, the Reddihough *et al*. article lacked adequate follow-up because it lacked a detailed description of the study design which made it difficult to follow subject involvement. Additionally, the lack of well-explained study designs and data analyses in the Reddihough *et al.* and Williams *et al*. articles necessitated major assumptions to be made regarding how the authors performed their data analyses, which significantly threatened the confidence in data interpretation and conclusions.

The four studies had some similarities in eligibility requirements of children with spastic CP. The age range of participants was between approximately 2 and 12 years. While all four studies included children with spastic diplegic CP, two of the four studies also included children with spastic hemiplegic CP (Scholtes *et al.*) or mild to moderate quadriplegic CP (Reddihough *et al*.). In three of the four studies, CP severity was assessed according to the GMFCS. Out of the

three studies that utilized the GMFCS, two studies (Scholtes *et al.* and Reddihough *et al*.) included children from GMFCS levels I through IV, while the remaining study (Williams *et al*.) included children from GMFCS levels I through II.

The sample size was a threat in some of the studies. The Scholtes *et al*., El Etribi *et al*., and Reddihough *et al*. articles had decent sample sizes of n = 46, n = 40, and n = 49, respectively; thus, inadequate power was a minor threat to the internal validity of these three studies. Although the total sample size in the Williams *et al*. article was 15 subjects, which the authors found through a post-hoc power analysis to have adequate power to detect a meaningful difference ($\alpha = 0.05$), this critical analysis focused on a subgroup of eight children, which is approximately half of the total number of subjects the authors' power analysis was based on. Thus, inadequate power was a major threat to the Williams *et al*. study. The differences in the article in PICOs are outlined in Table 11.

Table 11. Comparison of PICO Descriptions

	Scholtes *et al.*	El Etribi *et al.*	Reddihough *et al.*	Williams *et al.*
Population	46 children with spastic hemiplegic or diplegic CP who walk with flexed knees, GMFCS levels I through IV Age: 4-11.5 years	40 children with spastic diplegic CP, GMFCS levels unspecified Age: 2-6 years	49 children with spastic diplegic CP or mild to moderate spastic quadriplegic CP, GMFCS levels I through IV Age: 1 year 10 months to 6 years 8 months	8 children with spastic diplegic CP, GMFCS level I through II Age: 5-12 years
Intervention	Multi-level BTX-A injections and comprehensive rehabilitation for 3 months	BTX-A injections and physiotherapy for 3 months	BTX-A injections and physiotherapy for 6 months	BTX-A injections and strength training for 10 weeks
Comparison	Usual physiotherapy for 3 months	Physiotherapy only for 3 months	Physiotherapy only for 6 months	BTX-A injections and normal care for 6 months
Outcome measures	Muscle spasticity (measured by the joint angle where a "catch" was felt in response to a single passive stretch occurring over <1 second), LE muscle length (measured by the ROM with a slow passive stretch occurring over >3 seconds), lower extremity ROM during gait (measured by a digital screen goniometer through video-recorded gait analysis)	Muscle spasticity (via MAS), passive ankle dorsiflexion ROM (via standard goniometer), dynamic gait patterns (via Physician Rating Scale)	Muscle spasticity (MAS), GMFM, lower extremity joint ROM (via standard goniometer), parental perception questionnaire, and Vulpe Assessment Battery (VAB)	Muscle spasticity (MAS), muscle strength (via Biodex dynamometer and hand-held dynamometer), muscle volume (via MRI), Goal Attainment Scale (GAS), and voluntary motor control (via the Selective Control Assessment of the Lower Extremity)

Duration of treatment in all four studies was sufficient to see improvements due to the interventions (range between 3 and 6 months). In terms of similarities to my clinical PICO, the populations in each study included children with spastic CP who were between GMFCS levels I through IV. In terms of interventions, all four studies used BTX-A injections in conjunction with PT or strength training programs, while the study by Scholtes *et al*. also included orthoses or serial casting as needed. Regarding the comparison treatment, three of the four studies used either only usual care or a PT program. The exception was the study by Williams *et al*. in which BTX-A injections with "normal care" were the comparison treatment. For the outcome measures, three of the four studies assessed muscle spasticity. The exception was the Williams *et al.* study where muscle spasticity was not assessed in the control group of eight children that was the focus of this analysis. All four studies included outcome measures relating to motor function, including muscle length, lower extremity ROM, gait parameters, GMFM, and isometric strength and peak torque. Three of the four studies included measures of ROM and two of these studies assessed ankle ROM specifically. Muscle isometric strength and peak torque was only assessed in the Williams *et al*. article.

Based on the results of these four studies, BTX-A injections in conjunction with physical therapy was found to resulted in only modest statistically significant improvements in muscle spasticity and motor function for children with spastic CP. However, BTX-A is a known biological substance that blocks acetylcholine (ACh) release at the neuromuscular junction, which causes temporary local paralysis of the injected muscles. These effects start to diminish when the nerve terminals begin to regenerate, and this process takes approximately three months[1]. Given this timeframe of expected physiological efficacy of BTX-A injections to skeletal muscles, the assessment time points of each study (6, 12, and 24 weeks for Scholtes *et al*.; 1, 2, and 3 months for El Etribi *et al*.; baseline, 3, and 6 months for Reddihough *et al*.; and approximately 5 and 12 weeks for Williams *et al*.) were appropriate to see effects from the interventions. Since the peak BTX-A effect is typically around 6 weeks post-injection, 7 of the 11 assessment time points (~64%) from these four studies are likely beyond the timeframe of peak BTX-A effect. In addition, the wide interval of assessment time points may have contributed to the lack of statistically significant outcomes across all four studies, as significant changes may have been missed in the beginning of the intervention periods as well as between assessment time points. The outcome measures that would be *most* affected by BTX-A injections would be muscle spasticity and ROM due to the temporary local paralysis effect on injected muscles. Thus, another possible reason why these studies did not show better improvements is suboptimal selection of outcome measures, as some of the outcome measures may not have been suited to best capture the effects of the BTX-A injections. Last, some major assumptions needed to be made including assessment time points of the control group in the Reddihough *et al*. article, as well as the timing of BTX-A injections in relation to initiation of the strength training program for the 8 control group subjects and total number of hours of strength training in the Williams *et al*. article. These assumptions significantly threatened the confidence in data interpretation and conclusions drawn from these studies. Only the Reddihough *et al*. study included outcome measures assessing functional improvements (the GMFM) and parent satisfaction (parental questionnaire). For the other three studies, it would have been helpful to know if the small improvements in muscle spasticity and ROM allowed the children and/or parents to more easily perform functional ADLs or IADLs. Future studies should include the use of outcome measures that capture participation level activities.

References:

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