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Review

Adjunct therapies to improve outcomes after botulinum toxin injection in children: A systematic review

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ABSTRACT

Background: Botulinum toxin (BTX) injection alone is not sufficient to treat spasticity in children, notably those with cerebral palsy; thus, there is an emerging trend for adjunct therapies to offer greater outcomes than BTX alone.
Objective: The aim of this systematic review was to evaluate the general effectiveness of adjunct therapies regardless of their nature in children with spasticity.
Methods: Medline, Cochrane and Embase databases were searched from January 1980 to March 15, 2018 for reports of parallel-group trials (randomized controlled trials [RCTs] and non-RCTs) assessing adjunct therapies after BTX injection for treating spasticity in children. Two independent reviewers extracted data and assessed the risk of bias by using the PEDro scale for RCTs and Downs and Black scale (D&B) for non-RCTs.
Results: Overall, 20 articles involving 662 participants met the inclusion criteria. The average quality was good for the 16 RCTs (mean PEDro score 7.4 [SD 1.6]) and poor to moderate for the 4 non-RCTs (D&B score 9 to 17). Adjunct therapies consisted of casting/posture, electrical stimulation, resistance training and rehabilitation programmes. Casting associated with BTX injection improved the range of passive and active motion and reduced spasticity better than did BTX alone (9 studies), with a follow-up of 1 year. Resistance training enhanced the quality and performance of muscles without increasing spasticity. Only 3 rehabilitation programmes were studied, with encouraging results for activities.
Conclusion: Lower-limb posture with casting in children has a high level of evidence, but the long-term efficacy of short-leg casting needs to be evaluated. A comparison between the different modalities of casting is missing, and studies specifically devoted to testing the different kinds of casting are needed. Moreover, the delay to casting after BTX injection is not clear. Data on electrical stimulation are not conclusive. Despite the small number of studies, resistance training could be an interesting adjunct therapy notably to avoid loss of strength after BTX injection. Rehabilitation programmes after BTX injection still need to be evaluated.

1. Introduction

As for adults, for children, spasticity is a common consequence of upper motor-neuron disorders due to spinal cord injury, traumatic brain injury, stroke, brain tumour and cerebral palsy (CP). CP, defined as a permanent motor disorder due to non-progressive damage to the developing brain, is a major cause of motor disability in children and accounts for most of the spasticity cases seen in children, in contrast to adults, in whom CP is not the major cause of spasticity. Among these CP children, approximately 80% to 90% have spastic forms (unilateral or bilateral) that result in abnormal motor function. In addition to a motor deficit cause, spasticity contributes to reduced motor ability [1–4] and is a cause of musculoskeletal deformities in children and *a fortiori* in children with CP [5,6].

Despite no cure for CP, motor impairment can be minimized with neuro-rehabilitation. An increasing number of studies in the

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last decade have highlighted multiple interventions in children with CP. A recent systematic review revealed what does and does not work, to help clinicians keep up to date and thus provide children and their families with effective, evidence-based interventions in motor rehabilitation [7,8].

Current rehabilitation interventions to treat motor impairments in CP are mainly based on techniques aimed at repeatedly stimulating the paretic limb and hence reducing spasticity [9,10]. Protection of the musculoskeletal system also remains a major issue because it is required to preserve motor functions at the end of the growth period and prevent early ageing [6] of the joints.

Botulinum toxin type A (BTX-A) is one of the most effective and safest treatments for focal spasticity in children with CP [8] and more generally children with spasticity due to other causes. BTX reduces spasticity [8,9] and maintains a favourable range of motion so as to prevent vicious joint patterns [11,12].

However, the level of evidence for the improvement of motor function with BTX is weak [10,13]. One explanation is that BTX injection must be associated with a specific, personalised rehabilitation programme (adjunct therapies). A large heterogeneity of practices concern adjunct therapies after BTX injections to optimise the results. Although BTX treatment is highly recommended to treat focal spasticity (grade A level of evidence [8]) in children with CP (and by extrapolation to treat focal spasticity in children), no clear data are available to provide recommendations for the optimal adjunct therapies after such treatment.

The aim of this study was to evaluate, via a systematic literature review, the general effectiveness of all types of adjunct therapies used after BTX injection on outcomes related to impaired body function and structure limited to the activity and participation of children with spasticity.

2. Methods

2.1. Study eligibility criteria

Three authors (LM, JLB and MD) performed a systematic review of the literature in accordance with PRISMA guidelines (http://www.prisma-statement.org). We included any English reports of adjunct therapies after BTX injection to treat spasticity in children. Only parallel clinical studies (i.e., comparing least 2 groups [adjunct vs no adjunct therapies]) were included. Articles concerning adjunct therapies after phenolisation were excluded because since 2009, phenolisation is no longer recommended for treating spasticity in children [14]. Literature reviews were not analysed.

Medline, Cochrane, PEDro and Reedoc databases were searched from 1980 to March 15, 2018 with the keywords: "botulinum toxin" and "children" (or "child"; "kids"; "childhood"; "infant"; "adolescent") and "spasticity". We deliberately chose not to use the term "cerebral palsy" because spasticity is also present in children after stroke; traumatic brain injury etc. (see Introduction). Related articles and links were also searched. Additional articles were identified by a manual search of references in key articles retrieved.

