Should botulinum toxin A injections be repeated in children with cerebral palsy? A systematic review

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ABBREVIATIONS

ICF	International Classification of Function, Disability and Health
ICF-CY	International Classification of Function, Disability and Health – Children and Youth Version
ROM	Range of motion

AIM The aim of this study was to determine the effects of repeat botulinum toxin A (BoNT-A) injections in children with spastic cerebral palsy (CP) on the basis of a best evidence synthesis.
METHOD This study included 13 original articles after searching the literature to retrieve information. We used the critical review form produced by McMaster University to determine the methodological quality of the studies, and then confirmed the levels of evidence from Sackett. The studies were also evaluated using the International Classification of Function, Disability and Health – Children and Youth Version (ICF-CY).
RESULTS A total of 893 children with spastic CP who had been administered repeat BoNT-A injections were evaluated. The evidence level was II in four of the thirteen studies, III in four studies, and IV in five studies. The McMaster review form score was 14 in two studies, 13 in four studies, and 12 in seven studies. The results showed that repeat BoNT-A may be a safe and an effective approach. The first two injections/one repeat especially relieve spasticity and improve fine and gross motor activities.
INTERPRETATION Future studies to investigate the effectiveness of repeat BoNT-A in children with spastic CP may be planned within the framework of the ICF-CY to include well-designed randomized controlled trials and those conducted on larger homogenous groups.

Cerebral palsy (CP) is a neuromuscular pathology that is caused by an injury to the immature brain, and that limits activity by affecting the development of body function and posture.[1,2] CP is the most common childhood disability, and about 70% to 80% is of the spastic type.[3]

Spasticity is the rate-dependent increased resistance against passive movements, related to the development of hyperactive reflexes following upper motor neuron lesions. The features include increased muscle tonus, tendon jerks, clonus, and hyperactive reflexes such as the Babinski reflex. Decreased coordination, strength, and endurance can also be seen, together with increased muscle fatigability and loss of fine motor control and dexterity.[4,5] This spasticity causes limited function, in addition to limiting daily living activities and social participation.[6,7]

Intervention strategies, such as rehabilitative services (physical therapy, occupational therapy, adaptive equipment, orthoses, etc.), oral pharmacotherapy (baclofen, diazepam, tizanidine, dantrolene), chemical denervation (botulinum toxin [BoNT-A] injections, phenol injections), orthopaedic surgery, selective dorsal rhizotomy, and intrathecal baclofen pump are used as therapeutic interventions for spasticity.[8] BoNT-A injections have often been used as an accepted method to reduce spasticity in children with CP.[9,10] This treatment is based on the physiological effects of intramuscular BoNT-A that have been shown to diminish muscle activity by blocking the release of acetylcholine at the synaptic junction. This dose-dependent treatment has been used as a single session for the relief of spasticity, but sometimes repeat injections are required for aggressive muscle tone.[10–12] The number of repetitions and the interval between them are also important features in BoNT-A interventions. However, there is no scientific consensus regarding how often and how many times BoNT-A should be repeated. Although several studies have investigated the effects of BoNT-A in children with CP, the effects of repeat BoNT-A injections have not attracted much attention and remain unclear, as far as we know.

The International Classification of Functioning, Disability and Health (ICF) is an effort by the World Health Organization to create a joint and standard language and framework to define health and health-related conditions. Health status is investigated under the topics of body

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structure and function, activity and participation, and environmental and personal factors within the framework of the ICF.[13] ICF – Children and Youth version (ICF-CY) has been studied as a standardized method in the identification of functional skills that require activity and social participation in children and adolescents with CP.[14] ICF can be used to systematize the assessment of functioning for CP in neurorehabilitation services.[15] To map the evaluation methods according to the subsections of ICF-CY provides an important perspective in the areas of disability and health for clinicians and researchers.[16]

The present systematic review aimed to determine the effects of repeat BoNT-A injections in children with CP, and whether repeat injections are worthwhile, on the basis of a best evidence synthesis.

