

BOTULINUM TOXIN A INJECTION IN TREATMENT OF UPPER LIMB SPASTICITY IN CHILDREN WITH CEREBRAL PALSY

A Systematic Review of Randomized Controlled Trials

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Abstract

Background: Cerebral palsy (CP) is the most common cause of childhood disability globally. Botulinum toxin A injections are widely used to manage limb spasticity in children with CP. Intramuscular botulinum toxin A has been used in the upper limbs of children with CP to manage preoperative and postoperative pain, facilitate nursing, and achieve functional and/or cosmetic improvement of hand position. These goals are achieved primarily through reduction of spasticity. The aim of this review was to assess the evidence for the effect of botulinum toxin A injections used to manage upper limb spasticity in children with spastic CP. Specifically, we examined the role of botulinum toxin A as an adjunctive treatment to other physical therapy modalities. Additionally, we analyzed the associated complications.

Methods: The literature extraction process involved 4 phases: identification, screening, eligibility, and inclusion. We used a combination of Google Scholar, PubMed, and ScienceDirect. The choice of the search terms was based on the Medical Subject Headings. We extracted the relevant studies using a combination of words or terms related to (1) patient population, (2) pathology, (3) clinical intervention, and (4) anatomical distribution of pathology. Studies were included if they were randomized controlled trials conducted on children and/or adolescents with CP targeting the upper extremities in which botulinum toxin A was used as an adjunctive treatment to a primary intervention.

Results: The literature extraction process yielded 15 randomized controlled trials for inclusion in this review. The total number of participants enrolled in the included studies was 499, with 255 in the intervention group (51%) and 244 controls (49%). All participants in the eligible studies had unilateral spastic CP except for those in 4 studies (27%) with 198 participants (40%) that included a heterogeneous sample of unilateral and bilateral spastic CP. The mean age of participants in the intervention group ranged from 2.6 to 10.7 years among the individual studies. The mean age of participants in the control group ranged from 3.1 to 10.55 years among the individual studies. This review indicated that botulinum toxin A had a positive effect on the degree of spasticity and cosmetic appearance of the

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injected upper limb. The results with respect to functional gains and quality of life were either conflicting or not significant.

Conclusions: Randomized controlled trials of botulinum toxin A injection in the treatment of upper limb spasticity in children with CP used variable outcome measures and yielded mixed results. Overall, there is some evidence to support the use of botulinum toxin A as an adjuvant treatment to other physical therapy regimens or placebo to reduce spasticity in the short term. There is insufficient evidence to support its use as an adjunctive treatment to improve upper limb function or quality of life. The complications were acceptable and did not outweigh the clinical gains incurred.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Cerebral palsy (CP) is the most common cause of childhood disability globally¹. It manifests in restricted functional mobility and negatively impacts the quality of life². Although the primary brain insult is nonprogressive, the secondary musculoskeletal impairments are progressive³. Intramuscular botulinum toxin A (BTX-A) use is widespread in both the upper and lower limbs⁴⁻⁷. BTX-A impairs the release of acetylcholine at the neuromuscular junction, which in turn reduces the spasticity of skeletal muscle. Single-event multilevel injection, in which several muscles or muscle groups are injected at each session, is a popular practice^{4,8}. Intramuscular BTX-A has been used in the upper limbs of children with CP to manage preoperative and postoperative pain^{4,9}, facilitate nursing⁴, and achieve functional and/or cosmetic improvement of hand position⁴⁻⁶. These goals are achieved primarily through reduction of spasticity. Thus, static contracture deformities cannot be treated by BTX-A. Casting, splinting, exercises, and electrical stimulation are adjunctive treatment modalities that aim to potentiate the effect of BTX-A^{2,10-13}. In a broader context, intramuscular BTX-A injections should be looked at as a part of a multimodal management approach that includes single-event multilevel

surgery in the upper¹⁴ or lower¹⁵ extremities.

There is a lack of consensus in the literature on the use of intramuscular BTX-A in children with CP as to the exact therapeutic indications, treatment goals, optimal dosing, selection of target muscles, and techniques to guide injection, and on its role as an adjunctive treatment (to other treatment modalities)^{4,10,12,16,17}. Furthermore, the presence of a wide array of subjective and objective outcome measures for patient evaluation before and after BTX-A injection complicates evidence extraction and scholarly communication^{16,18}. Most clinical practices relating to BTX-A injection are based on expert opinion⁴. We therefore conducted a verifiable literature review of the clinical evidence for the use of BTX-A to improve function in the upper extremities of children with CP. To our knowledge, this topic has not been critically appraised in the literature. We formulated the following research questions: (1) What is the evidence for the use of intramuscular BTX-A to improve function of the upper extremities in children with CP? (2) What are the important complications following BTX-A injection?

Materials and Methods

Literature Search

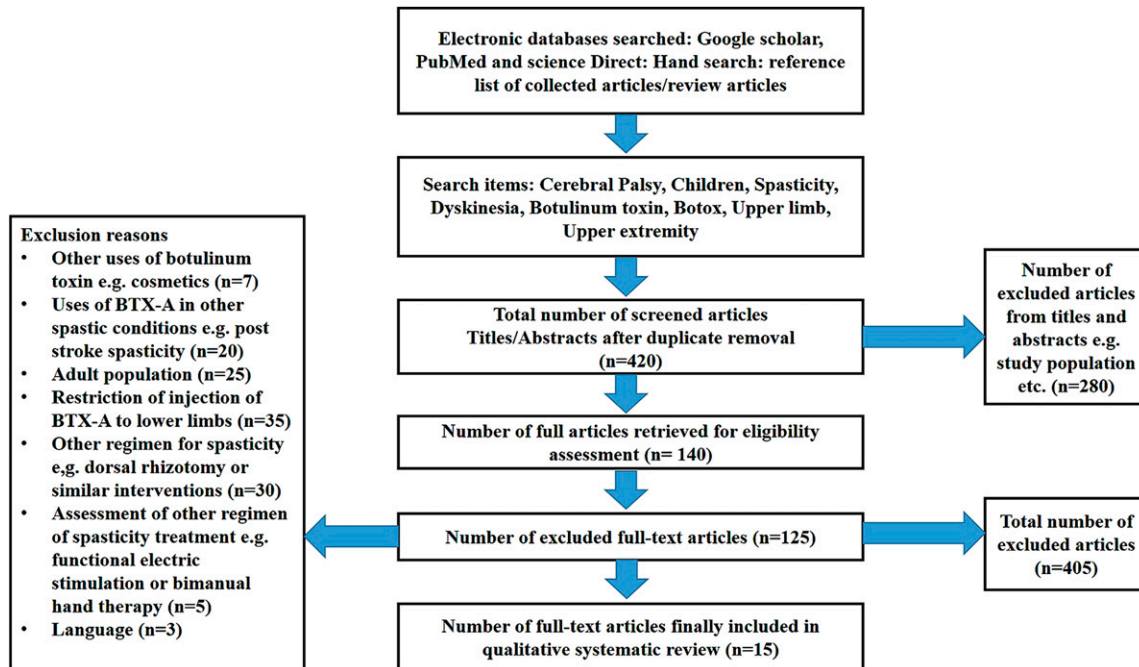
The literature extraction process involved 4 phases: (1) identification, (2)