2.2. Quality analysis

The quality of RCTs was analysed by the specific PEDro scale [15]. The score ranged from 0 to 11. A score of 0 to 4 was considered poor quality, 5 or 6 moderate, 7 or 8 good, and ≥ 9 excellent. The quality of non-RCTs was analysed by the specific Downs and Black scale (D&B) [16], with scores ranging from 0 to 27 (high quality). The following cut-points have been suggested to classify studies by quality: excellent (26–27), good (20–25), fair (15–19) and poor (0–18) [17]. Quality was analysed independently by both LM and JLB, with any disagreements resolved after discussion with a third evaluator (MD). To provide the reader with a clear overview of our findings, we assigned each adjunct therapy to 1 of 3 categories: "do it"; "probably do it", or "don't do it", inspired by Novak et al. [8].

3. Results

Among 519 articles published from January 1980 to March 15, 2018 from the 4 data sources (Fig. 1), after reading the titles and abstracts, 39 articles were initially selected (Table 1). After reading the full text, 19 articles were excluded; 20 articles were finally deemed relevant. At the time of this work, no previous systematic review had focused on adjunct therapies after BTX injection in children. All 20 articles had been published between 2001 and March 2018, 9 after 2010; 16 were RCTs and 4 prospective interventional studies.

3.1. Quality of articles

The quality analysis is presented in Table 1. The mean PEDro quality score for the 16 RCTs was 7.4 (SD 1.6; range 4–9), for good quality. The D&B quality score for the 4 non-RCTs ranged from 9 to 17, for poor to moderate quality. The total number of participants included was 662, with a large sample size (> 50) in 3 studies [18–20]. The number of subjects needed for statistical power was not calculated in the articles retained, apart from 2 studies with 50% and 60% of the calculated sample size recruited [21,22].

CP was exclusively investigated in all studies; we found no studies related to other aetiologies of spasticity in children. The motor deficit was mainly mixed unilateral and bilateral in 9 studies, exclusively unilateral in 6 studies, and exclusively bilateral in 1 study. The functional level of participants was good. Upper-limb function was investigated in 5 studies, with a Manual Ability Classification System level reported as 1 to 3 in 2 studies [22,23]. The other studies investigated lower-limb function, with a Gross Motor Function Classification System (GMFCS) level of at least 3 and at least 2 in 7 studies.

Every study fully described the experimental protocol. Most studies compared adjunct therapy associated with BTX injection versus BTX alone. In 2 studies [21,24], adjunct therapy was investigated alone in comparison with BTX $\pm$ adjunct therapy. In terms of the components of the World Health Organization's International Classification of Functioning, Disability and Health (ICF, WHO 2001), all studies focused on outcomes related to body structure and function, such as range of motion, spasticity, and muscle strength. For activity, the Gross Motor Function Measure (GMFM) was used in 7/15 studies that investigated lower-limb function. Upper-limb function was investigated with many scales with good metrological properties (Table 1). Only one RCT focused on quality of life with the Child Health Questionnaire (CHQ) [25].

Meta-analysis is generally considered a more powerful estimate of the true effect size than a single study. However, meta-analysis was precluded in our study because of the heterogeneity of study designs regarding the different kinds of adjunct therapies (posture, serial casting, casting or splints etc.), diversity of participants (different ages, different inclusion criteria, localisation of spasticity etc.) and number and variability of outcomes studied (impairment [range of motion, spasticity etc.] and activities [Assisting Hand Assessment, GMFM etc.]).

3.2. Synthesis of the literature

The different adjunct therapy protocols proposed in the available literature were classified as relating to posture ($n = 10$ articles), electrical stimulation ($n = 4$) and rehabilitation procedures ($n = 6$).

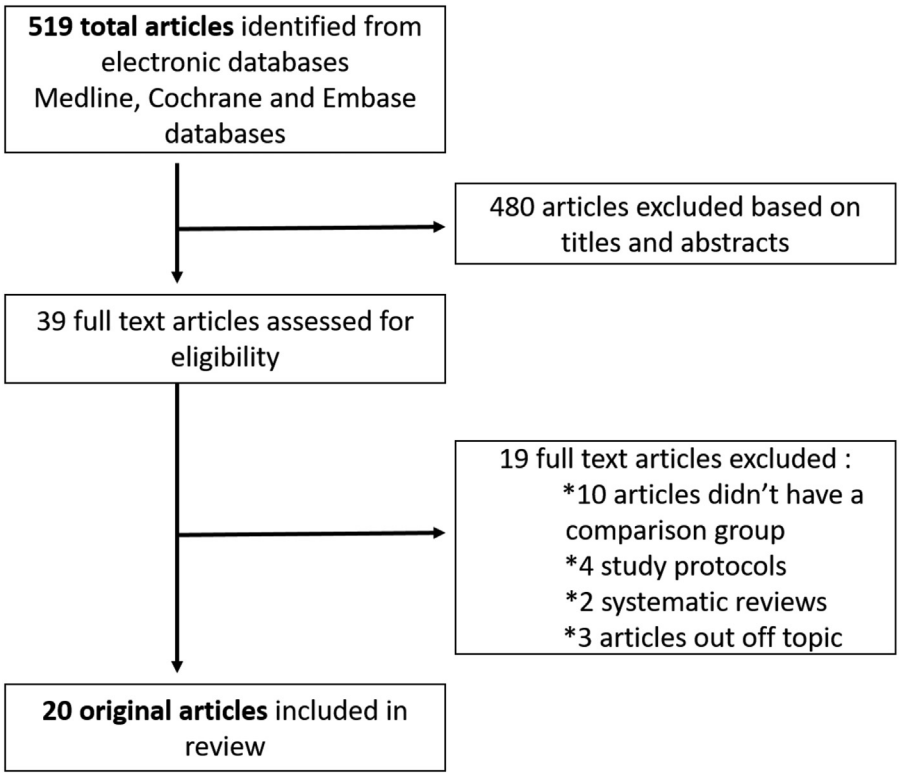

Fig. 1. Flow of studies in the review.

