

Indications and effects of botulinum toxin A for obstetric brachial plexus injury: a systematic literature review

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AIM To give an overview of indications for the use of botulinum toxin A (BoNT-A) treatment for children with obstetric brachial plexus injury (OBPI), and to present the best available evidence of the effectiveness of this treatment.

METHOD Searches were performed in Cinahl, Cochrane Library, Embase, PubMed, and Web of Science, using the keywords 'botulinum' and 'plexus', to identify articles reporting on the use of BoNT-A as a treatment for children with OBPI. Studies found through the references of related articles were also selected.

RESULTS Ten full-text papers and six congress abstracts were included, involving 343 children. Four groups of indications could be identified: internal rotation/adduction contracture of the shoulder, limited active elbow flexion, limited active elbow extension, and pronation contracture of the lower arm. Overall, positive results were reported for all except the indication for limited active elbow extension. However, only one study was comparative in nature; all others were classified as having a low level of evidence. There was a large variation in outcome measures.

INTERPRETATION To provide better evidence for the already partly promising results of BoNT-A treatment for children with OBPI, multicentre randomized controlled trials are needed.

Obstetric brachial plexus injury (OBPI) is commonly caused by traction during delivery. A recent study on its incidence showed a decrease over time in hospitals in the USA from 1.7 per 1000 live births in 1997 to 1.3 per 1000 in 2003.¹ A higher, and somewhat increasing, incidence has been found in various European studies, ranging from 3 per 1000 in Norway² and 3.3 per 1000 in Sweden³ to 4.6 per 1000 live births in a Dutch university hospital.⁴ Explanations for these different trends are probably related to the percentage of Caesarean sections performed, the incidence of infants with a high birthweight, the multiple-birth rates, the rates of preterm labour induction, and different systems for reporting OBPI. Conservative management starts during the first weeks of life, the main aim of the treatment being to prevent contractures and joint deformities. At an older age, the aim of exercise therapy is to improve bimanual, school, and daily self-care activities. The decision to perform neurosurgical repair of the brachial plexus depends on the severity of the plexus injury. Avulsion is a clear indication for early neurosurgical reconstruction.⁵ In the case of a rupture, microsurgical repair is performed when the infant is between 3 and 9 months of age. The time range is a consequence of non-conforming supporting evidence for the predictive value of the antigravity function of the biceps brachii muscle. Complete recovery rates vary from 66% to 92%,^{4,6-10} depending on the criteria used to define complete recovery.

Children with delayed complete neurological recovery and those with incomplete neurological recovery, sustaining muscle denervation, and, therefore, muscle imbalance and co-contraction, are at high risk of problems such as contractures, osseous deformities, and abnormal motor performance.

This article aims to give an overview of current indications for the use of botulinum toxin A (BoNT-A) treatment for OBPI and to present the best available evidence of the effectiveness of BoNT-A treatment for children with this injury.

From classical indications for BoNT-A treatment, such as muscle spasticity, dystonia, and the management of wrinkles, the use of BoNT-A has spread to many medical fields, including urology (sphincter and detrusor muscle) and gastroenterology (oesophagus, stomach, gall bladder, and anorectum).¹¹ In the past 10 years an increasing number of reports on the treatment of BoNT-A for OBPI have been published. In combination with conservative treatment, such as long-term physiotherapy, occupational therapy, and functional orthopaedic or plastic surgery, BoNT-A has been used for many different indications.

Even after neurosurgical re-innervation, children with incomplete recovery from OBPI often have involuntary movement of the antagonist muscles. This results in an impaired active range of motion due to co-contraction,⁶ which can be explained as the consequences of axonal repair with axonal

splitting and aberrant nerve outgrowth. Instead of activating the intended muscle, axons connecting to muscle fibres, forming motor units, might also activate antagonists or even a muscle with a completely different function.¹² In this case, treatment of the co-contracting muscle with BoNT-A aims to weaken the antagonist to improve the function of the agonist.

Another indication for BoNT-A treatment is imbalance of muscle groups, when muscles paralysed by OBPI are dominated by less involved muscles. In this case, BoNT-A is often used in addition to surgical treatment to release contracture and improve the function of the weaker muscle group (e.g. imbalance between internal and external rotators of the shoulder).