screening, (3) eligibility, and (4) inclusion. To make the most effective use of the online scholarly databases with respect to coverage, recall, and precision, we used a combination of Google Scholar, PubMed, and ScienceDirect¹⁹. The choice of the search terms was based on the Medical Subject Headings. To increase the accuracy of our search results, we used the Boolean operators AND, OR, and NOT. We extracted the relevant studies using a combination of words or terms related to (1) patient population, (2) pathology, (3) clinical intervention, and (4) anatomical distribution of pathology. These terms were (Children OR Childhood) AND (Cerebral Palsy OR Static Encephalopathy) AND (Spasticity OR Dyskinesia) AND (Botulinum Toxin Type A Injection OR Botox Injection) AND (Upper Limb OR Upper Extremity).

All authors shared in the selection and data extraction process pertaining to the use of BTX-A for the upper extremities in children with spastic CP (Fig. 1). All titles and abstracts were checked for eligibility. Studies were included if they were (1) randomized controlled trials conducted on children and/or adolescents with CP, (2) studies targeting the upper extremities wholly or in conjunction with other anatomical regions, (3) studies in which BTX-A was used as an adjunctive treatment to a primary intervention, and (4) studies in the English language, without date restrictions. Studies were excluded if they were (1) studies conducted on neuromuscular disorders other than CP, (2) studies conducted exclusively on adult patients with CP, (3) studies exclusively targeting anatomical regions other than the upper extremities, (4) studies of other uses of BTX-A (stroke, cosmetic, ophthalmology, intraparotid, etc.), (5) narrative or systematic review articles, (6) experimental studies, or (7) not retrievable in full-text form.

Methodological Quality

This systematic review was performed in concordance with the PRISMA (Preferred Reporting Items for Systematic



A schematic representation of literature extraction process with exclusions. BTX-A, Botulinum toxin-A

Fig. 1

Schematic representation of the extraction process. BTX-A = botulinum toxin A.

Reviews and Meta-Analyses) statement²⁰. The methodological quality of included studies was assessed according to the Modified Jadad Scale^{21,22}, an easily applicable scale for appraisal of randomized controlled trials that consists of 8 items (randomization if it was reported and appropriate, blinding if it was reported and appropriate, withdrawals/dropouts, methods for assessing adverse effects, methods of statistical analysis, and the inclusion and exclusion criteria for the participants). The total score can range from 0 to 8 points^{21,22}. A score of 5 to 8 was considered to indicate that the study had high quality; 3 to 4, moderate quality; and <3, poor quality. The level of evidence of the eligible studies was assessed as described by Sackett and Straus, as has been done in a previous review on this subject^{23,24}.

Results

Study Demographics

All 15 studies included in this systematic review were randomized controlled trials²⁵⁻³⁹. Three studies were performed

at multiple centers^{30,37,39}. All of the included studies investigated the effect of BTX-A injection in the upper limb(s), and all were conducted on the spastic type of CP in children. All of the studies had Level-II evidence according to Sackett and Straus²³. All of the studies were of high quality; 1 study²⁹ scored 8 points on the Modified Jadad Scale, 10 studies^{25,27,28,30,31,34,36-39} scored 7 points, 1 study²⁶ scored 6 points, and 3 studies^{32,33,35} scored 5 points.

Patient Demographics

The total number of participants enrolled in the included studies was 499, with 255 in the intervention group (51%) and 244 controls (49%). All participants in the studies had unilateral spastic CP except those in 4 studies^{25,29,31,36} (27%) with 198 participants (40%) that included a heterogeneous sample of unilateral and bilateral spastic CP. The mean age of participants in the intervention group ranged from 2.6 to 10.7 years among the individual studies. The mean age of participants in the control group

ranged from 3.1 to 10.55 years among the individual studies. The studies that reported patient sex included 262 male patients (53% of the total in the 15 studies) and 162 female patients (32%); the remaining 3 studies^{33,35,39} with 75 patients (15%) did not indicate the sex distribution of the participants. Participant characteristics are detailed in Table I.

Interventions

The BTX-A injection characteristics, including the dose and type and the primary treatment provided with the BTX-A injection, are described in Table II.