3.2.1. Joint posture procedure

Different joint posture procedures were reported. Six articles adopted serial casting protocols and 3 evaluated the effects of fixed casting. Potential confounding factors such as day or night posture and duration of casting were not systematically mentioned and therefore could not be taken into account. Also, because length of follow-up never exceeded 12 months, long-term effects could not be evaluated.

3.3. *Serial casting* (n = 6)

This consisted of applying 3 progressive casts: 5 studies used a short-leg cast [18,20,24,26,27] and the other a long-leg cast [25]. The timing of serial cast application ranged from immediate [26] to 4 weeks [27], 1 week [18] or 3 weeks [20,25] or 1 to 3 weeks [24] after BTX injection in the triceps surae [18,20,24,26,27]. Casts were applied continuously except in one study [18] in which casts were applied for 72 hr/week. Only 1 study [24] compared BTX injection with casting versus casting alone. The quality of the studies was good for the 4 RCTs, with an average PEDro score of 8.3 [18,24,25,27] and moderate for the 2 non-RCTs [20,26], with an average D&B score of 16.5 [20,26]. The total number of participants was 280. All 6 studies evaluated body structure and function outcomes. Only one RCT focused on quality of life with the CHQ.

Whatever the protocol of serial casting, the improved passive range of motion and the reduced spasticity (Modified Ashworth Scale [MAS] and Tardieu Scale [TS]) were better when associating casting with BTX than BTX alone, even when the casts were applied sequentially [18]. Kay et al. [24] showed that the reduced spasticity (MAS) was maintained longer (up to 1 year) with casting without than with BTX injection (3 months). In this study, serial casting was applied until $\geq 5^{\circ}$ of dorsiflexion was reached with the knee extended, then fixed casting was applied during follow-up. This protocol could be considered a prolonged mixed casting regimen, so one cannot discriminate specific serial casting effects from those of other interventions (prolonged fixed casting or BTX alone). No conclusions could be drawn from this result.

Concerning activity measurements related to gross motor function and/or functional mobility, very few improvements were reported. In the short-leg cast protocol, GMFM scores were initially unchanged [24,26] but started to increase after the first 3 months of treatment, with no significant difference between the 2 groups in 1 study [24]. In the long-leg cast protocol, GMFM and CHQ scores were markedly elevated in both groups after 6 weeks [25].

Some adverse effects from serial casting were noted: pain and atrophy (measured from calf and thigh perimeters) were higher versus BTX injection alone [25,27]. The casts also seemed more difficult to bear immediately after BTX injection than 4 weeks later, with no difference when evaluating body structure and function outcomes [27].

3.4. *Casting* (n = 4)

Continuous fixed casting consisted of applying one short-leg cast immediately after BTX injection in the triceps surae for 2 weeks [28] or 3 weeks [21,29] and for single [29] or multiple sessions of treatment [21,28] with a long follow-up (at least 8 months). All treatment groups had physiotherapy several times a week after BTX injection. The quality of the studies was good for 2 studies (PEDro scores 9 and 7) [22,28] and poor (PEDro score 5) for the third RCT [29], for a total of 69 patients.

Concerning outcomes representing the ICF component of body functions and structures, casting associated with BTX injection and even casting alone improved passive range of motion and ankle motor selectivity, reduced spasticity (MAS, TS) [21,28] and improved gait parameters as measured by the GMFM [28] or Observational Gait Scale [28] and even improved the spatiotemporal parameters and ankle kinematics on quantified gait analysis [21]. These results were maintained in the relative long term with 2 or 3 sessions of treatment (between 8 months and 1 year). Of

Table 1
Synthesis of the 20 selected studies: type of study, population, methods and results. Results are presented as mean ± SD or (min–max) Group 1 vs Group 2 (± Group 3) for pre- and post-treatment values at the end of follow-up.

