Review Article

Botulinum Toxin Type A Injection for Management of Upper Limb Spasticity in Children with Cerebral Palsy: a Literature Review

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The aim of this article was to present a review of the research literature on the outcome of botulinum toxin type A (BTX-A) injection for management of upper limb spasticity in children with cerebral palsy (CP). We searched the electronic databases of MEDLINE, CINAHL and PUBMED for all published studies with full-length English text available. For each study, the quality of the methods and the strength of evidence were assessed by 2 independent reviewers based on the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) guidelines. Four studies of level I, 8 studies of level IV and 4 studies of level V were identified. Due to the limited number of studies with high quality evidence and inconsistent results among studies, we were unable to support or refute the usefulness of BTX-A injection for management of upper limb spasticity in children with CP. Moreover, we identified several variables that may affect the outcome of injection, such as timing of age, dosage, dilution volumes, localization techniques of target muscles and participant characteristics. In summary, we have presented a review the literature and a discussion of the considerable uncertainty and variation associated with the clinical use of BTX-A injection for management of upper limb spasticity in children with CP.

Key Words: Cerebral palsy, botulinum toxin type A, spasticity, upper limb

INTRODUCTION

Cerebral palsy (CP) is a non-progressive clinical syndrome that occurs after damage to the motor areas of the immature brain, resulting in a variety of motor deficits.[1,2] The spastic type is the most common form of CP. Spasticity has been considered to be a main contributor to both the impairment of function and decreased longitudinal muscle growth in the children with spastic CP, leading to deformity.[3-7] Thus, reduction of spasticity in children with CP is important for management of the disease. Several treatment options have been used to reduce the spasticity and to improve functions in children with CP. Among them, botulinum toxin type A (BTX-A) injection has become a popular treatment for the spasticity in the absence of fixed deformities in the pediatric population. Further, the use of BTX-A is considered an effective and safe treatment for spasticity or dystonia.[8]

BTX-A produces a dose-dependent, reversible chemodenervation of the injected muscle by blocking the presynaptic release of acetylcholine at the neuromuscular junction.[9] There have been many reports demonstrating that BTX-A can reduce the spasticity/tone in lower limbs and thereby improve locomotor ability in children with spastic CP. In contrast, relatively few studies are available on the use of BTX-A in the management of upper limb spasticity in children with CP.

There are several issues of concern associated with improving the outcome from BTX-A injections into muscles of the upper limb: (1) selection of target muscles, (2) localization of target muscles, (3) optimal dose, (4) optimal timing of age, and (5) dilution volume. In addition, a major issue that needs attention is whether there is sufficient evidence to support the use of BTX-A injection into the muscles of upper limb

in children with CP. Thus, this article presents the results of a systematic review of the research literature and an assessment of the issues associated with the clinical use of BTX-A for management of upper limb spasticity in children with CP.

MATERIALS AND METHODS

Literature search

An extensive search of electronic databases (MEDLINE, CINAHL and PUBMED) through June 2006 was used to identify relevant citations and appropriate references. The search terms included botulinum toxin, Botox, Dysport, cerebral palsy, upper limb, or extremity. The literature search was limited to published studies where full-text was available in English. The articles were reviewed and chosen as reference citations if they met the following inclusion criteria: (1) participants were children with CP aged 0 to 19 years of age, and (2) BTX-A was injected into the upper limb muscles for management of spasticity. To classify the quality of evidence and other aspects of the studies we used the recommendations of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM).[10] Generally speaking, level I studies produce the most credible evidence and, thus, yield the most definitive results. Level II studies are based on less convincing evidence and produce tentative conclusions. Level III and IV reflect still less persuasive evidence and merely suggest causation. No conclusions regarding treatment efficacy can be drawn from level V evidence. The quality of the studies was rated as strong (S), moderate (M) or weak (W), depending on the quality of the methods and how rigorously the study design had been followed.

Our literature search identified one double-blinded randomized controlled trial (RCT), three single-blinded RCTs of level I evidence, 8 prospective uncontrolled studies of level IV evidence, and 4 case studies of level V evidence (Table 1).

RESULTS

Timing of age

It is likely that there is an optimal time during growth and development for management of upper limb dysfunction in children with CP. Given this, the best responses from toxin injection will be achieved if the toxin is injected into the muscles of the upper limb at the optimal age. In our literature review, the age when the children were injected with BTX-A into the muscles of upper limb ranged from 1 to 19 years old (Table 1). Young children below 4 years old were injected in 7 studies.[11-17] It is unknown if the responses in these cases were better than those in older children. Among the previous studies, only one report addressed the effect of age on the improvement after BTX-A injection,[12] and there was no significant relationship between age and functional gain. On the other hand, the cases of a previously published randomized controlled study (RTS)[11] were reanalyzed in a succeeding report[18] in order to identify a positive response group for BTX-A injection. In the reanalysis, they found a trend for younger children to respond positively to the injection, but the p-value did not reach the cutoff level for significance.