In 7 studies^{27,28,30,31,34,38,39}, the investigators injected the BTX-A using anatomical landmarks and electrical stimulation of muscles. Three studies^{25,26,29} with 83 patients (17%) used only anatomical landmarks for muscle localization. Two studies^{36,37} with 100 patients (20%) used ultrasound for localization. The remaining 3 studies^{32,33,35} did not report the method of muscle localization. Twelve of the

TABLE I Patient Demographics, Assessment, and Outcomes After BTX-A Injection*

Study	No. of Participants	Randomization	Mean Age (yr or yr+mo)	Sex, M:F	Bilateral CP Included†	Time of Follow-up Assessment	Assessment of Spasticity and Muscle Tone	Result Compared with Controls	Functional Assessment	Result Compared with Controls
Corry et al. ²⁵	14	7 treatment, 7 control	9	5:9	Yes	Baseline and 2 and 12 wk	Ashworth Scale, ROM, wrist resonance	All scores on these scales improved in treatment group	Grasp and release score, coin pickup for fine motor assessment	Improvement in grasp and release score, but not coin pickup score, in treatment group
Fehlings et al. ²⁶	30	15 treatment, 15 control	BTX-A, 5.6 ± 2.6; control, 5.3 ± 2.3	20:10	No	Baseline and 1, 3, and 6 mo	MAS, PROM	No significant differences between groups	QUEST, grip strength, PEDI	Significant improvement in QUEST and slight improvement in PEDI in treatment group, but no significant difference in grip strength between groups
Speth et al. ²⁷	20	10 treatment, 10 control	BTX-A, 9.4; control, 9.7	11:9	No	Baseline and 2 and 6 wk and 3, 6, and 9 mo	Ashworth Scale, AROM	Significant increase in ROM and tone reduction at the wrist in treatment group	MA, PEDI, 9-hole peg test	No significant difference between groups
Lowe et al. ²⁸	42	21 treatment, 21 control	4	31:11	No	Baseline and 1, 3, and 6 mo	Ashworth Scale	Significant improvement in degree of spasticity and muscle tone in treatment group	QUEST, GAS, COPM, PEDI	Improvement in all scores except PEDI, which showed nonsignificant difference, in treatment group
Kawamura et al. ²⁹	39	21 high dose (treatment), 18 low dose (control)	Low dose, 3.1; high dose, 2.6	22:17	Yes	Baseline and 1 and 3 mo	ROM	Slight improvement in both groups, but no difference between doses	QUEST, GAS, COPM, PEDI, grip strength	Small improvement in arm and hand function, but no significant difference between groups on any scale
Russo et al. ³⁰	43	21 treatment, 22 control	BTX-A, 8.4; OT control, 8.7	23:20	No	Baseline and 3 and 6 mo	MAS, Tardieu Scale	Significant improvement in degree of spasticity and muscle tone in treatment group	AMPS, GAS, self-perception, PEDI, PedQL	Improvement in GAS at 3 mo after injection, but no difference between groups on any scale at 6 mo
Wallen et al. ³¹	72	20 treatment group 1, 20 treatment group 2, 17 control group 1, 15 control group 2	BTX-A + OT, 5+8 ± 3+1; BTX-A, 6+7 ± 3+9; OT, 5+2 ± 2+11; control, 5+11 ± 2+10	46:26	Yes	Baseline, 2 wk, and 3 and 6 mo	Tardieu Scale, AROM, PROM	No significant difference between groups in all scales	COPM, GAS, QUEST, MA, PEDI	Significant improvement in COPM and GAS, but no significant difference between groups
Redman et al. ³²	22	12 treatment, 10 control	BTX-A, 10.74; control, 10.55	10:12	No	Baseline and 1, 3, and 6 mo	NM	NM	NM	NM
Rameckers et al. ³³	20	10 treatment, 10 control	9.5	NM	No	Baseline (2 wk before injection), 2 wk, 3 and 6 mo (end of therapy), and 3 mo after end of therapy	Ashworth Scale, AROM, PROM, SRA	Improvement in both groups, but no significant difference between groups	Isometric generated force, force production error, MA	No significant difference between groups, and report of weakness caused by BTX-A (treatment group)
Olesch et al. ³⁴	22	11 treatment, 11 control	3+8	19:3	No	Primary outcomes, 3 mo; secondary outcomes, 3 and 6 mo later	Modified Tardieu Scale	Significant reduction in muscle tone in treatment group	COPM, GAS, QUEST, PDMS-FM	Significant improvement in GAS score in treatment group over control group, but no difference between groups in COPM, QUEST, and PDMS-FM
Rameckers et al. ³⁵	20	10 treatment, 10 control	9.5	NM	No	2 wk and 6 mo (end of therapy) and 3 mo after end of therapy	Ashworth Scale, SRA, AROM, PROM	Improvement in both groups, but no significant difference between groups	Kinematic analysis (speed, accuracy, end point spread, performance)	Slight increase in speed and performance in BTX-A treatment group

continued

TABLE I (continued)

Study	No. of Participants	Randomization	Mean Age (yr or yr+mo)	Sex, M:F	Bilateral CP Included†	Time of Follow-up Assessment	Assessment of Spasticity and Muscle Tone	Result Compared with Controls	Functional Assessment	Result Compared with Controls
Koman et al. ³⁶	73	38 treatment, 35 control	BTX-A, 9; control, 9+11	47:26	Yes (45% of treatment group and 49% of control group)	By OT: screening, baseline, and 4, 8, 14, and 20 wk; by physician: baseline and 7, 20, and 27 wk	UERS for assessment of ROM of upper-limb joints	No significant difference between groups in UERS (shoulder, elbow, forearm, or hand), but greater improvement in mean wrist ROM scores in treatment group	MA, HC, Modified HC	Improvement on MA in treatment group (BTX-A) but not in HC and Modified HC
Ferrari et al. ³⁷	27	11 treatment, 16 control	BTX-A, 7.36; control, 5.51	14:13	No	Baseline and 1, 3, and 6 mo	MAS, physician rating scale	No significant difference between groups	GAS, AHA, grip strength score, PEDI, CA, AK	Improvement on GAS and AHA scales in treatment group, but decrease in grip strength, in treatment group. PEDI, CA, and AK showed positive results but no significant difference between groups
Lidman et al. ³⁸	20	10 treatment, 10 control	3+1	14:6	No	Baseline and 3 mo; rerated at 6 and 9 mo	AROM	Significant improvement in AROM in both groups, but no significant difference between groups	AHA, COPM	Improvement on AHA scale in treatment group, but no difference on the COPM between groups
Speth et al. ³⁹	35	5 treatment group 1, 13 treatment group 2, 11 control group 1, 6 control group 2	7.14	NM	No	Baseline and 6, 12, 18, and 24 wk	NM	NM	COPM, GAS, AHA, OSAS, AK	Increase in amount of use of both hands and OSAS quality scores in the 2 treatment groups. No significant difference between groups regarding AHA. The BITT control group showed significantly better results than the 2 treatment groups on the GAS.