METHOD

Search strategy

An extensive search was conducted independently by five physiotherapists using the electronic databases specified below between 1 January 1990 and 1 February 2015 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations for conducting and reporting systematic reviews.[17] Articles were identified from PubMed, Google Scholar, Web of Science, ScienceDirect, and the Physiotherapy Evidence Database using the keyword combinations of 'repeated botulinum toxin', 'repeat botulinum toxin' and 'Cerebral Palsy'. Keywords were matched to the Medical Participant Headings index and explored or searched as keywords where appropriate. Figure 1 presents the flow chart of the search strategy. Articles were included if the following eligibility criteria were met: (1) investigated the effects of at least two BoNT-A/one repeat injections in the extremities of children with CP; (2) children aged between birth and 21 years at the initial BoNT-A injection; (3) investigated physical functional changes; and (4) full text publications in English. Articles were excluded if they: (1) investigated the effects of BoNT-A on non-physical function such as salivatory function; (2) described only the pathophysiological effects of BoNT-A; (3) were systematic reviews including the effect of BoNT-A on childhood disabilities other than CP; and (4) were single-participant designs.

Procedure

Articles on upper extremities after repeat BoNT-A injections were reviewed by the second (KS) and third (UD) authors, while articles on lower extremities after repeat BoNT-A injections were reviewed by the first (AK) and fourth (SK) authors. Any disagreements about the studies were resolved through discussion during regular meetings, as well as by the fifth author (AM), the most experienced physiotherapist, until a consensus was reached and the final decisions were made.

The methodological quality of the included studies was assessed according to the guidelines for the critical review form from McMaster University,[18,19] a quantitative appraisal tool (Appendix S1, online supporting information). The level of evidence of the included studies was determined with the Sackett levels of evidence.[20,21]

What this paper adds

- Children with spastic cerebral palsy show functional gains especially after the first two injections/one repeat of botulinum toxin A (BoNT-A).
- The effect of multiple repeats of BoNT-A is not clear due to insufficient evidence.
- Adverse events following repeat BoNT-A administration are short-lived, transient, and rare.

All study outcomes were assessed based on ICF-CY. We also categorized the outcome measures used in the studies under the subtitles of body structure and function, activity and participation, personal and environmental factors, as used in the ICF framework, in our systematic review. Range of motion (ROM) and spastisity were assessed as body structure and function; Canadian Occupational Performance Measure, Physician Rating Scale, Quality of Upper Extremity Skills Test, Gross Motor Function Measure (GMFM), Gross Motor Function Classification System (GMFCS), Paediatric Evaluation of Disability Inventory, Gait Analysis, Assisting Hand Assessment as activity and participation; Goal Attainment Scale as environmental factors of ICF.

RESULTS

A total of 586 articles were assessed based on the title and abstract. A total of 13 articles fulfilled the criteria and were included in the review.

The demographic characteristics of these studies are shown in Table I. There were 12 prospective studies and one retrospective study. Four studies investigated the effects of repeat BoNT-A in the upper extremities,[22–25] while nine studies were designed for lower extremities.[26–34] The number of participants varied across the different studies. Most of the studies used GMFCS to classify the motor functional levels of the participants. GMFCS levels were I to II in the studies conducted for the upper limb,[22,23] but varied between I and V in the studies conducted for the lower limb.[26,27,29,31,33] All studies were conducted on children with spastic type CP. They also demonstrated a large variability in the number of participants aged between 1 year and 19 years. A few of the studies were level IV[25,27,30,31] regarding the Sackett level of evidence; none were level I or V.

Using the McMaster review form, the total scores of the studies varied between 12 and 14 scores, as shown in Table SI (online supporting information). Only two studies attained 14 of 15, the highest score.[22,24] The sample size was not justified and co-intervention was not avoided in a few of the articles. Most of the studies included in this review did not provide information about contamination.[25–27,29–33]

Table SII (online supporting information) presents the characteristics of the BoNT-A injection including trademark, dose, muscle, interval between repetitions, etc. Dysport and Botox were the brands used. The doses varied according to the target muscle, body weight, and