Authors	Design	Adjunct therapy	Therapy protocol	Population	Assessment of deficiencies	Quality of life	Follow-up	Results	PEDro	D&B
Dai et al. [28] 2017	RCT	Serial casting	3 progressive long leg castings Lower extremities placed in abduction First one 3 weeks after BTX-A injection Each for 1 week Group 1: BTX + casting group Group 2: BTX alone	70 children Cerebral Palsy Bilateral Scissoring of the lower extremities Mean age: 3.3 years	Spasticity: MAS	GMFM-66	3 months	Pretreatment: MAS: 3.7 ± 5.2 vs 3.8 ± 3.4; GMFM–66: 41.2 ± 7.6 vs 42.3 ± 2.5; CHQ: 42.7 ± 2.9 vs 44.3 ± 5.4 Posttreatment: MAS: 1.9 ± 1.6 vs 2.8±6.3; GMFM–66: 77.4 ± 6.8 vs 64.6 ± 3.5**; CHQ: 76 ± 6.7 vs 64.6 ± 3.5** Mean Change group 1 vs group 2: MAS: 1.8 vs 1.0; GMFM–66: 36.2 vs 22.3; CHQ: 33.3 vs 20.3		
Dursun et al. [18] 2017	RCT	Serial casting (intermittent)	3 progressive short leg castings First one 1 week after BTX-A injection Each for 72 hours Group 1: BTX-A + casting group Group 2: BTX alone	51 children Cerebral Palsy Unilateral/Bilateral GMFCS 1,2,3 Mean Age: 7.2 years	Spasticity: MAS, TS PROM	Gait: OGS Physician Global Assessment (PGA)	3 months	Pretreatment: MAS: 4 ± 0 vs 44 ± 0; PROM: 79.84 ± 9.2 vs 79.4 ± 9.0; OGS: 7.54 ± 2.9 vs 8.54 ± 2.7; PGA: N/A Posttreatment: MAS: 2.44 ± 0.8 vs 3.14 ± 0.9*; ROM: 934 ± 11.5 vs 83.5±12.7*; GS: 10.54 ± 3.1 vs 9.54 ± 3.0; GA: 2.34 ± 0.9 vs 1.34 ± 0.7** Mean change group 1 vs group 2	8	
Lee et al. [20] 2011	Prospective, Non RCT	Serial Casting	3 progressive consecutive short leg castings First one 3 weeks after BTX-A injection Each for 1 week Group 1: BTX-A + casting group Group 2: BTX alone	86 children Cerebral Palsy Unilateral/Bilateral GMFCS 1,2 Mean age: 5 years	Spasticity: MAS, TS PROM	Gait: Physician Rating Scale (PRS)	3 months	Pretreatment: MAS: 1.7 ± 0.3 vs 1.5 ± 0.4; PROM: – 0.5 ± 4.6 vs 0.7 ± 5.2; PRS: 7.9 ± 3.5 vs 8.2 ± 3.4 Posttreatment: MAS: 1.2 ± 0.3* vs 1.1 ± 0.2; PROM: 9.0 ± 3.4** vs 5.8 ± 3.7*; PRS: 11.3 ± 2.4** vs 10.3 ± 3.5* Mean change group 1 vs group 2: MAS: 0.5 vs 0.4; PROM: 9.5 vs 5.1; PRS: 3.4 vs 2.1	17	
Park et al. [29] 2010	Prospective, Non RCT	Serial Casting	3 progressive consecutive short leg castings First one immediately after BTX-A injection Each for 1 week Group 1: BTX + casting group Group 2: BTX alone	38 children Cerebral palsy Unilateral/Bilateral GMFCS 1,2,3 Mean age: 4.7 years	Spasticity: MAS, TS PROM	GMFM-66 (Dimension D and E)	1 month	Pretreatment: MAS:2.9 ± 0.8 vs 3.2 ± 0.7; PROM: – 1.2 ± 11.5 vs 2.2 ± 4.6; GMFM (D): 75.3 ± 29.6 vs 72.4 ± 23.9 Posttreatment: AS: 2.0 ± 0.3* vs 2.3 ± 0.7*; PROM: 9.8 ± 9.5* vs 7.20 ± 6.30*; MFM (D): 79.5 ± 26.60* vs 73.5 ± 19.3 Mean change group 1 vs group 2: MAS: – 1.0 ± 0.9 vs -1.0 ± 0.7; PROM: 11.0 ± 9.8 vs 5.0 ± 6.1***; GMFM (D): 4.2 ± 5.7 vs 1.1 ± 9.1	16	