*BTX-A = botulinum toxin A, CP = cerebral palsy, ROM = range of motion, PROM = passive ROM, QUEST = Quality of Upper Extremity Skill Test, PEDI = Pediatric Evaluation of Disability Inventory, AROM = active ROM, MA = Melbourne Assessment, GAS = Goal Attainment Scale, COPM = Canadian Occupational Performance Measure, OT = occupational therapy, MAS = Modified Ashworth Scale, AMPS = Assessment of Motor and Process Skill, PedQL = Pediatric Quality of Life, NM = not mentioned, PT = physical therapy, SRA = stretch resistive angle, PDMS-FM = Peabody Motor Scale-Fine Motor, UERS = Upper Extremity Rating Scale, HC = House Classification, AHA = Assistive Hand Assessment, CA = Caregiver Assistance, AK = ABILHAND-Kids, OSAS = Observational Skill Assessment Scale, and BITT = Bimanual Task-Oriented Therapy. †GMFCS level was reported in only 1 study²⁸.

studies specified Botox as the brand name of BTX-A used for the injections; the remaining 2 studies^{25,39} with 49 patients (10%) used both brand names Botox and Dysport for injection. Only one study³² did not mention the brand name. The doses varied according to the injected muscle size and bulk, body weight, and degree of spasticity. The BTX-A injection was performed during a single session in 12 studies and repeated sessions in 3 studies^{30,34,38} with 85 patients (17%). Thirteen studies restricted the injection of BTX-A to the upper limb and 2 studies^{31,32} with 94 patients (19%) performed additional injections of the lower limb muscles on demand.

Only light general anesthesia was used before injection in 2 studies^{34,37} with 49 patients (10%), only local anesthesia was used in 1 study²⁹ with 39 patients (8%), and a combination of both was used in 4 studies^{25,28,31,38} with 148 patients (30%). Only general anesthesia was used in 3 studies^{27,30,39}. The remaining 5 studies^{26,32,33,35,36} did not report the type of anesthesia used before injection.

Some of the participants in 4 studies^{25,29,31,36} with 198 patients (40%) were diagnosed with bilateral spastic CP. The side to be injected with BTX-A was selected in 3 of these studies^{25,29,36} according to the degree of spasticity and patient needs; in the

remaining study³¹ with 72 patients (14%), BTX-A was injected in the dominant limb. The biceps, wrist flexors, pronator teres, and adductor pollicis were injected in at least 12 of the studies; the remaining 3 studies^{30,32,36} referred to the targeted anatomical regions rather than specifying the injected muscles. The shoulder muscles were injected in 3 studies^{31,36,37} with 172 patients (34%), and the pronator quadratus was injected in 3 studies^{28,31,39} with 149 patients (30%) (Table II).

The participants in the control group received a placebo injection in 2 studies^{25,36} and physical therapy (PT) and splinting with placebo in 1 study³⁷. The controls received occupational

TABLE II Characteristics, Precautions, and Adjunctive Treatment with BTX-A Injection*

Study	Dose and Type	Injection Placement and Technique	Muscles Injected	Adjunctive Treatment with BTX-A Injection
Corry et al. ²⁵	Botox (Allergan, USA) and (Dysport, Ponton, UK). Total amount injected, 250 U Botox at dose of 4-7 U/kg body weight or 160-400 U Dysport at dose of 8-9 U/kg. Max. dose, 0.4 mL volume	Location of injection determined by anatomical landmarks. EMLA local anesthetic cream (lignocaine)-lidocaine was applied before injection. Light general anesthesia used in 1 case	Biceps, brachialis, FCR, FCU, FDS and FDP, flexor pollicis longus, pronator teres	None
Fehlings et al. ²⁶	Botox (Allergan, USA). 2-6 U/kg	Location determined by muscle palpation and anatomical landmarks	Biceps, pronator teres, FCU, adductor pollicis, finger flexors	OT
Speth et al. ²⁷	Botox (Allergan). Max. per site, 50 U. Max. dose, 400 U	Location determined by electrical muscle stimulation. Injection was done under general anesthesia	Biceps, brachioradialis, pronator teres, FCU, FCR, flexor pollicis brevis, adductor pollicis	PT, OT, splinting
Lowe et al. ²⁸	Botox (Allergan). Max. total dose, 8 U/kg, 100 U BTX-A with 5 mL normal saline solution	Location determined by electrical muscle stimulation. A combination of local anesthetic cream with light general anesthesia was used	Elbow flexors, pronator teres, pronator quadratus, wrist flexors, wrist extensors, finger flexors, thumb adductor, thumb opponens, thumb flexors	OT
Kawamura et al. ²⁹	Botox (Allergan). High-dose group: 1.5 U/kg, max. 20 U/kg. Low-dose group, 30% of above dose	Location determined by anatomical landmarks and muscle palpation. Topical anesthetic was applied before injection	Biceps, brachioradialis, wrist/finger flexors, pronator teres, adductor pollicis, opponens pollicis	OT
Russo et al. ³⁰	Botox (Allergan, Australia). Min. dose, 5.0 U/kg. Max. dose, 11.6 U/kg	Location determined by electrical muscle stimulation. Injection was done under general anesthesia	Elbow and wrist muscles, without specifying particular muscle injected	OT
Wallen et al. ³¹	Botox (Allergan, Australia). Dose per muscle, 0.5-2 U/kg. Max. dose, 12 U/kg	Location determined by electrical muscle stimulation. Injection was done under local anesthesia and nitrous oxide inhalation	Shoulder (pectoralis complex, latissimus dorsi, teres major), pronators, elbow flexors, wrist flexors, finger flexors, and thumb flexors, adductor, and opponens	OT in 1 group, none in another group
Redman et al. ³²	BTX-A. Dose per upper limb muscle group, 0.5-2 U/kg. Max. dose, 12 U/kg	Not mentioned	Upper limb muscles, without specifying particular muscles	PT, OT
Rameckers et al. ³³	Botox (Allergan). Max. per injection site, 50 U. Overall max., 400 U	Not mentioned	Adductor pollicis, flexor pollicis brevis, FCU, FCR, pronator teres, brachioradialis, biceps	PT, OT
Olesch et al. ³⁴	Botox (Allergan, Australia). 10 U/0.1 mL. Total dose depended on weight of child	Location determined by electrical muscle stimulation. Injections was done under light general anesthesia (a short general anesthesia using sevoflurane)	Biceps, pronator teres, FCU, FCR, adductor pollicis, flexor pollicis longus, FDS, FDP	OT
Rameckers et al. ³⁵	Botox (Allergan, USA). Max. per injection site, 50 U. Overall max., 400 U	Not mentioned	Adductor pollicis, flexor pollicis brevis, FCU, FCR, pronator teres, brachioradialis, biceps	OT
Koman et al. ³⁶	Botox (Allergan). 1.4-12.5 U/kg	Location determined by anatomical landmarks; ultrasound-guided localization for smaller and deeper muscles	Shoulder, arm, forearm, hand, without specifying particular muscles	None