Muscle selection

The muscles selected for BTX-A injection for the management of upper limb spasticity varied among studies. For management of elbow flexor spasticity, the biceps brachii was commonly selected for injection.[11,13-15,19-21] Less frequently, the brachialis and brachioradialis were chosen to be injected.[13,14,19] Comparisons of the outcomes according to the muscle injected have not been reported. For improvement of forearm supination, the pronator teres[11,13,15,19,22,23] was commonly selected for injection and in a few cases, the pronator quadratus[15] was injected. Flexor carpi ulnaris and radialis for wrist spasticity and flexor digitorum superficialis and profundus and flexor pollicis longus for clenched hand were chosen.[11,14,15,19,22] The flexor pollicis brevis, opponens pollicis, adductor pollicis, and flexor pollicis longus were also chosen to be injected for the

Table 1. Summary of Articles Reviewed

Authors	Level/Quality*	Study design	Type of CP (No. of cases)	Age (range, yrs)
Corry et al.[22]	I/S	RCT	Spastic hemiplegia (12) Spastic quadripelgia (1) Spastic triplegia (1)	4 - 19
Fehlings et al.[18]	I/S	RCT	Spastic hemiplegia (29)	2.5 - 10
Speth et al.[23]	I/S	RCT	Spastic hemiplegia (20)	4 - 16
Lowe et al.[17]	I/S	RCT	Spastic hemiplegia (42)	2 - 8
Wall et al.[35]	IV/W	Case series†	Hemiplegia (5)	Not mentioned
Denislic et al.[29]	IV/W	Case series†	Dystonic (10)	7 - 15
Autti-Ramo et al.[16]	IV/W	Case series†	Not mentioned (49)	2 - 16
Friedman et al.[12]	IV/W	Case series†	Spastic quadriplegia (17) Spastic hemiplegia (14) Spastic triplegia (1)	1 - 18
Wong et al.[15]	IV/W	Case series†	Spastic hemiplegia (9) Spastic diplegia (1) Spastic quadriplegia (1)	2 - 15
Yang et al.[21]	IV/W	Case series†	Spastic diplegia (9) Spastic hemiplegia (2) Spastic quadriplegia (4)	4 - 13
Hurvitz et al.[19]	IV/W	Case series†	Spastic hemiplegia (9)	7 - 16
Wallen et al.[14]	IV/M	Case series†	Spastic (16)	1 - 14
Gooch et al.[13]	V/W	Descriptive case report	Spastic hemiplegia (1)	3
Hurvitz et al.[20]	V/W	Descriptive case report	Spastic hemiplegia (1)	16
Arens et al.[28]	V/W	Descriptive case reports	Dystonic hemiplegia (4) Mixed hemiplegia (1) Mixed quadriplegia (1)	12 - 19
Mall et al.[24]	V/W	Descriptive case reports	Spastic quadriplegia (2)	13 & 16

*determined by AACPDM levels of evidence classification.[10]
†before and after case series without control group.
CP, cerebral palsy; S, strong; M, moderate; W, weak; RCT, randomized controlled trial.

management of thumb spasticity. The triceps brachii, pectoralis muscles,[19] teres major,[24] and deltoid[12] were injected in a few cases due to shoulder deformity.

How to inject

Type of interventions before injection
The use of interventions to ease the pain and anxiety before injection of BTX-A into the muscles of the upper limb in children with CP varied from general anesthesia to no intervention. A summary of the types of interventions for BTX-A injection from our literature review is shown in Table 2. We found no relationship between the type of intervention and the number of injected muscles, the age of subjects or the method of target muscle localization.

Table 2. Type of Interventions Before Injection and Localization Techniques

Type of interventions	No. of studies	Localization techniques (No. of studies)
General anesthesia	2	Electrical stimulation (1)
		Not mentioned (1)
Topical anesthesia	4	Anatomic knowledge and palpation (3)
		Electrical stimulation (1)
Oral sedation	1	Anatomic knowledge and palpation (1)
Combination of topical anesthesia and oral sedation	2	EMG-guided (1)
		EMG-guided and electrical stimulation (1)
No intervention	7	Anatomic knowledge and palpation (1)
		Electrical stimulation (1)
		Not mentioned (5)

EMG, electromyography.

Injection technique

There are several techniques used for needle placement in the target muscles of the upper limbs. The simplest method is to localize the target muscle by anatomic knowledge and palpation. This procedure is usually performed by finding the largest bulk of the muscle and injecting toxin into several sites at mid-belly. Other methods that have been used to increase accuracy include electromyographic guidance, electrical stimulation of the target muscle, and ultrasound guidance.

Injection techniques used in the literature are summarized in Table 2. Six reports did not mention which localization technique was used for the needle placement. Many of the reports appeared to use surface landmark localization for needle placement. Three studies[12,14,23] used electrical stimulation, and one study[16] used electromyography (EMG) guidance for needle placement. Both EMG and electrical stimulation were used together in one report.[17] The dual-mode localized administration of low-dose, high-concentration BTX-A injections seemed to be an effective method for precise needle placement. The effectiveness of sonography-guided BTX-A injections has not been reported.