Newman et al. [30] 2007	RCT	Serial casting immediately or delayed	3 progressive consecutive short leg castings First one: 6 children immediately after BTX-A injection and 6 children 4 weeks later Each for 1 week Group 1: BTX + immediate serial casting Group 2: BTX + delayed serial casting	12 children Cerebral Palsy Unilateral/bilateral GMFCS 1,2 Mean age: 5.3 years	Spasticity: TS	Gait: Observational Gait Scale (OGS)	6 months	Pretreatment: R1: –24.3 ± 12.0 vs –25.7 ± 5.3; ROM: -6.0 ± 7.7 vs –3.9 ± 4.0; OGS: 9.4 ± 2.1 vs 11.2 ± 2.7 Posttreatment: 1: –21.1 ± 11.2 vs –7.1 ± 7.6**; PROM: 0.0 ± 4.8 vs 2.6 ± 7.1*; OGS: 10.3 ± 5.3 vs 13.4 ± 3.3* Mean change group 1 vs group 2: R1: 3.1 ± 11.0 vs 18.6 ± 10.4 *; PROM: 6.0 ± 9.2 vs 6.4 ± 6.0; OGS: 0.9 ± 5.3 vs 2.2 ± 2.8	8	
Kay et al. [27] 2004	RCT	Serial Casting	Progressive consecutive short leg casting changed every two weeks until ≥ 5? of dorsiflexion was reached with knee extended Group 1: Casting + BTX Group 2: Casting only	23 children Cerebral Palsy Unilateral/Bilateral GMFCS 1,2,3 Mean age: 7.1 years	Spasticity: MAS PROM Computarized gait analysis: peak dorsiflexion (PD) swing	GMFM (C,D,E)	1 year	Pretreatment: MAS: 2.6 ± 1.2 vs 2.6±1.1; PROM: −6.4 ± 8.3 vs −3.7 ± 8.7; PD swing: −12.3 ± 11.1 vs −16.9 ± 15.1; GMFM: 75.8 ± 20.1 vs 66.4 ± 23.1 Mean change group 1 vs group 2: MAS: −0.9 ± 1.0* vs −1.1 ± 1.2*; PROM: 18.4 ± 11.7* vs 13.9 ± 11.8**; PD swing: 12.5 ± 9.3* vs 15.1 ± 11.8**; GMFM: 2.5 ± 7.5 vs −1.3 ± 5.1	9	
Hayek et al. [31] 2010	RCT	Casting	Casts were applied on the day of the first injection and retained for 2 weeks	20 children Cerebral Palsy Unilateral/Bilateral GMFCS: 1,2,3 Mean age: 13.5 years	Spasticity: TS PROM Selective motor control of the ankle	Gait analysis: Spatio-temporal parameters OGS GMFM-66	8 months	Pretreatment: 1: –20.0 ± 13.9 vs –21 ± 12.6; ROM: 3.5 ± 12.5 vs 8.7 ± 7.5; GS: N/A; Gait Speed: 0.6 ± 0.1 vs 0.6 ± 0.1; GMFM: 54.0 ± 15.4 vs 52.2 ± 15.6 Mean change group 1 vs group 2: R1: −12.3 ± 3.4** vs −13.3 ± 3.8**; PROM: 9.8 ± 9** vs 11.9 ± 7.5*** OGS: 12.6 ± 1.4** vs 10.5±1.5** *** Speed: 0.9 ± 0.3** vs 0.9 ± 0.3**; GMFM: 64.3 ± 3.7** vs 55.6 ± 4.8**	7	
Ackman et al. [26] 2005	Multicentre, RCT	Casting	Casts were applied on the day of the first injection and retained for 3 weeks 3 cycles of treatment Group 1: BTX alone Group 2: Placebo injection + casting Group 3: BTX + casting	39 children Cerebral Palsy Unilateral/bilateral GMFCS 1,2 Mean age: 6 years	Spasticity: MAS, TS PROM, AROM Ankle dorsiflexion and plantar flexion strength Ankle power generation Ankle kinematics	Gait analysis: Spatio-temporal parameters	1 year	N/A (results presented in diagrams) Groupe 1: no significant change Group 2 and group 3: significant improvements in spasticity, PROM and dorsiflexion strenght and ankle kinematics	9	
Bottos et al. [32] 2003	RCT	Casting	Casts applied on the day of the first injection and retained for 3 weeks Group 1: BTX + casting group Group 2: BTX alone	10 children Cerebral Palsy Bilateral GMFCS 1,2,3 Mean age: 6.4 years	Spasticity: MAS	GMFM Computarized gait analysis	1 year	Mean change group 1 vs group 2 at 4 months: MAS: N/A (diagrams) GMFM: N/A (diagrams) Both improved significatively in group 1 Stride lenght: 10.5 (N/A) vs 5.5 (N/A)*** Speed walking: (cm.s^{-1}) 5.3(N/A) vs 0.6***	5	