continued

TABLE II (continued)

Study	Dose and Type	Injection Placement and Technique	Muscles Injected	Adjunctive Treatment with BTX-A Injection
Ferrari et al. ³⁷	Botox (Allergan). Total dose, <300 U	Location determined by ultrasound-guided muscle localization. Injections were done under light general anesthesia	Pronator teres, FCU, FCR, adductor pollicis, opponens pollicis, biceps, pectoralis major, FDS, flexor digitorum brevis, subscapularis	PT, splinting
Lidman et al. ³⁸	Botox (Allergan Norden, Sweden). 3-30 U/mL. Dose was according to size of the muscles, degree of spasticity, and body weight	Injections guided by neuromuscular electrical stimulation using Teflon-coated BTX-A needle. Injections were done under general anesthesia or nitrous oxide sedation after local anesthetic EMLA cream was applied to injection sites	Biceps, brachialis, brachioradialis, pronator teres, pronator quadratus, adductor pollicis, flexor pollicis brevis	OT, splinting
Speth et al. ³⁹	Dysport (Ipsen) or Botox (Allergan). Max. total Dysport dose, 1,000 U per session; max. total Botox dose, 333 U per session	Location determined by electrical stimulation using Teflon-coated needle. Injections were done under general anesthesia	Arm muscles, forearm muscles, intrinsic muscles of the hand. The most frequently injected muscles were the adductor pollicis, FCR, FCU, and pronator teres	Bimanual task-oriented therapy and splinting in 1 group, none in another group

*BTX-A = botulinum toxin A, FCR = flexor carpi radialis, FCU = flexor carpi ulnaris, FDS = flexor digitorum superficialis, FDP = flexor digitorum profundus, OT = occupational therapy, and PT = physical therapy.

therapy (OT) in 7 studies^{26,28-31,34,35}. In 1 study³⁸, the control group received OT with splinting, and in 2 studies^{32,33} the controls received OT and PT. In 1 study³⁹, the controls received bimanual task-oriented therapy and splinting, and in 1 study²⁷ they received PT, OT, and splinting. Notably, 2 of the above studies^{31,39} also had an additional control group that did not receive any treatment or placebo injection.

Participants in the intervention group received BTX-A injection without another treatment regimen in 4 studies^{25,31,36,39} or combined with OT in 7 studies^{26,28-31,34,35}. In 1 study each, the participants received OT combined with splinting³⁸, PT and splinting³⁷, bimanual task-oriented therapy with splinting³⁹, and PT, OT, and splinting²⁷. In 2 studies^{32,33}, they received OT and PT. One of the above studies²⁹ was a dose comparison (high versus low-dose groups).

Outcome Measures

Various scales were used for follow-up of the changes in the degree of spasticity or functional changes in the injected

limb after BTX-A injection. Eight studies^{25-27,29,31,33,35,38} with 235 patients (47%) used range of motion (ROM). Six studies^{25-28,33,35} with 146 patients (29%) used the Ashworth Scale. Three studies^{26,30,37} with 100 patients (20%) used the Modified Ashworth scale (MAS). Two studies^{30,31} with 115 patients (23%) used the Tardieu Scale, and 1 study³⁴ with 22 patients (4%) used the Modified Tardieu Scale. The stretch resistive angle (SRA) was used in 2 studies^{33,35} with 40 patients (8%). A physician rating scale of the upper limb was used for assessment of ROM by 1 study³⁷ with 27 patients (5%). The Upper Extremity Rating Scale was used only in 1 study³⁶ with 73 patients (15%). Various functional assessment scales were used: 7 studies^{28-31,34,37,39} with 280 patients (56%) used the Goal Attainment Scale (GAS), 7 studies^{26-31,37} with 273 patients (55%) used the Pediatric Evaluation of Disability Inventory, 6 studies^{28,29,31,34,38,39} with 230 patients (46%) used the Canadian Occupational Performance Measure, 5 studies^{26,28,29,31,34} with 205 patients (41%) used the Quality

of Upper Extremity Skill Test, 4 studies^{27,31,33,36} with 185 patients (37%) used the Melbourne Assessment, and 3 studies³⁷⁻³⁹ with 82 patients (16%) used the Assistive Hand Assessment. Additionally, 2 studies^{32,36} with 95 patients (19%) used health-related quality of life, the House Classification, and the Modified House Classification. The ABILHAND-Kids (AK) was used in 2 studies^{37,39} with 62 patients (12%). The Assessment of Motor and Process Skills³⁰ (43 patients, 9%), the Fine Motor Scale of the Peabody Motor Scale³⁴ (22 patients, 4%), and Care-giver Assistance³⁷ (27 patients, 5%) were used in 1 study each. The most common scales used for spasticity assessment were ROM and the Ashworth Scale, and the most common scales for functional assessment were the Quality of Upper Extremity Skill Test and the Canadian Occupational Performance Measure (Table I).