Dose and dilution volume

BTX-A toxin is known to produce a dose-dependent chemical denervation resulting in reduced muscular activity. However, systemic side effects or untoward responses occur as the total dose of BTX-A is increased. Therefore, the BTX-A dose is a crucial determinant of outcome. The BTX-A dosing regimens used in the published studies varied, as seen in Table 3. The total dose units per session, total dose units per muscle and dose units per injection site were used to define the dosing regimen. The injection doses for each muscle or muscle group were calculated based on body weight in 6 out of 16 reports (Table 3).

The total dose of toxin used per session was less than 400 units or 12 units/kg body weight for BOTOX® (Allergan, Irvine, CA, USA) and less than 500 units or 29 units/kg body weight for Dysport® (Porton, Speywood, UK). These values are in accordance with the current usage guidelines from 1997[2] and 2000.[25] The doses per kg of body weight used for each muscle, which were described in 6 reports, showed a significant range of variation: 0.5 - 3.2 units/kg/muscle for arm, 0.5 - 4.9 units/kg/muscle for forearm, and 0.9 - 1.8 units/kg/muscle for adductor pollicis.

There has been a report suggesting an optimal dose of BTX-A for the flexor carpi radialis muscle with the amount of reduction in the area of the M responses.[16] In this report, they suggested that the best responses to the toxin without causing weakness of grip strength could be achieved if the maximal forearm doses of BOTOX® were restricted to 1.5 units/kg. However, the optimal dose of the toxin for other muscles has not been

Table 3. Summary of Injection Dose in Articles Reviewed

Authors	Product (dilution volume/dose)	Total dose	Muscle (dose)	Dose per site
Corry et al.[22]	Botox (1 mL/100 U) Dysport (2.5 mL/500 U)	Botox 90 - 250 U (4 - 7 U/kg) Dysport 160 - 400 U (8 - 9 U/kg)	-	Botox (< 40 U) Dysport (< 80 U)
Fehlings et al.[18]	Botox (?)	2 - 5 U/kg	Biceps (1.6 - 3.2 U/kg) Volar flexors (1.1 - 4.9 U/kg) Pronator teres (1.1 - 1.6 U/kg) AP (0.9 - 1.8 U/kg)	-
Speth et al.[23]	Botox (2 mL/100 U)	< 400 U	Arm (2 - 3 U/kg) Forearm (1 - 2 U/kg)	< 50 U
Lowe et al.[17]	Botox (0.5 mL/100 U)	< 8 U/kg (mean: 139 ± 37.48 U range: 82 - 220 U)	Arm (3.5 U/kg) Forearm (1.0 - 3.3 U/kg) Hand (0.6 - 0.8 U/kg)	-
Wall et al.[35]	-	-	AP (5 ng of 0.5 cc solution)	-
Denislic et al.[29]	Dysport (1 mL/500 U)	-	Not mentioned (357.3 ± 99.2 U)	-
Autti-Ramo et al.[16]	Botox (?)	-	AP (5 - 10 U) FPL (10 - 20 U) Forearm (1.5 U/kg) Arm (1 - 2 U/kg)	-
Friedman et al.[12]	-	6 U/kg	-	-
Wong et al.[15]	-	6 - 10 U/kg (limited at about 100 U due to expensiveness)	Hand (25 U) Forearm (50 U) Arm (75 - 100 U)	∼ 25 U
Yang et al.[21]	Botox (1 mL/100 U)	100 - 200 U (mean 159 ± 43 U)	Nor mentioned (1 - 2 U/kg)	-
Hurvitz et al.[19]	Botox (2 mL/100 U)	200 - 300 U	Arm (50 - 100 U) Forearm (30 - 50 U)	-
Wallen et al.[14]	Botox (1 mL/100 U)	< 400 U (12 U/kg)	Not mentioned (0.5 - 2 U/kg/muscle)	< 50 U
Gooch et al.[13]	-	-	Biceps (20 U) BR (10 U) FCR (10 U)	-
Hurvitz et al.[20]	Botox (2 mL/100 U)	200 U	Biceps (100 U) FCR (50 U) FCU (50 U)	-
Arens et al.[28]	Botox (5 mL/100 U)	4 - 6 U/kg	-	-
Mall et al.[24]	Dysport (?)	500 U (8.3 - 29 U/kg)	Teres major (500 U) FCU (200 U) FDP (200 U) APB (100 U) GCM (500 U)	-

Botox (Allergan, Irvine, CA, USA), Dysport (Porton, Speywood, UK).
AP, adductor pollicis; FPL, flexor pollicis longus; BR, brachioradialis; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; APB, abductor pollicis brevis; GCM, gastrocnemius.

reported.