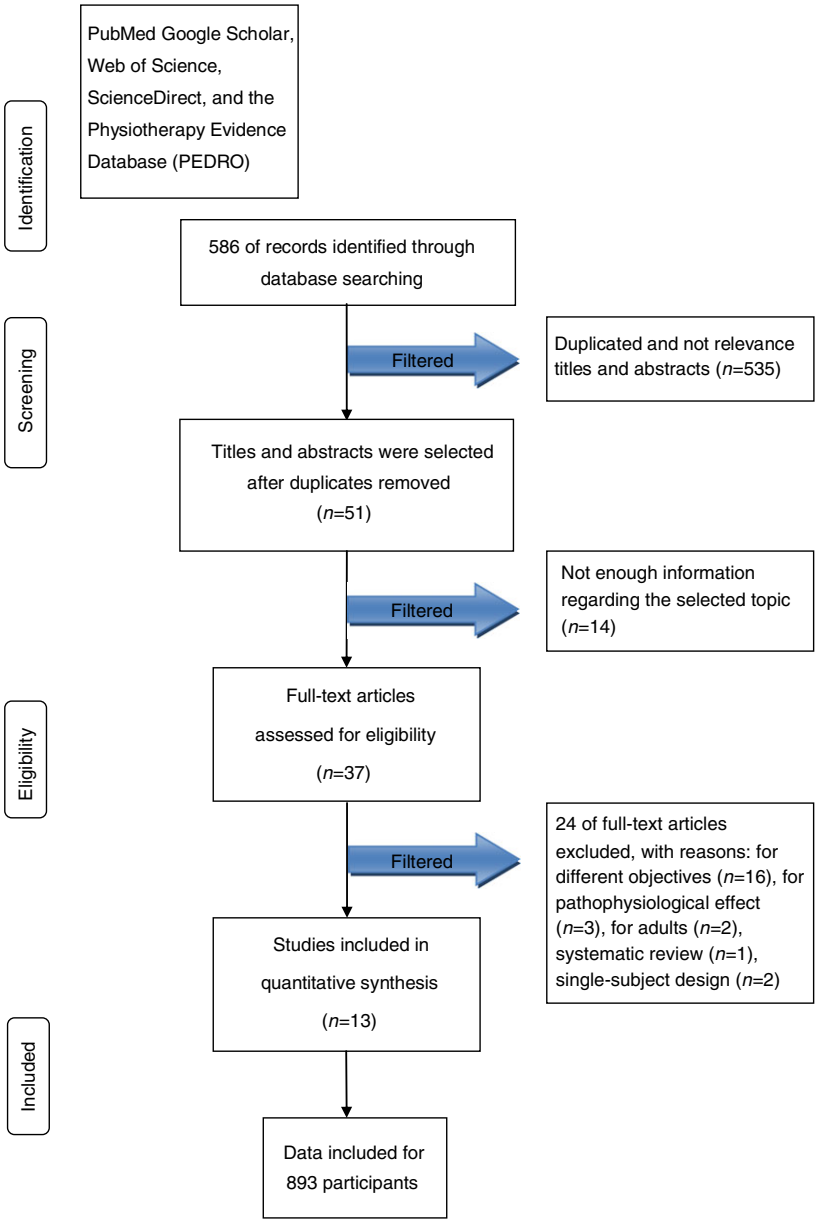

Figure 1: Flow chart depicting the search strategy.

degree of spasticity. The interval between repetitions varied from 3 months to 12 months. The injection was repeated a minimum of one and a maximum of 13 times. Casting and splinting approaches were used following the BoNT-A injections in two studies.[29,33] Three studies did not mention any information on local or general anaesthesia or sedation,[23,28,29] but these tecniques were used in all the remaining studies except one.[30] Side effects related to BoNT-A application were found in all papers except Papavasiliou et al.[26] and Wong et al.,[28] who did not provide information on adverse events following the treatment (Table SII).