Outcomes of BTX-A Injection

Four studies^{25,31,36,39} with 194 patients (39%) used the BTX-A without

additional rehabilitation regimen. They reported that it had a clinically important effect on upper limb function; however, 1 study²⁵ with 14 patients (3%) reported no effect on fine motor activity. Six studies^{26,28,30,31,34,38} with 229 patients reported that the BTX-A injection plus OT generally had a positive effect on upper extremity function. One study³⁷ also found a beneficial effect of BTX-A plus the adjunctive use of an orthosis and PT. Two studies^{28,29} examined the effect of BTX-A dose, and they supported the use of a low dose²⁹ and a low dose at a high concentration²⁸ to improve upper extremity function. Three studies^{30,32,36} with 138 patients (28%) reported no effect of BTX-A injection on health-related quality of life. Three studies^{27,33,35} with 60 patients (12%) reported no evidence of additional benefit of BTX-A in patients receiving OT to improve the function and strength of the upper extremity. One study³⁵ with 20 patients (4%) reported a positive effect of BTX-A injection on the kinematic outcome measures for speed and performance of alternating tasks. One study³⁹ assessed the effect of BTX-A and bimanual task-oriented therapy, and reported that BTX-A injection had no additional effect on the bimanual performance but did have a positive effect on the quality of movement and amount of use of the upper extremity.

The effect of BTX-A injection on cosmetic appearance of the injected upper limb was reported in 2 studies^{25,30} with 57 patients (11%). One of them²⁵ reported that it had a positive effect on cosmesis, and the other reported that this positive effect had disappeared at the time of the final 1-year assessment. Self-perception was mentioned in 1 study³⁰, which reported a positive effect of BTX-A injection on body structures, activity participation, and self-perception.

Complications Following BTX-A Injection

No serious, life-threatening complications were described in the studies included in this systematic review, but

other complications were reported. These complications arose from either anesthesia or BTX-A injection. Complications related to BTX-A injection were reported in 8 studies^{25,26,29-31,34,36,37}. Nausea and vomiting were reported as complications of general anesthesia in 2 studies, occurring in 4 patients (9%)³⁰ and 5 patients (7%)³¹. Excessive and clinically appreciable weakness of the injected muscles was reported in 6 studies, occurring in 2 patients (14%)²⁵, 1 patient (3%)²⁶, 5 patients (13%)²⁹, 5 patients (12%)³⁰, 2 patients (9%)³⁴, and 2 patients (3%)³⁶. Influenza-like symptoms (fever, malaise) were reported in 3 studies, occurring in 1 patient (7%)²⁵, 1 patient (2%)³⁰, and 5 patients (7%)³¹. Upper respiratory tract infection was reported in 1 study, occurring in 4 patients (6%)³¹. A maculopapular rash after injection was reported in 1 study, occurring in 1 patient (5%)³⁴. General fatigue was reported in 2 studies, occurring in 3 patients (8%)²⁹ and 1 patient (1%)³⁶. Seizures in patients with epilepsy, headache, and depression were reported in 1 study, occurring in 3 patients (7%)³⁰. Soreness of the injected muscles was reported in 2 studies, occurring in 4 patients (6%)³¹ and 5 patients (7%)³⁶; soreness in relation to the placebo injection, rather than BTX-A injection, was reported in 1 study, occurring in 1 patient³⁷. Three studies^{27,28,38} reported that there were no complications related to BTX-A injection. Four studies^{32,33,35,39} did not report the complications of injection.

Funding

Allergan donated the BTX-A in 8 studies^{25,26,28,30,31,34,36,37} with 323 patients (65%). Ipsen donated the Dysport in 1 study³⁹ with 35 patients (7%). Funding in 4 studies^{27,29,33,38} was provided by other sources. Funding was not mentioned in 2 studies^{32,35}.

Missing Data

Of the 15 eligible studies, 8 (53%) studies^{26,30,32,33,35,36,38,39} did not report the following: sex distribution in 3 studies^{33,35,39} with 75 patients (15%), complications of BTX-A injection in

4 studies^{32,33,35,39}, the method of muscle localization before injection in 3 studies^{32,33,35} with 62 patients (12%), the anesthesia used before injection in 5 studies^{26,32,33,35,36} with 165 patients (33%), the individual injected muscles in 3 studies^{30,32,36} with 138 patients (28%), and funding in 2 studies^{32,35} with 42 patients (8%). The Gross Motor Function Classification System (GMFCS) level was reported in only 1 study²⁸.

Discussion

Summary of Evidence

BTX-A is widely used to avoid or delay multilevel orthopaedic surgery in children with CP through correction of the dynamic lever arm deformities^{4,8}. The findings of this systematic review cast doubt on the role of BTX-A as an adjunctive treatment to interventions in children with CP, such as OT and orthotic splinting, especially with regard to functional gains. Nevertheless, there is evidence to support the use of BTX-A as an adjunctive treatment to other PT regimens or placebo to reduce spasticity. Generally, the nonsignificant or rather mixed functional results may in part be attributed to the muscle weakness that may be encountered after botulinum toxin injection.

Strengths and Limitations

Our study has limitations, particularly ones inherent to the features of the included studies. Uncertain and redundant indications for the use of BTX-A in children with CP may strain the health resources in developing countries. In general, the outcome measures used by the studies included in our systematic review were diverse, both among studies and within individual studies. For spasticity assessment, the Ashworth Scale^{26,33} and ROM^{29,31} were the most commonly used. The most common scales used for functional outcome measures were the GAS^{28-31,34,37,39}, Pediatric Evaluation of Disability Inventory^{26-31,37}, Quality of Upper Extremity Skill Test^{28,29}, and Canadian Occupational Performance Measure^{34,38}.

Key quality-of-life outcome measures included health-related quality of life^{30,32,36} and Caregiver Assistance³⁷. Additionally, the diversity in the techniques of muscle localization and in the BTX-A dose calculation may have had an impact on the quality of evidence extracted. Multilevel and multidirectional extremity deformities are both essential features of children with CP. This adds to the complexity of patient evaluation and management. It is therefore not surprising that subjective patient-reported outcome instruments such as functional scales and quality-of-life questionnaires are being increasingly recognized as pivotal assessment tools^{32,36,37}. In contrast, the objective physician-reported outcome instruments such as joint ROM are becoming less practical assessment tools, especially from a patient's perspective. The types of outcome instruments used in our systematic review conform to the previous observations.