The dilution volume is a determinant for the diffusion and spread of the toxin from the site of injection. As BTX-A is injected into a muscle, there is an immediate diffusion of toxin in the muscle within a few centimeters of the needle tip.[26] With a higher volume, the areas of diffusion appear to increase.[27] The dilution volume for 100 U of BOTOX® varied from 0.5 mL[17] to 5 mL[28] in the literature. The dilution volume for Dysport® was only mentioned in one report, in which 2.5 mL of saline was used to dilute the toxin.[22] Furthermore, a recommended dilution volume for Dysport® has yet to be found in the literature. The ideal dilution volume for both BOTOX® and Dysport® injection into muscles of the upper limbs in children with CP has yet to be shown.

The weakening of grip strength was the only reported untoward response to the toxin injection. According to one report,[16] impairment of grip strength was related to an overdose of the toxin. This report found that grip strength did not weaken if the maximum forearm dose was limited to 1.5 units/kg/muscle. In addition, grip strength impairment was reported in other reports. Fehling et al. reported a case with temporary grip strength weakness in a single blinded RCT.[11] In their study, doses of BOTOX® ranging from 1.1 to 4.9 units/kg/muscle were injected into forearm muscles, with doses above 1.5 units/kg/muscle injected in 10 cases (66.7%). The untoward reaction of grip strength weakness was also noted in three cases from the study of Wallen et al.[14] Two cases exhibited excessive and prolonged weakness after toxin injection into the long finger flexors. And in the remaining case, the long finger flexors were not injected. They reported that the weakness of grip strength seemed to result from the spread of toxin from the injection site of the flexor pollicis longus to the long finger flexor. Since dosages of BTX-A in these three cases were not mentioned in the study, it is not known whether the untoward reactions in these three cases were related to overdose. Grip strength weakness after injection was also noted in other studies, but information about doses, target muscles and possible explanation for the untoward reaction were not described.[22,29]

Effects of BTX-A

Effects of BTX-A on spasticity/tone and range of motion

Spasticity or tone was measured in four RCTs (level I), six uncontrolled studies (level IV) and two case studies (Level V) based on different methods and different joints (Table 4). Five studies used the Ashworth Scale[30] and seven studies used the Modifies Ashworth Scale.[31] Wrist resonance frequency[32] and Tardieu method[33] were also used as a measure of spasticity/tone. Two RCT studies showed significantly lower values with the Ashworth scale in the BTX-A intervention group.[17,22] Four uncontrolled studies also reported a significant reduction in spasticity/tone after intervention.[12,14,15,21] The reduction of spasticity/tone lasted up to three months. However, the other two RCTs and two uncontrolled studies did not reveal any significant differences in spasticitiy/tone.[18,19,23] Although many of the uncontrolled studies showed positive responses to BTX-A, the quality of evidence in level IV studies is too weak to support the benefits of the toxin in spasticity/tone. However, half of the level I studies had high quality evidence for positive responses in spasticity/tone from BTX-A injections into the upper limb muscles.

Range of motion (ROM) was measured in three RCTs, six uncontrolled studies and one case study based on different methods and different joints (Table 4). Active ROM, passive in ROM, the webspace method and the Norkin and White procedure[34] were used as a measure of ROM. Two RCTs[22,23] showed significant improvement in active ROM and one RCT (level I with evidence of high quality)[18] did not show any changes in passive ROM after the toxin injection. In addition, only two uncontrolled studies (level IV evidence of weak quality)[12,15] showed significant improvement in ROM and the other four uncontrolled studies[14,16,19,35] did not show any significant changes after the toxin injection.

Thus, the findings of the reports did not reveal sufficient evidence to support or refute the benefits of BTX-A injection on the spasticity/tone and ROM of the upper limbs in children with CP.

Table 4. Effects of Botulinum Toxin Type A on Spasticity/Tone and Range of Motion in the Articles Reviewed

Authors	Spasticity/Tone		Range of motion	
	Method	Results	Method	Results
Corry et al.[22]	AS	Significant reduction at elbow ($p = 0.01$) and wrist ($p = 0.003$) after 2 weeks, and wrist ($p = 0.01$) after 12 weeks	AROM	Significant increase at elbow ($p = 0.026$) and thumb ($p = 0.036$) after 2 weeks
	WRF	Significant reduction after 2 weeks ($p = 0.02$) and after 12 weeks ($p = 0.045$)		
Fehlings et al.[18]	MAS	Not significant	PROM	Not significant
Speth et al.[23]	AS	Not significant	AROM	Significant increase in supination ($p = 0.006$)
Lowe et al.[17]	AS	Significant reduction ($p < 0.001$)		Not assessed
Wall et al.[35]		Not assessed	Web space, PROM	Not significant
Denislic et al.[29]	AS	Decrease in tone (not statistically analyzed)		Not assessed
Autti-Ramo et al.[16]		Not assessed	PROM, AROM	Not significant
Friedman et al.[12]	MAS	Significant reduction ($p < 0.02$)	ROM (Norkin and white Procedure)	Significant increase at wrist ($p = 0.001$) and thumb ($p = 0.023$) after 1 month
Wong et al.[15]	MAS	Significant reduction ($p < 0.003$)	Web space, AROM	Significant increase ($p < 0.043$)
Yang et al.[21]	MAS	Significant reduction ($p < 0.05$)		Not assessed
Hurvitz et al.[19]	MAS	Not significant	PROM, AROM	Not significant
Wallen et al.[14]	MAS	Significant reduction at pronators ($p < 0.0001$), elbow ($p = 0.001$) and wrist ($p = 0.001$) after 2 weeks, and at wrist ($p = 0.017$) after 3 months	PROM, AROM	Not significant
	TS	Significant reduction at pronators ($p = 0.008$) and elbow ($p = 0.001$) after 2 weeks, and at elbow ($p = 0.001$) after 3 months		
Gooch et al.[13]	AS	Reduction		Not assessed
Hurvitz et al.[20]	MAS	Reduction	PROM, AROM	No difference
Arens et al.[28]		Not assessed		Not assessed
Mall et al.[24]		Not assessed		Not assessed