The overall objective of rehabilitation treatment should always be to improve the performance of age-appropriate daily activities.¹³ This is in accordance with the International Classification of Functioning, Disability and Health (ICF).¹⁴ It is important to evaluate the effect of BoNT-A, changes at the level of body functions and structures, such as range of motion and muscle strength, as well as improvement in the performance of activities during development. We will use the ICF system throughout this review to categorize the diversity of outcome measures used in the various studies.

METHOD

Literature search

Two reviewers (DG and HB) independently performed the literature search. Five databases were searched to identify full-text articles and congress abstracts: Cinahl, Cochrane Library, Embase, PubMed, and Web of Science. The keywords used for the search were 'botulinum' and 'plexus'. Owing to the different variations of nomenclature for OBPI, 'plexus' was chosen as a search keyword, being used consistently throughout all variations, including the mesh term 'brachial plexus neuropathies'. Other studies were found through the references of related articles. No dates were specified for the search, and foreign language publications were not excluded. The findings of the two reviewers were combined. No ongoing controlled trials on the topic of OBPI and BoNT-A could be found in clinical trial registers (<http://www.controlled-trials.com>).

Selection

Studies were reviewed if (1) they included children with the diagnosis of OBPI, (2) the use of BoNT-A for the affected arm was described, and (3) they were published as a full report or as a congress abstract.

The study designs could include (randomized) controlled trials, uncontrolled studies, cohort studies, case-control studies, and case series. All age groups were included. Congress abstracts and proceedings are mostly preliminary announcements of forthcoming publications that may constitute a valuable pool of new data. If an abstract was not followed by publication of a full article, the congress abstract was included to present a complete overview of the various indications and the effectiveness of the treatment.

The recommended Cochrane Highly Sensitive Search Strategy for identifying randomized trials in combination with

What this paper adds

- Worldwide, BoNT-A is used in obstetric brachial plexus injury.
- We identified four indications in obstetric brachial plexus injury.
- Strong evidence about the effectiveness of BoNT-A is not yet available.

our keywords did not succeed.¹⁵ Potentially relevant articles were difficult to find because the number of articles on this topic was low, and some references were only published as congress abstracts. Therefore, both reviewers combined the search results rather than investigating the reproducibility of their search strategies.

We refrained from assessing the methodological quality (i.e. internal validity) other than presenting the level of evidence. The study design and level of evidence were rated according to the National Health and Medical Research Council (MRC) Hierarchy of Evidence.¹⁶

Data extraction and analysis

A data-extraction form was used to register (1) child characteristics, (2) number of children treated, (3) indication for treatment with BoNT-A, (4) muscles injected, (5) doses of BoNT-A, (6) number of repeated injections, (7) outcome measures, (8) study design, (9) follow-up period, (10) side-effects, and (11) results.

To review treatment indications of BoNT-A in children with OBPI, we summarized the information of all studies. For summarizing the effectiveness, we combined studies that described the same study population. If two or more studies were published referring to the same study population and time frame, publications were combined. If necessary, authors were contacted by e-mail to clarify whether publications by the same authors were describing identical populations.

RESULTS

Included studies

The searches resulted in 201 hits. After applying the inclusion and exclusion criteria and completing the secondary search by reviewing the reference lists of other related papers, 10 full-text papers and six congress abstracts were included. Table I gives an overview of all 16 studies, their study designs, and levels of evidence.^{17–32}

The publications of Rollnik et al. and Hierner et al.,^{24,29} as well as the congress abstract of Schubert et al.,³⁰ refer to the same study population with identical results. To review the effectiveness, we merged the data of these studies to obtain a maximum of information. E-mail contact with the study group of Basciani showed that the abstract¹⁷ and the full article¹⁸ were referring to different populations; the abstract was not followed by the publication of a full article. Therefore, both were included. For the abstract²⁷ and full article²⁸ of Price et al., it should be noted that the study populations were overlapping. Whereas the abstract published in, 2005, describes the results of a large study population ($n=74$), the full article, published in 2007, only deals with 13 patients. Also different surgical procedures were included. Consequently we reviewed both studies^{27,28} (Table I).