The degree to which the conclusions of a systematic review are valid and generalizable will be dependent on the level of evidence of its original studies. Randomized controlled trials have the highest levels of evidence⁴⁰. However, case series studies without a control group can yield strong recommendations and generate credible evidence, provided that these studies adopt strict methodological rigor and control sources of bias originating from confounding variables⁴¹. Our systematic review comprised randomized controlled trials, which rank high in the evidence hierarchy. Additionally, the eligible studies of this review demonstrated a recognizable degree of methodological rigor. Nevertheless, we believe that the abovementioned inherent study limitations have a negative impact on our ability to derive strong recommendations from this systematic review of randomized controlled trials.

The studies included in this systematic review used a wide array of outcome instruments. This diversity was demonstrated both across different studies and within individual studies.

Additionally, there were a number of confounding variables that presented a potential source of bias, especially with regard to the diversity of injection techniques, methods of localization, and regimens used for the control group. Furthermore, the overall results were mixed and occasionally conflicting with respect to different outcome measures used within an individual study. We thus presumed that performing a meta-analysis would not overcome the above inherent design deficiencies and biases of the original studies included in this review. The above criticisms have been echoed in a number of other studies, including 2 large systematic reviews on the use of BTX-A as an adjunctive treatment for limb spasticity in general: namely, the inconclusive evidence at least with respect to some clinical settings, the diversity of confounding variables, and the need for further research to elucidate the lingering research questions^{10,16,42}.

Conclusions

There is evidence to support the use of BTX-A as an adjunctive treatment to other modalities such as regular PT and OT with regard to reduction of spasticity. With respect to the functional gains, it is extremely difficult to provide clear-cut recommendations on the efficacy of using BTX-A as an adjunctive treatment. The complications were acceptable and did not outweigh the clinical gains incurred.

Recommendations

The continued use of BTX-A as an adjunctive treatment for the upper limbs of children with spastic CP is encouraged at least with regard to improvement of spasticity and joint mobility. Such improvement would provide a potential advantage for children with CP, especially with regard to delay of the occurrence of fixed contractures.

We encourage the use of validated quality-of-life questionnaires, especially given that they have been less commonly used as subjective assessment tools throughout the studies in this review.

Treatment decisions may need to be individualized on a case-by-case basis, particularly when functional improvement is used as an outcome measure.

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References

1. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2013 Jun;55(6):509-19. Epub 2013 Jan 24.
2. Pavone V, Testa G, Restivo DA, Cannavò L, Condorelli G, Portinaro NM, Sessa G. Botulinum toxin treatment for limb spasticity in childhood cerebral palsy. *Front Pharmacol*. 2016 Feb 19;7(7):29.
3. Rose J, Cahill-Rowley K, Butler EE. Artificial walking technologies to improve gait in cerebral palsy: multichannel neuromuscular stimulation. *Artif Organs*. 2017 Nov;41(11):E233-9.
4. Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, Placzek R. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. *Toxins (Basel)*. 2015 May 11;7(5):1629-48.
5. Hefter H, Rosenthal D. Improvement of upper trunk posture during walking in hemiplegic patients after injections of botulinum toxin into the arm. *Clin Biomech (Bristol, Avon)*. 2017 Mar; 43:15-22. Epub 2017 Jan 26.
6. Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral

- palsy: a meta-analysis. *Pediatrics*. 2014 Jan; 133(1):e175-204. Epub 2013 Dec 23.
7. Thorley M, Donaghey S, Edwards P, Copeland L, Kentish M, McLennan K, Lindsley J, Gascoigne-Pees L, Sakzewski L, Boyd RN. Evaluation of the effects of botulinum toxin A injections when used to improve ease of care and comfort in children with cerebral palsy whom are non-ambulant: a double blind randomized controlled trial. *BMC Pediatr*. 2012 Aug 9;12:120.
8. Juneja M, Jain R, Gautam A, Khanna R, Narang K. Effect of multilevel lower-limb botulinum injections & intensive physical therapy on children with cerebral palsy. *Indian J Med Res*. 2017 Nov;146(Supplement):S8-14.
9. Sandahl Michelsen J, Normann G, Wong C. Analgesic effects of botulinum toxin in children with CP. *Toxins (Basel)*. 2018 Apr 19;10(4):E162.
10. Mathevon L, Bonan I, Barnais JL, Boyer F, Dinomais M. Adjunct therapies to improve outcomes after botulinum toxin injection in children: a systematic review. *Ann Phys Rehabil Med*. 2019 Jul;62(4):283-90. Epub 2018 Jul 29.
11. Flemban A, Elsayed W. Effect of combined rehabilitation program with botulinum toxin type A injections on gross motor function scores in children with spastic cerebral palsy. *J Phys Ther Sci*. 2018 Jul;30(7):902-5. Epub 2018 Jul 3.
12. Hoare B, Imms C, Villanueva E, Rawicki HB, Matyas T, Carey L. Intensive therapy following upper limb botulinum toxin A injection in young children with unilateral cerebral palsy: a randomized trial. *Dev Med Child Neurol*. 2013 Mar;55(3):238-47. Epub 2012 Dec 12.
13. Elvrum AK, Brændvik SM, Sæther R, Lamvik T, Vereijken B, Roelvelde K. Effectiveness of resistance training in combination with botulinum toxin-A on hand and arm use in children with cerebral palsy: a pre-post intervention study. *BMC Pediatr*. 2012 Jul 2;12:91.
14. Smitherman JA, Davids JR, Tanner S, Hardin JW, Wagner LV, Peace LC, Gidewall MA. Functional outcomes following single-event multilevel surgery of the upper extremity for children with hemiplegic cerebral palsy. *J Bone Joint Surg Am*. 2011 Apr 6;93(7):655-61.
15. Amen J, ElGebeily M, El-Mikkawy DM, Yousry AH, El-Sobky TA. Single-event multilevel surgery for crouching cerebral palsy children: correlations with quality of life and functional mobility. *J Musculoskelet Surg Res*. 2018;2(4): 148-55.
16. Schasfoort F, Pangalila R, Sneekes EM, Catsman C, Becher J, Horemans H, Stam HJ, Dallmeijer AJ, Bussmann JBJ. Intramuscular botulinum toxin prior to comprehensive rehabilitation has no added value for improving motor impairments, gait kinematics and goal attainment in walking children with spastic cerebral palsy. *J Rehabil Med*. 2018 Aug 22; 50(8):732-42.
17. Çağlar Okur S, Uğur M, Şenel K. Effects of botulinum toxin A injection on ambulation capacity in patients with cerebral palsy. *Dev Neurorehabil*. 2019 May;22(4):288-91. Epub 2018 Aug 10.
18. Hastings-Ison T, Sangeux M, Thomason P, Rawicki B, Fahey M, Graham HK. Onabotulinum toxin-A (Botox) for spastic equinus in cerebral palsy: a prospective kinematic study. *J Child Orthop*. 2018 Aug 1;12(4):390-7.
19. Bramer WM, Giustini D, Kramer BM. Comparing the coverage, recall, and precision of searches for 120 systematic reviews in Embase, MEDLINE, and Google Scholar: a prospective study. *Syst Rev*. 2016 Mar 1;5:39.
20. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015 Jan 2;350:g7647.
21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996 Feb;17(1):1-12.
22. Abduljabbar T, Vohra F, Javed F, Akram Z. Antimicrobial photodynamic therapy adjuvant to non-surgical periodontal therapy in patients with diabetes mellitus: a meta-analysis. *Photodiagnosis Photodyn Ther*. 2017 Mar;17:138-46. Epub 2016 Nov 22.
23. Sackett DL, Straus SE. Finding and applying evidence during clinical rounds: the "evidence cart". *JAMA*. 1998 Oct 21;280(15):1336-8.
24. Kahraman A, Seyhan K, Değer Ü, Kutlutürk S, Mutlu A. Should botulinum toxin A injections be repeated in children with cerebral palsy? A systematic review. *Dev Med Child Neurol*. 2016 Sep;58(9):910-7. Epub 2016 Apr 22.
25. Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. *Dev Med Child Neurol*. 1997 Mar;39(3):185-93.
26. Fehlings D, Rang M, Glazier J, Steele C. An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr*. 2000 Sep;137(3):331-7.
27. Speth LA, Leffers P, Janssen-Potten YJ, Vles JS. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy. *Dev Med Child Neurol*. 2005 Jul;47(7):468-73.
28. Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy. *Dev Med Child Neurol*. 2006 Mar;48(3):170-5.
29. Kawamura A, Campbell K, Lam-Damji S, Fehlings D. A randomized controlled trial comparing botulinum toxin A dosage in the upper extremity of children with spasticity. *Dev Med Child Neurol*. 2007 May;49(5):331-7.
30. Russo RN, Crotty M, Miller MD, Murchland S, Flett P, Haan E. Upper-limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial. *Pediatrics*. 2007 May;119(5): e1149-58. Epub 2007 Apr 23.
31. Wallen M, O'Flaherty SJ, Waugh MC. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial. *Arch Phys Med Rehabil*. 2007 Jan;88(1):1-10.
32. Redman TA, Finn JC, Bremner AP, Valentine J. Effect of upper limb botulinum toxin-A therapy on health-related quality of life in children with hemiplegic cerebral palsy. *J Paediatr Child Health*. 2008 Jul-Aug;44(7-8):409-14.
33. Rameckers EA, Speth LA, Duysens J, Vles JS, Smits-Engelsman BC. Botulinum toxin-A in children with congenital spastic hemiplegia does not improve upper extremity motor-related function over rehabilitation alone: a randomized controlled trial. *Neurorehabil Neural Repair*. 2009 Mar-Apr;23(3):218-25. Epub 2008 Dec 23.
34. Olesch CA, Greaves S, Imms C, Reid SM, Graham HK. Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial. *Dev Med Child Neurol*. 2010 Jan;52(1):79-86. Epub 2009 Jul 3.
35. Rameckers EA, Duysens J, Speth LA, Vles HJ, Smits-Engelsman BC. Effect of addition of botulinum toxin-A to standardized therapy for dynamic manual skills measured with kinematic aiming tasks in children with spastic hemiplegia. *J Rehabil Med*. 2010 Apr;42(4):332-8.
36. Koman LA, Smith BP, Williams R, Richardson R, Naughton M, Griffin L, Evans P. Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum A toxin. *J Hand Surg Am*. 2013 Mar;38(3):435-46.e1.
37. Ferrari A, Maoret AR, Muzzini S, Alboresi S, Lombardi F, Sgandurra G, Paolicelli PB, Sicola E, Cioni G. A randomized trial of upper limb botulinum toxin versus placebo injection, combined with physiotherapy, in children with hemiplegia. *Res Dev Disabil*. 2014 Oct;35(10): 2505-13. Epub 2014 Jul 2.
38. Lidman G, Nachemson A, Peny-Dahlstrand M, Himmelmann K. Botulinum toxin A injections and occupational therapy in children with unilateral spastic cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol*. 2015 Aug;57(8):754-61. Epub 2015 Mar 22.
39. Speth L, Janssen-Potten Y, Rameckers E, Defesche A, Winkens B, Becher J, Smeets R, Vles H. Effects of botulinum toxin A and/or bimanual task-oriented therapy on upper extremity activities in unilateral cerebral palsy: a clinical trial. *BMC Neurol*. 2015 Aug 19;15: 143.
40. Atkins D, Briss PA, Eccles M, Flottorp S, Guyatt GH, Harbour RT, Hill S, Jaeschke R, Liberati A, Magrini N, Mason J, O'Connell D, Oxman AD, Phillips B, Schünemann H, Edejer TT, Vist GE, Williams JW Jr; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system. *BMC Health Serv Res*. 2005 Mar 23;5(1):25.
41. El-Sobky TA, El-Sayed M. Situational ethics of study designs for orthopedic surgery interventions in children with cerebral palsy. *Curr Orthop Pract*. 2019;30(2):178-80.
42. Mills PB, Finlayson H, Sudol M, O'Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. *Clin Rehabil*. 2016 Jun;30(6):537-48. Epub 2015 Jul 21.