AS, Ashworth scale; MAS, modified Ashworth scale; WRF, wrist resonance frequency; AROM, active range of motion; PROM, passive range of motion; TS, Tardieu scale.

Effects of BTX-A on functional gains of upper limb

The functional changes of the upper limb were assessed in various ways. All results are displayed in Table 5. Two RCTs, which used the Quality of Upper Extremity Skills Test (QUEST),[36] showed significant differences in favor of the intervention group.[17,18] Three RCTs and two uncontrolled studies assessed Pediatric Evaluation of Disability Inventory (PEDI), and the significant improvement in the self-care domain of PEDI in one RCT[18]

and one uncontrolled study,[21] as well as the functional skill of PEDI in another RCT,[17] were noted. One RCT[23] and one uncontrolled study[14] used the Melbourne Assessment of unilateral upper limb function (Melbourne Assessment)[37] and did not reveal any significant changes in the scores. The existing heterogeneity among studies in measuring the outcome of the upper spastic limb makes it difficult to compare the results.

Three RCTs with higher quality of evidence showed significant differences in functional activities favoring the intervention group.[17,18,22] In the report by Fehlings et al.,[18] only nine out of 14 individuals who received the toxin injection improved. In additional analyses to determine the predictive factors for a positive response to the BTX-A injection, they found that adequate grip strength before injection and younger age appear to correlate with greater response to BTX-A. However, one level I study did not show any difference in functional activity between the intervention and control groups, which had both received rehabilitation therapy.[23] And five level IV studies with weak quality of evidence showed some changes in function, compared with baseline measurement.[12,14,15,21,29] Another three level IV studies failed to show significant changes in function after the toxin injection.[16,19,35] Additionally, the reported functional benefits of BTX-A varied from simple posturing improvement to functional improvement based on the measurements used, with the effects for most studies lasting up to three months after injection. Most of the other studies did not control for factors that might affect the outcome of the BTX-A toxin injection. The type or intensiveness of post injection therapy such as occupational therapy, electrical stimulation and splint might also be a factor affecting the outcome of BTX-A injections. Further, dilution volume, dose of toxin, muscle selection method and accurate localization of target muscles might affect the outcome of the toxin.[16] The considerable variation in these factors in the literature makes it difficult to demonstrate evidence that BTX-A injection is beneficial. Also, the patient's characteristics such as distal voluntary control,[11] grip strength,[18] intact sensation, level of motivation and motor learning capacity[16] might affect the response. The inclusion and exclusion criteria in

the literature varied widely from none to strict regulation (Table 5). The difference in criteria for these studies might be a factor contributing to the wide range of toxin responses. In conclusion, the available evidence for the short to medium term efficacy of BTX-A injection for functional gains in the upper limbs is promising, but not definite.

DISCUSSION

In contrast to the use of BTX-A injection into the lower limb, the use of BTX-A injection into the upper limb in the children with CP is currently evolving. We only identified sixteen reports to review for this paper. It can be said that the ultimate goal of the clinical use of BTX-A is to get the best results. There are several factors that may influence the outcome of BTX-A injection: (1) optimal timing of age, (2) selection of target muscles, (3) dose and dilution volume of the toxin, and (4) ability to correctly identify the target muscle. These factors need to be discussed before determining if there is sufficient evidence to support the usefulness of BTX-A injection for upper limb spasticity in children with CP.

Optimal timing of age

The timing of BTX-A injection plays a central role for maintaining elasticity in the muscle and reducing the development of contracture and deformity. Some spastic muscles of the upper limbs, such as the pronator teres and wrist flexors may progress to muscle contracture at a faster rate than other muscles.[38] If left untreated, contracture of these muscles may lead to bony rotational abnormalities of the radius and ulnar. Therefore, early use of BTX-A would be beneficial for maintaining muscle elasticity and reducing development of contracture and deformity.[38,39] Additionally, a BTX-A injection during the period of dynamic motor development, where there is the greatest chance of modifying the course of the disease, might have the potential to enhance motor skill development.[25,38] However, the results of the studies did not show the benefits from early use of BTX-A injection.