Table 1 (*Continued*)

Authors	Design	Adjunct therapy	Therapy protocol	Population	Assessment of deficiencies	Quality of life	Follow-up	Results	PEDro	D&B
Kanellopoulos et al. [24] 2009	RCT	Night splint	Thermoplastic night splint applied 6 months after 2 BTX injections in the upper limb Group 1: BTX + night splint Group 2: BTX alone	20 children Cerebral Palsy Unilateral MACS? Mean age: 7 years		Quality of Upper Extremity Skills Test (QUEST)	6 months	Mean change group 1 vs group 2 (%): QUEST: 15.9 vs 4.2***	4	
Pieber et al. [33] 2011	RCT	Functional electrical stimulation (FES)	Stimulation of wrist and hand extensor muscles started 5 to 7 days after the injection Twice a day, 15 min for 3 months Biphasic rectangular current with a frequency of 30 Hz, 0.2 ms pulse width, 2–5 s on time Group 1: BTX + FES Group 2: BTX alone	6 girls Cerebral Palsy Unilateral MACS? Mean age: 11.7 years	Spasticity: MAS, TS PROM AROM BMRC scale	Movement ABC checklist	6 months	Mean change Group 1 vs Group 2: N/A: Descriptive data for each participant In both groups: AROM, PROM, MAS, BMRC improved ABC checklist improved only in Group 1	5	
Seifart et al. [34] 2010	Randomised single subject trial	Functional electrical stimulation (FES)	Stimulation of gastrocnemius and tibialis anterior beginning at 5 different times post injection into TS for 4 weeks home programme: at 1, 7, 14, 32, 35 days No control group	5 children Cerebral Palsy Unilateral GMFCS 1 Mean age: 4.5 years	Isometric muscle strength of the ankle plantar flexors and dorsiflexors (Hand-held dynamometer)	Self-selected walking speed (10 m Walking test)	2 months	Mean change Group 1 vs Group 2: N/A: Descriptive data for each participant Some increase in isometric plantar flexor strength No change in walking		
Rha et al. [31] 2008	RCT	Electrical stimulation (ES)	Stimulation of gastrocnemius 7 consecutive days after injection and a sham stimulation on the other side 30 min a day 2 groups: HFES (25Hz) and LFES (4Hz) Biphasic rectangular current, 0.25 ms pulse	23 children Cerebral Palsy Bilateral GMFCS 1,2,3 Mean age: 46 months	Compound Motor Action Potentials for gastrocnemius Spasticity (MAS, TS)		1 month	Mean change Group 1 vs Group 2: N/A: no control group Earlier denervating action of BTX-A Not correlated to clinical reduction of spasticity	8	
Detrembleur et al.[32] 2001	RCT	Electrical stimulation (ES)	Stimulation in injected muscles beginning on the day of BTX 30 minutes, 6 times a day for 3 days Continuous trains of current pulses (20 Hz, 0.2 msec, 50–90 mA) Group 1: Group 1: BTX+ES Group 2: BTX alone	12 children Cerebral Palsy Unilateral/Bilateral GMFCS 1,2 Median age: 5 years	Spasticity: MAS PROM Ankle muscle stiffness	Gait: Physician Rating Scale 3D-Instrumented Gait analysis	6 months	Mean change Group 1 vs Group 2: N/A: descriptive data for group1 are not presented Adjuvant ES had no significant effect ($p > 0.05$) on clinical measurements, ankle stiffness and gait varaibles	8	
Williams et al. [35] 2013	Crossco-mparison design with a 6-month preinter-vention controlled period	Resistance training (RT)	Lower limb Home-based training programme 3 times a week for 10 weeks Progressive strengthening exercices Initially, work on motor control and then more complex movements and functional tasks Group 1: BTX+RT Group 2: BTX alone 2 subgroups: either pre or post BTX RT	15 children Cerebral Palsy Bilateral GMFCS 1,2 Mean age: 8 years	Spasticity: MAS Selective Control Assessment of the lower extremity Muscle isometric and isokinetic strength of the knee and ankle muscles Muscle Volume (MRI)	GAS	3 months	Many evaluations for many muscles: MAS: significantly reduced after BTX. No significant change over the strenght training for either group Strenght: significant isokinetic strength gains in the intervention period compared to the control period GAS: significant improvement compared to the control period MV: significant improvement in all assessed muscles compared to the control period	9	
Elvrum et al. [23] 2012	RCT	Resistance training (RT)	Upper limb RT: 3 times a weeks for 8 weeks with a physiotherapist 0–40 minutes core strengthening and singlejoint resistance training with increasing intensity by 0.25–0.5 kg Group 1: BTX+RT Group 2: BTX alone	10 children Cerebral Palsy Unilateral/Bilateral MACS 2 Mean age: 13.4 years	AROM of elbow and forearm Muscle tone and strength in the elbow and forearm Isometric grip force	Hand and arm use: Melbourne AHA	9 months	Mean change Group 1 vs Group 2: N/A: results are presented in box plot In group 1: muscle strenght increased in injected and non injected muscles without increasing muscle tone No difference between goups at 5 months Both groups had very small improvements in AHA and Melbourne	6	
Bandholm et al. [36] 2012	A randomised pilot study	Resistance training (RT)	Lower limb RT: 2 times per week for 12 weeks 10 minutes of gait and balance 5 minutes of stretching 15 minutes of progressive resistance training Group 1: BTX + RT Group 2: BTX alone	14 children Cerebral Palsy Unilateral GMFCS: 1 Mean age: 9.5 years	Spasticity: MAS Dorsiflexion Maximal Torque (MT) Plantarflexion MT	Balance (biomechanical force plate) GMFM 3D – Gait analysis (Vicon)	3 months	Mean change Group 1 vs Group 2: MAS: 1.5 (N/A) vs 1.2 (N/A) Dorsiflexion MT: N/A no change Plantarflexion MT: +0.12 (N/A) vs −0.11 (N/A)*** GMFM: +1.8 (/NA) vs +4.2 (N/A) No changes in postural control, kinematics and gait parameters in both groups	9	
Speth et al. [22] 2015	Multicentre RCT	Bimanual taskoriented therapy (BTOT)	30 min of physiotherapy (PT) and one hour of occupational therapy (OT) 2 times a week, for 12 weeks Bimanual goals were set using the Canadian Occupational Performance Measure (COPM) Group 1: BTX+BTOT Group 2: BTX alone Group 3: BTOT alone	35 children, Cerebral Palsy Unilateral MACS levels 1-3 Mean age: 7.1 years	Spasticity in wrist and elbow: SPAT PROM and AROM of wrist, elbow and thumb Grip strength	Functional grip strength	6 months	Pretreatment: Functional strengh: One hand: 162 ± 173 vs 95.0 ± 118 vs 131±163; Two hands: 3304 ± 2272 vs 3210 ± 4121 vs 3182 ± 1604 Posttreatment: Functional strengh: One hand:215 ± N/A vs N/A vs 309±N/A; Two hands: 5192 ± N/A vs N/A vs 5302 ± N/A Mean change Group 1 vs Group 3: Functional strengh: One hand: 62 (N/A) vs 178 (N/A)*; Two hands: 1188(N/A) vs 2120(N/A)	8	

Table 1 (*Continued*)