Table 1: Overview of all studies (in alphabetical order of first author) and description of study design

Article	Year of publication	Country	Full-text article or congress abstract	Study design ^a	Level of evidence ^b	Indication for BoNT-A treatment ^c	Use of data to determine effectiveness
Basciani and Intiso ¹⁷	2002	Italy	Abstract	Prospective Case series Pretest/posttest	IV	1, 3, 4	Articles 17 and 18 refer to different study populations
Basciani and Intiso ¹⁸	2006	Italy	Full-text article	Prospective Case series Pretest/posttest	IV	1, 3, 4	Articles 17 and 18 refer to different study populations
DeMatteo et al. ¹⁹	2006	Canada	Full-text article	Prospective Case series Pretest/posttest	IV	1, 2	
Desiato and Risina ²⁰	2001	Italy	Full-text article	Prospective Case series Pretest/posttest	IV	1, 3, 4	
Grossman et al. ²¹	2003	USA	Full-text article	Retrospective Case series	IV	1	
Grossman et al. ²²	2004	USA	Full-text article	Retrospective Case series	IV	1	
Grossman et al. ³²	2004	USA	Full-text article	Expert experience	1	1	
Heise et al. ²³	2005	Brazil	Full-text article	Prospective Case series Pretest/posttest	IV	2, 3	
Hierner et al. ²⁴	2001	Germany	Full-text article	Case series Pretest/posttest ^d	IV	2	Data merged with those in articles 29 and 30
Johnstone et al. ²⁵	2007	Australia	Abstract	Case series ^d	IV	1, 2, 3	
Michaud et al. ²⁶	2007	USA	Abstract	Retrospective Case series	IV	1, 2, 3	
Price et al. ²⁷	2005	USA	Abstract	Case-control study ^d	III-3	1	Articles 27 and 28 largely refer to different study populations
Price et al. ²⁸	2007	USA	Full-text article	Retrospective Case-control study with historical control group	III-3	1	Articles 27 and 28 largely refer to different study populations
Rollnik et al. ²⁹	2000	Germany	Full-text article	Case series Pretest/posttest ^d	IV	2	Data merged with those in articles 24 and 30
Schubert et al. ³⁰	1998	Germany	Abstract	Case series Pretest/posttest ^d	IV	2	Data merged with those in articles 24 and 29
Stanton and Bainbridge ³¹	2002	UK	Abstract	Case series ^d	IV	1	

^aA case series/case-control study is a type of observational study. It draws inferences about the possible effects of a treatment on participants. To differentiate retrospective versus prospective, the following analogy can be considered. A retrospective (historic) study is different from a prospective study in the manner in which it is conducted. In a retrospective study, the investigator collects data from past records. ^bNational Health and Medical Research Council Hierarchy of Evidence: III-3, a comparative study without concurrent controls; historical control study, two or more single arm study, interrupted time series without a parallel control group; (IV) case series with either posttest or pretest/posttest outcomes. ^cFour groups of indications for BoNT-A treatment for children with OBPI: (1) internal rotation/adduction contracture of the shoulder; (2) limited active elbow flexion; (3) limited active elbow extension; (4) pronation contracture of the lower arm. ^dUnclear whether the study was prospective or retrospective.

Table II: Shoulder: internal rotation/adduction contracture (12 studies, more than 311 children)