On the other hand, repetitive use of an affected

Table 5. Effect of Botulinum Toxin Type A on Functional Activities of Upper Limb and Inclusion/Exclusion Criteria

Authors	Functional activities		Post injection therapy	Inclusion criteria	Exclusion criteria
	Method	Results			
Corry et al.[22]	Coin transfer, grasp/release	Significant difference of grasp/release in BTX-A group at 3 month ($p = 0.01$) Improve in cosmetic appearance	Not mentioned	None	None

Fehlings et al.[18]	QUEST, PEDI	Significant difference in QUEST at 1 month ($p = 0.039$) and self care domain in PEDI ($p = 0.04$)	Usual care	1) 2.5 - 10 year-old
				2) Spastic hemiplegia
				3) MAS of elbow, wrist or thumb ≥ 2
				4) Full passive range
				  Elbow: extension to neutral
				  Wrist extension 30° past neutral with finger extension
				  Forearm: supination 30° past neutral
				  Thumb: extension to neutral
				5) Ability to initiate voluntary movement of the digits
					Using rigid splint

Speth et al.[23]	Melbourne Assessment, PEDI, Nine hole peg	Not significant	Intensive therapy	1) Spastic hemiplegia 2) Minimum developmental age of 3 years	1) Deficit of elbow extension, supination and wrist dorsiflexion > 30° 2) Severe impairment of hand function 3) Unable to initiate voluntary movement
Lowe et al.[17]	QUEST, COPM, PEDI, GAS	Significant difference in QUEST at 1, 3 month ($p < 0.001$) and COPM ($p = 0.007$), functional skill of PEDI ($p = 0.03$), GAS ($p = 0.001$)	Usual care	1) 2 - 8 year-old 2) Spastic hemiplegia 3) Spasticity is at least MAS 2 interfering with functional movement 4) At least 10° active range of movement in antagonist 5) Volitional limb use when instructed to play bilaterally	1) Lower limb BTX-A in the past 6 months 2) Upper limb BTX-A in the past 12 months 3) Upper limb fixed contracture > 40° 4) Lack of sensory response to light touch or pain in affected limb 5) 100% inability of demonstrating volitional upper limb movement in response to instuctions
Wall et al.[35]	Grip strength, video and photo rating	Not significant Improve in cosmetic appearance	Not mentioned	None	None
Denislic et al.[29]	Upper limb disability score	Significant changes in dystonia (up to maximum 4 months) ($p < 0.01$)	Not mentioned	None	None
Autti-Ramo et al.[16]	Grips, 2-handed functions, Box & Block, Purdue Peg Board, Grip strength	Not significant	Intensive home therapy and splint	None	None

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Table 5. Continue

Authors	Functional activities		Post injection therapy	Inclusion criteria	Exclusion criteria
	Method	Results			
Friedman et al.[12]	Care giver rating	Significant improvement for up to 3 - 4 months (Not statistically analyzed)	Usual care	1) <21 year-old 2) Upper limb spasticity 3) First BTX-A injection	1) With contracture
Wong et al.[15]	Jebsen hand function test	Significant improvement for upto 6 months ($p < 0.03$)	Usual care	1) At least MAS 2 in upper limb 2) Dynamic deformity	1) Fixed joint contractures
Yang et al.[21]	PEDI, BO, PRS	Significant difference at self-care domain in PEDI at 3 months, BO at 6weeks and 3 months ($p < 0.05$)	Usual care	1) Moderate to severe degree of upper limb spasticity (interfere with functional use or maintenance of hygiene) 2) >2 year-old 3) Ability to initiate voluntary movement of at least the digits	1) Significant contractures
Hurvitz et al.[19]	PEDI, FIM, Perdue pegboard, BO	Not significant	No treatment	None	1) Previous BTX-A injections, surgery or significant injury to upper limb 2) Inability to cooperate with motor control testing 3) Joint contracture limiting elbow, wrist or finger by more than 25% 4) Inability to attend all testing sessions
Wallen et al.[14]	Melbourne Assessment, COPM, GAS	Significant difference in COPM performance rating at 3 and 6 months ($p = 0.004$ and 0.002) Not significant difference in Melbourne Assessment, GAS	Usual care treatment	1) MAS 2-3 in at least 1 upper-limb muscle group 2) Family goal is improving function, hygiene, splint tolerance or limb positioning	1) Fixed contracture 2) Lack of motor control 3) Fluctuating muscle tone
Gooch et al.[13]	Subjective measure	Improve in use and awareness (up to 2 weeks)	Not mentioned	None	None
Hurvitz et al.[20]	FIM, PEDI	Not significant	No treatment	None	None
Arens et al.[28]	Achievement of aim	Aim achieved in 50% (partially or completely) at 6 to 8 weeks	Not mentioned	None	None
Mall et al.[24]	Subjective measures	Improvement in posture, pain, easier to handle	Usual care	None	None

BTX-A, botulinum toxin type A; QUEST, quality of upper extremity skills test; PEDI, pediatric evaluation of disability inventory; COPM, Canadian occupational performance measure; GAS, goal attainment scaling; BO, Bruninks-Oseretsky test of motor proficiency; PRS, upper limb physician's rating scale; FIM, functional independence measure; MAS, modified Ashworth scale.

muscle in daily functional tasks may reinforce the effects of the BTX-A injection. Thus, a child's motivation to use the affected part in daily functional task seems to play a critical role in achieving functional changes. Preschool aged children (four to six years of age) are often very motivated to train bimanual functions and have good motor learning capacity.[16] Therefore, four to six years of age might seem to be an optimal age range for getting maximal responses with the toxin injection. This correlates with the recommendation of guidelines published in 2000 by a group of experienced BTX-A users.[25] However, since there are not sufficient numbers of reports looking at the relationship between age of injection and response, the optimal timing for age of BTX-A injection for management of upper limb spasticity still remains to be answered in children with CP.