Authors	Design	Adjunct therapy	Therapy protocol	Population	Assessment of deficiencies	Quality of life	Follow-up	Results	PEDro	D&B
Jianjun et al. [19] 2013	RCT	Rehabilitation program	Group 1: BTX-A injection + 2 h/day rehabilitation Group 2: BTX-A injection + < 2 h/day rehabilitation	244 Cerebral Palsy Localisation? GMFCS? Mean age: 6.4 years	Spasticity: MAS	GMFM	1 year	Pretreatment: MA: 2.6 ± 1.0 vs 2.7 ± 1.1 GMFM: 45.7 ± 8.5 vs 44.5 ± 9.1 Posttreatment: MAS: 1.6 ± 0.5* vs 1.6 ± 0.6* at 1 month post BTX GMFM: 60.9 ± 10.6* vs 56.0 ± 9.0* at 1 year post BTX Mean change Group 1 vs Group 2: MAS: N/A; GMFM: 15.2 ± 3.5 vs 11.5 ± 3.2**	8	
Park et al. [26] 2009	Casecontrolled non randomised study	Modified constraintinduced movement therapy (mCIMT)	Group 1: A combined therapy of mCIMT and BTX-A injections during 3 weeks Group 2: BTX-A injections only	29 children Cerebral Palsy Unilateral MACS? Median age: 4 years	Spasticity: MAS, MTS PROM	Upper Limb Physician's rating scale (ULPRS) How Often scale and How Well scale in the revised Paediatric Motor Activity Log (PMAL)	3 weeks	Pretreatment: MAS: 1.5 (0.3–2.3) vs 1.5 (0.3–2.5); R1: 11.3 (−37.5–58.8) vs 22.5 (−23.8–55.0) How often scale: 0.6 (0.0–1.5) vs 0.6 (0.2–1.2) How well scale: 0.5 (0.0–1.4) vs 0.6 (0.0–1.6) Posttreatment: MAS: 1.0 (0.0–2.0)* vs 1.3(0.0–2.5)* R1: 37.5 (6.3–63.8)* vs 36.3 (0.0–65.0)* How often scale: 1.2 (0.0–1.5)* vs 0.8 (0.3–1.4)*** How well scale: 1.2 (0.0–1.9)* vs 0.5 (0.0–1.6) Mean change Group 1 vs Group 2: MAS: 0.4 (0.0–1.0) vs 0.3 (0.0–1.0) R1: 10.6 (0.0–52.5) vs 10.0 (−6.3–43.8) How often scale: 0.4(−0.0–0.9) vs 0.0(−0.1–0.2)*** How well scale: 0.8(0.0–1.2) vs 0.0(−0.3–0.9)***	17	

RCT: randomized controlled trial; BTX: botulinum toxin type A; MAS: Modified Ashworth Scale; TS: Tardieu scale; PROM: Passive Range of Motion in degrees; R1: spastic catch in Tardieu's scale in degrees; OGS: Observational Gait Scale; PGA: Physician Global Assessment; QUEST: Quality of Upper Extremity Skills Test; MACS: Manual Ability Classification System; GMFM: Gross Motor Function Measure; GMFCS: Gross Motor Function Classification System; GAS: Goal Attainment Scaling. Speed gait in $km.h^{-1}$ or $cm.min^{-1}$ or $m.s^{-1}$; stride length in cm; maximal torque in 0.1 Nm/kg; functional strength in g.

* $P < 0.05$.

** $P \leq 0.001$ compared to pretreatment values.

*** $P \leq 0.05$. When the mean change between pre- and post-treatment was calculated for each group, it is presented with SD values *** $P < 0.05$ (difference between groups).

note, the use of BTX alone conferred no improvement in terms of impairment and gait parameters [21]. No adverse effects were reported.

The use of a night splint after BTX injection in the upper limb was evaluated in a single RCT with poor quality (PEDro score 4) [30] and surprisingly, suggested that upper-limb function (Quality of Upper Extremity Skills Test score) was significantly better than with BTX alone after 6 months of regular use ($P < 10^{-4}$).

3.4.1. Electrical stimulation (n = 4)

Two kinds of protocols were found.

The first [31,32] ($n = 2$) used electrical stimulation in the gastrocnemius muscles after BTX injection in the triceps surae versus BTX alone. Different modalities of stimulation exist in terms of type of current (continuous or rectangular biphasic, high or low frequency), duration (15 to 30 min) and frequency of application (1–6 times/day for 3 days to 6 weeks). The quality of these 2 RCTs was good (PEDro score 8 for both) but with only 35 total participants. Electrical stimulation did not provide any additional effects as compared with BTX alone in terms of reduced spasticity or improved gait (Physician Rating Scale, 3D Instrumented Gait analysis).

The second protocol [33,34] ($n = 2$) consisted of functional electrical stimulation in antagonist muscles after BTX injection in the wrist and finger flexors [33] and in the triceps surae [34] associated with a physical therapy programme. The quality of these 2 studies was poor (PEDro score 5 and D&B score 9, respectively) and no conclusions can be drawn.

3.4.2. Multimodal Rehabilitation Procedures

3.4.2.1. Resistance training (n = 3). This training consisted of a global progressive programme tailored to each individual for strengthening the spastic and antagonist muscles in the lower [35,36] or upper limb [23] twice or 3 times/week for 8 to 12 weeks. These programmes were compared to physiotherapy without resistance training (gait, balance, stretching) with good methodological quality [35,36] (PEDro score 9) or nothing after BTX injection in the upper limb, with moderate quality (PEDro score 6) [23]. The total number of participants was 39. Resistance training improved muscle strength in injected muscles [35] without increasing spasticity. Williams et al. attributed the decrease in muscle atrophy after BTX observed on MRI to the resistance training [35]. These RCTs showed no impact on body functions, structures or activity (assisting hand assessment [23], biomechanical force plate [36], gait parameters with GMFM and instrumented gait analysis [36]), but personalised goals were achieved (Goal Attainment Scaling) [35].

3.4.2.2. Rehabilitation programmes (n = 3). Surprisingly, only 3 studies evaluated a rehabilitation programme after BTX injection: Modified Constraint Induced Therapy [37] (mCIMT) ($n = 29$, D&B score 17) and Bimanual Task Oriented Therapy (BTOT) [22] ($n = 35$, PEDro score 8) for the upper limb and a poorly documented global rehabilitation programme for 2 hr/day [19] ($n = 244$, PEDro score 8) for the lower limb.

"Rehabilitation" associated with the BTX injection conferred more improvement in the functional scales than with BTX alone: GMFM [19], Upper Limb Physician's Rating Scale, and How Often scale and How Well scale in the revised Paediatric Motor Activity Log [37]. Of note, 6 months after the treatment, functional grip strength was significantly better with BTOT alone than with BTOT associated with BTX injection [22].