Table SIII (online supporting information) presents detailed information about the methodology of intervention, outcome measures according to ICF domains, the results and conclusions of the studies. Six of the studies[26,28,30–33] included only BoNT-A injections while the others used co-interventions including rehabilitation technique. Papavasiliou et al.[25] evaluated only body function and structure of ICF outcome measures, while all other studies evaluated body function and structure as well as activities and participation.[22–24,26–34]

Evaluation of body function and structure

The majority of the studies used the Modified Ashworth scale to assess spasticity.[25–29,31,32] Only Olesch et al.[22] and Papavasiliou et al.[26] used the Tardieu scale or the Modified Tardieu scale. Most of the studies showed that BoNT-A

Table I: Demographic characteristics of included studies

Study	Participants	Age	Clinical type of CP	GMFCS level	Study design	Sackett level of evidence scores
Upper limbs						
Olesch et al. (2010)[22]	*n*=22 (19 M, 3 F) Group OT: *n*=11 (10 M, 1 F) Group BoNT-A+OT: *n*=11 (9 M, 2 F)	Range:1y 10mo–4y 10mo Mean age: 3y 8mo±9mo	Hemiplegic: *n*=22	GMFCS I: *n*=14 GMFCS II: *n*=8	Randomized controlled trial – parallel-group design	II
Lowe et al. (2007)[23]	*n*=42 (31 M, 11 F) Group 3×BoNT-A: *n*=21 Group 2×BoNT-A: *n*=21	Range: 2y–8y Mean age: 4y±1y 7mo	Hemiplegic: *n*=42	GMFCS I: *n*=42	Evaluator-blinded, randomized, prospective controlled, two group trial	II
Lidman et al. (2015)[24]	*n*=20 (14 M, 6 F) Group OT: *n*=10 (3 F, 7 M) Group BoNT-A+OT: *n*=10 (3 F, 7 M)	Range: 1y 6mo–10y Mean age: 3y 1mo	Unilateral spastic: *n*=20	Not mentioned	Population based, randomized controlled design, evaluator-blinded	II
Papavasiliou et al. (2012)[25]	*n*=153 (52.94% F, 47.06% M)	Range: 1y–18y Mean age: 6y 4mo±4y 10mo	Diplegic or tetraplegic: *n*=81 Unilateral spastic: *n*=72	Not mentioned	Prospective trial	IV
Lower limbs						
Papavasiliou et al. (2006)[26]	*n*=57 (26 F, 31 M)	Range: 2y 6mo–13y 6mo Mean age: 4y 7mo	Hemiplegic: *n*=4 Diplegic: *n*=26 Quadriplegic: *n*=27	GMFCS I: *n*=13 GMFCS II: *n*=9 GMFCS III: *n*=16 GMFCS IV: *n*=15 GMFCS V: *n*=4	Prospective	III
Linder et al. (2001)[27]	*n*=25 (10 F, 15 M)	Range: 1y 6mo–15y 6mo Mean age: 5y	Tetraplegic: *n*=9 Diplegic: *n*=12 Hemiplegic: *n*=4	GMFCS I: *n*=5 GMFCS II: *n*=4 GMFCS III: *n*=7 GMFCS IV: *n*=6 GMFCS V: *n*=3	Prospective (open-label)	IV
Wong et al. (2005)[28]	*n*=81 (34 F, 47 M) BoNT-A group: *n*=22 (8 F, 14 M) SPR group: *n*=20 (8 F, 12 M) Rehabilitation group: *n*=20 (8 F, 12 M) Control group: *n*=19 (10 F, 9 M)	Range: 3y–7y	Diplegic: *n*=62	Not mentioned	Prospective (not randomized)	III
Tedroff et al. (2009)[29]	*n*=94 (45% F, 55% M)	Range: 11mo–17y 8mo Median age: 5y 4mo	Diplegic: 50% Hemiplegic: 22% Tetraplegic: 25% Dyskinetic: 3%	GMFCS I: 29% GMFCS II: 15% GMFCS III: 16% GMFCS IV: 17% GMFCS V: 23%	Prospective clinic cohort	III
Koman et al. (2001)[30]	*n*=207 (85 F, 122 M)	Range: 2y –18y Mean age: 5y 7mo±2y 9mo	Hemiplegic: *n*=77 Diplegic: *n*=130	Not mentioned	Prospective (open-label, double-blind trial)	IV
Valevski et al. (2008)[31]	*n*=26 (10 F, 16 M)	Range: 2y 2mo–7y 6mo Mean age: 3y 7mo±1y 2mo	Hemiplegic: *n*=7 Diplegic: *n*=19	GMFCS I: *n*=4 GMFCS II: *n*=9 GMFCS III: *n*=5 GMFCS IV: *n*=8	Prospective (open-label)	IV
Metaxiotis et al. (2002)[32]	*n*=21 (13 F, 8 M)	Range: 2y 6mo–8y 5mo Mean age: 5y 7mo	Diplegic: *n*=21	Not mentioned	Prospective	IV