Muscles selection

The selection of target muscles for BTX-A injection is individualized after careful analysis of the functional deficits, the postural deformities, the treatment goals, and the clinician's analysis of the muscular hypertonia and how it relates to the individual's abilities and disabilities.[18,22]

The most common target muscles seen in the literature were the biceps brachii for elbow flexor spasticity, pronator teres for pronated forearm, flexor carpi radialis and flexor carpi ulnaris for wrist flexion spasticity, and adductor pollicis for thumb in palm. In a few cases, the brachialis, or brachioradialis, was selected for injection in an attempt to reduce elbow flexor spasticity without causing the loss of supinating ability. The advantage or disadvantage of brachialis or brachioradialis muscle injection, compared with biceps brachii injection, has not been reported with regard to outcome. Further study of this issue will be helpful in selecting the target muscle for reduction of elbow spasiticy. Apart from the discomfort of the injection site, the only adverse events recorded were temporary post-injection grip strength weakness when injecting the forearm muscles, especially long finger flexor muscles. Therefore, it is recommended that injection to the long finger flexor muscle or forearm muscles should be carefully planned to prevent the untoward reaction of grip strength weakness.

Type of interventions before injection

Treating children before injection to ease pain and anxiety was done with topical anesthetics, oral sedation and general anesthesia in over 50% of the studies. Pain and discomfort during the procedure has prompted the use of these interventions. Although the injections are generally done quickly, they can be lengthened in the cases where multiple muscles are injected. In addition, the localization techniques used to improve the accuracy of needle placement can evoke discomfort and pain, which are not well tolerated in young children. When target muscles are localized with EMG guidance and/or electrical stimulation in a young child or multiple muscles are injected, pre-treating children before injection can improve the ease of the injection procedures and decrease anxiety during subsequent clinic visits. However, in the literature, the type of intervention before injection was not related to age, localization technique or number of injected muscles.

Techniques of muscle localization

The accuracy in target muscle localization may be a key factor determining the outcome of BTX-A injections, more so than dilution volume and dose. Various techniques to find the injection site for the delivery of BTX-A into spastic skeletal muscles have been described in the literature. The simplest method to deliver BTX-A into muscles is to localize the target muscle by simple palpation and surface anatomy. It is generally accepted that this method is suitable for large, subcutaneous muscles. However, the accuracy of this technique in the forearm and hand muscles is reported to be quite low, ranging from 13% to 35%.[40] Therefore, the use of EMG or the motor point stimulation method is recommended to identify muscles targeted for injection, particularly for the smaller muscles in the forearm and hand.[41] The EMG-guided method has been shown to be more accurate in needle placement than the manual technique. However, these methods are of limited

use in children because the procedure is painful and time-consuming and requires the cooperation of the patient.[41,42] Another alternative method for improving the accuracy of needle placement is electrical stimulation.[40] Electrical stimulation is easy to perform, does not require formal EMG training and does not prolong the procedure significantly. However, it is uncomfortable and usually painful. Thus, it does require the patient to have sedation or mask anesthesia. Although EMG guidance and electrical stimulation have been shown to be more accurate in needle placement than the manual technique, their limitations restrict the use of these techniques in children. Half of the studies reviewed used these techniques in needle placement. However, it remains uncertain whether the effort to improve the accuracy in needle placement will lead to better responses to the toxin.

Sonography is an emerging localization technique. The visual identification of muscles and depth control of needle placement are key features of sonography-guided injection. The use of sonography can prevent incorrect delivery of BTX-A toxin. This technique is easy, quick and painless, thus, it might be a suitable method for use in children. There is one report on the use of this technique for delivering BTX-A toxin into the muscles of the upper limb in children with CP.[42] This report suggested that the sonography-guided injection technique facilitates the reliable injection of the upper limb muscles in children with CP. However, the outcome with sonography-guided injection has not been reported.

One concern is whether there is a significant relationship between target muscle localization techniques and outcome from toxin injection. However, the heterogeneity in the characteristics of subjects and dosage and assessment tools makes it difficult to compare the results of the studies. Further research into the importance of the method of needle localization as related to outcome is an important area to be studied in treating children with CP.