4. Discussion

BTX injection alone is not sufficient to reach functional goals during a child's growth [8]. Surprisingly, although the number is

increasing, few studies have been published on adjunct therapies after BTX injection during the last decade [38]. Findings from this systematic review of the effectiveness of adjunct therapies are based on 20 studies involving 662 children with CP, essentially concerning posture, with only 6 studies investigating specific rehabilitation after BTX injection (3 of the upper limb). Nevertheless, the quality of these studies is good.

However, the number of participants needed for statistical power was not calculated or reported in any study included in our review, which reduces the strength of any conclusions that can be drawn from the results. Concerning outcome assessment in the studies included, few studies focused on outcomes related to activities, with most reporting outcomes related to only body structure and function. This finding is similar to the previous conclusions of Tustin et al. [39] and Blackmore et al. [38].

This systematic review confirms that BTX injections alone are not sufficient to improve outcomes [8], and adjunct therapies are clearly necessary: BTX injections alone cannot be recommended for children.

During growth, lower-limb posture with casting is recommended with a high level of evidence, although only the short-term efficacy of short-leg casting has been evaluated. To date, no study has compared the different modalities of casting, and further studies specifically devoted to testing these different kinds of casting are needed. No clear recommendation can be made concerning the delay after BTX injection before applying casting. Some authors have proposed that BTX begins to take effect 1 week after injection, but we found no evidence for this. Serial casting has not demonstrated greater efficacy than a single cast that should be worn for at least 2 weeks. In a recently published work [40] (not included in our analysis because the paper was published after our endpoint), the authors did not show any significant differences between serial or single casting after BTX injection in the triceps surae, and the magnitude of improvements was similar between single and serial casting procedures. If confirmed in a large sample, applying single casting may be preferred because of the greater convenience for both clinicians and children.

Moreover, adverse effects such as pain, muscle atrophy and cutaneous lesions were noted in serial casting rather than unique casting studies. Although clear evidence exists for the lower limb, the sparse number of studies for posture therapy in the upper limb after BTX injection in children with CP provides only a moderate level of evidence. However, we can extrapolate from the available literature concerning lower-limb spasticity treatment that posture therapy should also be recommended after BTX injection to treat spasticity in upper limbs.

Personalised resistance training involving both spastic and antagonist muscles and depending on individualised motor control helped reach personalised goals and treat spasticity. Moreover, adding resistance training seems able to control muscle atrophy after BTX injection. However, the sample size of these studies was very limited. Further studies with a larger sample size are needed. Moreover, the timing of a resistance training programme is unknown because such training pre- or post-BTX injection probably has different goals. The training before injection should help protect muscles against atrophy, whereas that after BTX aims to work on motor control in a personalised way [35].

In the upper limb, mCIMT and BTOT had positive results in terms of function with or without BTX injection. Further studies should be conducted with the use of BTX injection pre-mCIMT or BTOT only if spasticity is a major impairment regarding upper limb function.

Because of few studies for goal-directed rehabilitation programmes after BTX injection, we have only a moderate level of evidence for adjunct therapies. However, the available literature [7,8] regarding motor rehabilitation for children with CP after BTX injection considers such adjunct goal-directed approaches promising.

Finally, the results obtained with electrical stimulation are not encouraging, although the number of participants in these studies was very low. Electrical stimulation as adjunct therapy after BTX injection in children seems inefficient.

Table 2
Synthesis of level of evidence.

Adjunct therapy	Comments
Serial Casting	Variability of protocols concerning timing of serial casting In lower limb no studies exist involving other joints than theankle **Recommended – Do it**
Casting	No argument today in favour of serial casting rather than casting **Recommended – Do it**
Resistance training (RT)	Requires more studies Remaining issues: Timing of RT?; Intensity?; Task oriented to improve function? **Probably recommended – Probably do it**
Rehabilitation programme	To date very few studies are available Encouraging results concerning task-orientated reeducation but requires more studies **Probably recommended - Probably do it**
BTX-A alone	**Not recommended - Don't do it**
Electrical stimulation	**Not recommended - Don't do it**

5. Conclusions

Adjunct therapies such as posture (serial casting, casting or splints), goal-directed rehabilitation programmes and strength training may improve spasticity outcomes in children when used after BTX injection (see Table 2). This therapy has been clearly demonstrated for treating lower-limb spasticity. The level of evidence is low for the effectiveness of BTX injection without adjunct therapy for impairment (range of motion, spasticity) and activities (notably gait parameters). However, a high level of evidence suggests that posture therapy after BTX injection improves range of motion, spasticity and gait parameters. Further research is needed to test the best procedure for posture (serial casting, casting or splints) and to determine the optimal time window for applying these adjunct therapies. The level of evidence is moderate for small to moderate improvements in impairment (range of motion, spasticity) and activities (gross motor function) for resistance training and rehabilitation programmes. Finally, the level of evidence is low for the effectiveness of electrical stimulation. To give a clear overview of our conclusions, for each adjunct therapy listed in Table 2, we have provided a short comment and assigned it to one of three categories: "do it"; "probably do it", or "don't do it".

ICF domains of activities, participation and quality of life need to be considered in future studies to establish the clinical relevance of adjunct therapies in children. Finally, no study was conducted in children with spasticity due to other neurological conditions. Hence, the conclusions are strictly applicable to only children with CP. Further studies are needed to test adjunct therapies after BTX injection in children with other causes of spasticity.

Disclosure of interest

The authors declare that they have no competing interest.

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