Table I: Continued

Study	Participants	Age	Clinical type of CP	GMFCS level	Study design	Sackett level of evidence scores
Molenaers et al. (2009)[33]	*n*=106 (50 F, 65 M)	Range: 1y 11mo–18y 10mo Mean age: 4y 6mo	Diplegic: *n*=84 Quadriplegic: *n*=13 Hemiplegic: *n*=9	GMFCS I: *n*=18 GMFCS II: *n*=28 GMFCS III: *n*=44 GMFCS IV: *n*=12 GMFCS V: *n*=4	Retrospective	III
Moore et al. (2008)[34]	*n*=58 (22 F, 36 M) Group BoNT-A: *n*=30 Group placebo: *n*=28	Range: 2y–6y Mean age: BoNT-A: 5y 4mo±1y 8mo Placebo: 4y 9.8mo±1y 5.4mo	Diplegic: *n*=39 Hemiplegic: *n*=9 Quadriplegic: *n*=10	Not mentioned	Prospective randomized, double-blind, placebo-controlled, parallel-group study	II

F, females; M, males; OT, occupational therapy, GMFCS, Gross Motor Function Classification System; SPR, selective posterior rhizotomy; Sackett level of evidence score I, large randomized controlled trials with clear cut results; II, small randomized controlled trials with unclear results; III, cohort and case–control studies; IV, historical cohort or case–control studies; V, case series studies with no controls.

reduced spasticity. Valevski et al.[31] did not investigate the long-term effects of BoNT-A on spasticity but expressed that spasticity could be reduced in the short term ($p<0.05$). Moore et al.[34] reported that the dosage they administered might not have been sufficient to decrease spasticity, whereas Papavasiliou et al.[25] did not evaluate spasticity in their study. Goniometry was used to measure the ROM.

Papavasiliou et al.[25] and Valevski et al.[31] did not evaluate ROM in long term, but reported important improvements in the short term (1mo after the injection). Linder et al.[27] found ROM to increase 1 month after the first injection but to regress to the initial value in 12 months. Tedroff et al.[29] saw more improvement in ROM after the first injection than later injections, but reported no significant prevention against contractures. Koman et al.[30] found ROM to improve at each evaluation for 1 or 2 years and Moore et al.[34] found no change in ROM in 1 or 2 years.

Evaluation of activities and participation

Papavasiliou et al.[26] (injections administered at minimum 4mo intervals) reported that an important improvement occurred in the GMFCS level, 3 months after the first injection, but the improvement decreased in later injections ($p<0.001$). Linder et al.[27] (2–4 injections at an interval of 3–6mo) reported a significant increase especially in the GMFM level of the younger children in GMFCS level III within 12 months ($p<0.001$). Valevski et al.[31] (1–4 injections at 6mo intervals) found an increase in the GMFM level in the long term when initial and late injection results were compared ($p<0.001$). Moore et al.[34] (8 injections at 3mo intervals) reported that the dose they administered during 1 or 2 years was not enough to make a change in GMFM ($p=0.40$) nor the Paediatric Evaluation of Disability Inventory functional skills score ($p<0.05$). Lowe et al.[23] (2–3 injections at 6mo and 12mo intervals) demonstrated increasing Paediatric Evaluation of Disability Inventory scores after the first ($p=0.00$) and second ($p=0.04$) injections, but did not observe the same improvement with the third injection ($p=0.21$).

Papavasiliou et al.[26] (injections at minimum 4mo intervals) reported that 31.57% of children had an improvement in GMFCS, mostly from level IV to III.