Dosing and dilution volume

In the search for an optimal dose of toxin for each muscle, the ultimate goal is to achieve the

best outcome without causing the side effects of the toxin injection. Although dosing guidelines were established empirically by the consensus of experienced injectors in 1997 and 2000,[2,25] there is no supporting evidence for an optimal dosage for each muscle. Through our systemic review, we hope to determine the optimal dose that elicits the best response without causing untoward reactions. However, in our review of the literature, the heterogeneity in dosages used for spasticity management of the upper limb makes it hard to look at the dose-response relationship across the studies.

The optimal dose of toxin was studied for the flexor carpi radialis muscle in one report.[16] For other muscles of the upper limb, there is not sufficient data on the optimal dose for a positive response without side effects. Further, it is not certain whether a higher dose produces a better response and longer lasting effect.

An increased dilution volume can result in the increased spread of the toxin away from the injection site and an increased paralysis of large muscles of the lower limb in animal studies.[43,44] Increased diffusion of a higher dilution volume could potentially spread to adjacent muscles that are not target muscles for treatment.[45] The muscles of the upper limb in the children with CP are smaller than the muscles of the lower limb, and furthermore, the muscles in the hand and forearm are adjacent to each other. So, the spread of the toxin from the injection site could become problematic when it comes to toxin injections in the small muscles of the upper limb. Although 1 or 2 mL of preservative-free normal saline are typically recommended to dilute BOTOX®, 0.5 to 5 cc of normal saline have been used in the literature. Moreover, there is a recent report of a good response to an injection of a high concentration of BTX-A diluted with 0.5 cc of normal saline. The results from this report indicated that a better outcome might be possible through modifying the dilution volume with considerations for target muscle size and neighboring muscles.

Impairment of grip strength was the only unwanted side effect when the toxin was injected into the forearm muscle. A high toxin dose was the suggested causative factor for the untoward

reaction.[16] However, a lack of information about dosages used in each case made it difficult to study the relationship between grip strength weakness and dose. In addition, the area of diffusion and spread of the toxin increases as the volume increases. Therefore, it seems likely that a high dilution volume may be a factor causing the grip weakness. The influence of the dilution volume on the occurrence of grip strength impairment should be studied in order to improve the outcome of BTX-A injection into the upper limb muscles in children with CP. In addition, the inaccuracy of target muscle localization might also be a cause of the unwanted side effect. The techniques used for needle placement varied in the literature, and several studies failed to use techniques that enhance the accuracy of needle placement. However, it still remains uncertain whether the accuracy of needle placement affects the development of unwanted side effects from BTX-A injection.

Effects of BTX-A injections

Through a systematic review of the studies published, we tried to determine if there are sufficient data to support the benefits of BTX-A injection for the functional improvement in the upper limb muscles of children with CP. However, we found that the evidence is neither sufficient nor consistent to support or refute the clinical use of BTX-A injection for spastic upper limb management in the pediatric population. From our review, we were able to delineate the possible reasons for the inconsistent and insufficient results from the reviewed studies.

At first, as a child grows, there is natural improvement in CP that occurs with time and the acquisition of functional skills. Therefore, any changes after injection might be due to the toxin injection, to natural improvement over time, or both. Therefore, a good control group is vital for the study design. However, we could only find 4 studies that had a control group, and these studies reported various responses to the toxin. In addition, the sample size of 106 cases in 4 level I studies and of 137 cases in 8 level IV studies further weakened the evidence. Second, the assessment of the functional outcome was

quantified by methods such as QUEST and the Melbourne upper limb assessment in only 3 level I studies and 1 level IV study. Short-term improvements were found by QUEST in only 2 level I studies and no functional gains were found by the Melbourne assessment in one level I study and one level IV study. The measuring tools used in the studies varied considerably, depending, in part, on the therapeutic aims of the injection or other factors such as preference, availability etc. Therefore, the inconsistent methods of measurement obscure the evidence and make comparisons between studies difficult. In addition to the variability in assessment tools, the heterogeneity in dosing regime, localization technique and dilution volume make it even harder to compare the results of the studies. Finally, selecting the ideal candidate can affect the outcomes of BTX-A injection. A number of authors have suggested that children who have a favorable functional response to BTX-A tend to be those with a moderately high muscular tone,[18,22] preserved grip strength and younger age,[18] some distal voluntary control,[11] intact sensation and motivation to participate in post-injection training.[16] The considerable heterogeneity of the participants across the studies seemed to be one of the factors that led to the varying responses to BTX-A injection. We think that efforts to control these limitations are necessary to obtain consistent evidence for the benefit of the clinical use of BTX-A injection into the upper limb in children with CP.

In conclusion, our systematic review of the literature on the use of BTX-A injection for management of upper limb spasticity in children with CP revealed that there is not sufficient evidence to support or refute its benefits. The considerable variation in doses, dilution volume, method of administration, selection of target muscles, characteristics of subjects and assessment tools make it difficult to compare the results of the studies. In addition, the effects of the above variables on the outcome are still unknown. Further studies into how these variables affect the outcome are required to help clinicians optimize the injection strategy for BTX-A in the management of upper limb spasticity in children with CP.

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