Olesch et al.[22] (3 injections) and Lowe et al.[23] (2–3 injections at 6mo and 12mo intervals) saw no difference between the groups in terms of Quality of Upper Extremity Skills Test scores. Olesch et al.[22] (3 injections) found that Canadian Occupational Performance Measure performance score in the BoNT-A+occupational therapy group was higher than the occupational therapy group. Lowe et al.[23] (2–3 injections at 6mo and 12mo intervals) found no difference between the groups but an improvement was found within the groups. Lidman et al.[24] found improvement in both groups.[24] Papavasiliou et al.[26] (injections at minimum 4mo intervals) reported that functional targets could be reached in 18 months. Wong et al.[28] (injections at 4mo intervals) showed that walking speed, cadence, and step length had improved after each injection. However,

this improvement was not significant 12 to 20 months later. Koman et al.[30] (1–13 injections at intervals of over 3mo) demonstrated improvement in walking patterns with each injection and found that this development continued in the follow-up after 2 years. Metaxiotis et al.[32] (2–4 injections) found the walking parameters to improve in 6 and 18 weeks after the first and second injection respectively. Velocity and stride length increased significantly.

Molenaers et al.[33] (4–12 injections at 1y intervals) reported that higher dosage was required for children with diplegia compared with children with hemiplegia (p=0.001) or quadriplegia (p=0.053) (Table SIII).

DISCUSSION

The purpose of this study was to determine the effects of repeat BoNT-A injections in children with CP on the body function and structure, activity and participation, contextual factors of the ICF model, and to evaluate the evidence to determine whether BoNT-A injections should be repeated in children with CP.

BoNT-A injections have been widely used since the 1990s, especially to treat spasticity in children with spastic CP. The effectiveness of repeat BoNT-A treatment was investigated across various conditions such as adult spasticity, CP, esophageal spasm, dystonia, and chronic headache in patients of all ages in a review study by Gordon et al.[35] A 2010 Cochrane review reported a high level of evidence for the use of BoNT-A as an adjunct to managing the upper limbs in children with spastic CP and it was suggested that further research was needed to evaluate repeat injections of BoNT-A in these children.[36,37] Our study was the first review to investigate the efficacy of repeat BoNT-A in children with CP.

Participants

The total number of participants in the articles included in our review was 893 (range 20–207). The number of patients that were followed-up decreased as the number of repeat injections increased. This was an unfavorable development in terms of clearly revealing the effect of repeat BoNT-A injections. It is possible that contractures were enhanced and neurodevelopmental improvement decelerated with increasing age. It is believed that intensive treatment of spasticity during the earlier stages could provide more benefit regarding motor improvement. Metaxiotis et al.,[32] Linder et al.,[27] and Molenaers et al.[33] similarly reported more improvement in function when treatment was administered at earlier ages.

The age range of the children was 1 to 19 years with mean ages of 3 years 1 month to 6 years 4 months. Boyd et al.[38] have reported that BoNT-A administration should be started at the age of 1 to 5 years to obtain the maximum benefit. Taking this suggestion into account, the participants in the studies reviewed were advantageous in terms of age. The only study in this review to evaluate which age group was more advantageous for BoNT-A was by Papavasiliou et al.[25] We are therefore unable to generalize that repeat BoNT-A treatment could be more beneficial for younger children with CP.

The studies were conducted on participants covering all levels of GMFCS. They included patients with spastic hemiplegia, diplegia, and quadriplegia types in terms of CP involvement. It is difficult to speak of a homogeneous study group considering all the participants.

Methodological quality

Four of 13 studies were reported as randomized controlled trials and had level II as the highest score for Sackett levels of evidence.[22–24,34] Three of these four randomized controlled trials were related to the upper limb,[22–24] while the other study focused on lower extremities.[34] From the methodological point of view, it was found that all studies had insufficient information about contamination and co-intervention according to the McMaster review form. Co-intervention is known to be required for this population due to ethical rules. Therefore, negative score '0' for co-intervention is unavoidable. However, we believe that it is still difficult to distinguish whether any functional improvement is due to BoNT-A, any co-intervention, or just natural growth in the paediatric population.

A positive relationship is expected between the McMaster critical review scores and the Sackett levels of evidence. The scores obtained from the review are expected to increase with increasing levels of evidence. Interestingly, the studies in our review had a low level of evidence but high McMaster scores. The Sackett level of evidence varied according to the study design,[21] whereas the McMaster form addressed the studies from different aspects such as purpose, sample intervention, and so forth.[18]

Characteristics of BoNT-A

The physiological effect of BoNT-A on nerve terminals continues for 12 to 16 weeks.[39] This effect can continue for up to 1 and a half years depending on physiological characteristics of the muscle such as power, endurance, spasticity, connective tissue extensibility, and joint ROM before the injection.[38] Huang et al.[40] examined the pharmacological effects of BoNT-A and showed that it minimized potential antibody resistance and therefore utilized treatment intervals of more than 3 months. Since the effect is temporary, the injection needs to be repeated.[41] The time of the repeat injection varies according to the physiological characteristics of the muscle mentioned above. The duration between repetitions was not mentioned in two of the articles included in the review while it varied between 3 months and 12 months in the others. The BoNT-A number of repeats ranged from one to thirteen times although most studies used it two to four times. No information about the number of repeats was provided in three studies.[24,26,28] Tedroff et al.[29] reported more improvement in ROM with the first injection. Valevski et al.[31] and Papavasiliou et al.[26] found more significant improvement in GMFM with the first injection than with later injections. Metaxiotis et al.[32] and Wong et al.[28] found more

significant improvement in walking parameters with the first two injections than with later injections. Lowe et al.[23] showed significant improvement in upper extremity motion and function following the first and second injections. The first and second injection were found to provide more improvement in ROM compared with later injections and also to increase the GMFM level and provide an improvement in walking parameters in these six articles. Spasticity decreased after each injection in all the articles. Based on these results, we suggest that the first two injections can provide more improvement of function compared with the later injections. However, the effects of the number of BoNT-A injections and the interval between the repeats on the functionality of children with CP still need to be investigated.

Adverse events

Despite the large variety of doses, number of repeats, and intervals between repetitions, the adverse events or side effects thought to be due to BoNT-A were few in number, minor, and transient. There was no permanent adverse event, nor one causing a significant decrease in function (Table SII). These data indicate that repeat BoNT-A injections are safe. Pathophysiological changes at the tissue level are not the subject of this review and are open to further review studies.

ICF-CY

ICF is the common framework used widely to classify outcome measures in the paediatric population in both research and clinical settings.[16,42] According to the ICF-CY model, most of our review studies focused on body structure and function (Modified Ashworth, Tardieu, ROM) and also the activity and participation domains of the ICF model (GMFM, Canadian Occupational Performance Measure, Quality of Upper Extremity Skills Test, Assisting Hand Assessment, Paediatric Evaluation of Disability Inventory). Only Papavasiliou et al.[26] evaluated parent satisfaction as a domain of contextual factors of ICF in addition to all the other domains. Further studies dealing with contextual factors (personal motivation, parenting stress, social status, etc.) are required. Tonus was found to be decreased in all the articles evaluating spasticity. While Linder et al.,[27] Tedroff et al.,[29] and Moore et al.[34] found no improvement in ROM, it was found to have increased in the other five articles. Based on these results, we can say that repeat BoNT-A injections have positive effects on the body functions and structure domains of ICF. In the same way, repeat BoNT-A injections were found to improve GMFM, GMFCS, Assisting Hand Assessment, and gait parameters. This shows that repeat BoNT-A injections contribute to the activity and participation domains of ICF.

CONCLUSION

The first two BoNT-A injections/one repeat lead to functional gains in children with spastic CP. Although the articles found spasticity to have decreased, and the joint motion range, fine and gross motor function to have increased for the individual children, this systematic review's heterogenous sampling (participant) group can not reveal the effect of more than one repeat BoNT-A injection on children with spastic CP; this is due to the low methodological quality of the studies included in the review, and to the various numbers of repeats and intervals used. Randomized controlled trials designed with large homogenous groups, and which use all the domains of ICF-CY, are needed in the future to investigate the effects of repeat BoNT-A treatment in children with CP.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Methodological quality of articles: Critical Review Form – Quantitative Studies (18).

Table SI: McMaster Review Form.

Table SII: Characteristics of BoNT-A.

Table SIII: Methodology.

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