Author/year of publication	Number of included patients for this indication	Muscles treated	Additional treatment	Age at the time of intervention	Neurosurgical intervention	Botulinum toxin dosage	Outcome assessment at the ICF level of body functions	Outcome assessment at the ICF level of activities	Results	Overall positive results
Basciani and Intiso 2002 ¹⁷	28	Pectoralis major	Plaster cast for 14d Physiotherapy	Mean age 5y 10mo (SD 3y 2mo)	No information available	20 international units per kilogram Dysport (Ipsen)	MRC ROM (passive and active) Mallet score	Nine-hole peg test	MRC and Mallet scores were unchanged Nine-hole peg test scores improved significantly and persisted for 12mo (time of follow-up) Success rate: not applicable	Not on all outcome measures
Basciani and Intiso 2006 ¹⁸	22	Pectoralis major	Plaster cast for 30d with fixed elbow extension, which was lengthened each week for 2wks). Physiotherapy and occupational therapy	10 females: mean age 5y 7mo (SD 2y 10mo) 12 males: mean age 5y 6mo (SD 3y 11mo)	No information available	200–400 units per single session 22 (SD 5.1) per kilogram Dysport	MRC ROM (passive and active) Mallet score	Nine-hole peg test	MRC values of deltoid, biceps, triceps were unchanged at 3, 6, and 12mo of follow-up. Nine-hole peg test scores improved significantly and persisted for 12mo. Little change in Mallet scores. Success rate: not applicable	Not on all outcome measures
DeMatteo et al. 2006 ¹⁹	3	Latissimus dorsi and pectoralis major	Intensive occupational therapy	21, 12, 15mo	2/3	4 units per kilogram per muscle Botox, Allergan	AMS EMG and joint kinematics (n=2)	Parent report of change (z)	AMS total score (including children with treatment for other indications) changed significantly. No statistically significant change in this group. Parent report of change: generally positive Success rate: function (AMS): 0/3	No

AMS, Active Movement Scale; EMG, electromyography; ICF, International Classification of Functioning, Disability and Health; MRC, Medical Research Council muscle strength grading scale; ROM, range of motion; (z), parents' subjective impression, in some cases describing activities.

Table II: Continued

Author /year of publication	Number of included patients for this indication	Muscles treated	Additional treatment	Age at the time of intervention	Neurosurgical intervention	Botulinum toxin dosage	Outcome assessment at the ICF level of body functions	Outcome assessment at the ICF level of activities	Results	Overall positive results
Desiato and Risina 2001 ²⁰	52	Pectoralis major/minor, teres major, subscapularis, latissimus dorsi	Reflex locomotion according to Vojta	Mean age 4y 8mo (SD 3y 5mo)	No information available	220 mouse units per millilitre 14.4 (SD 5.3) mouse units per kilogram 311 (SD 139) mouse units per single session Dysport Total number of injections: 99	ROM (active) Video: spontaneous movement	Global clinical rating scale (functional parents' assessment; expressed as the percentage of benefit) (z)	All children but two showed a clinical improvement due to BoNT-A treatment as assessed by goniometry. Abduction and external rotation (n=52): 50.1 (SD 16) and 76.2 (SD 19) (p<0.01) Global clinical rating scale: 70% showed step-like increments of function which lasted for 3.9 (SD 0.8) wks. Success rate: ROM (abduction-external rotation): 50/52	Yes
Grossman et al. 2003 ²¹	19	Pectoralis major, latissimus dorsi	Neurolysis of the upper brachial plexus with bypass nerve grafting. Release of shoulder contracture by a subscapularis slide. After removal of the postoperative cast: occupational therapy and physiotherapy.	Mean age 16mo (range 11–29mo)	19/19	Pectoralis major 70 units Latissimus dorsi 30 units	Modified Gilbert shoulder grading system		At the latest follow-up examination, all had improved by a mean of two grades Success rate: 19/19	Yes
Grossman et al. 2004 ²²	2	Pectoralis major, latissimus dorsi	Neurolysis and nerve grafting. Weekly occupational and physiotherapy	10 and 11mo	2/2	10 units per kilogram	Modified Gilbert shoulder grading system		Improvement was 3 and 4 grades (n=2) on the modified Gilbert score Success rate: 2/2	Yes

Table II: Continued

Author/year of publication	Number of included patients for this indication	Muscles treated	Additional treatment	Age at the time of intervention	Neurosurgical intervention	Botulinum toxin dosage	Outcome assessment at the ICF level of body functions	Outcome assessment at the ICF level of activities	Results	Overall positive results
Grossman et al. 2004 ³²	>60	Pectoralis major, latissimus dorsi	No information available	No information available	No information available	10 units per kilogram	No information available		In more than 80%, chemoneurolysis was realized Success rate: not applicable	Yes
Johnstone et al. 2007 ²⁵	12	No information available	Physiotherapy	24mo (range 7–42mo)	No information available	4–10 units per kilogram Botox (Allergan)	No information available		6 of 12 children with restriction of passive external rotation: excellent results, 4 of 12 good results. Success rate: 10/12	Yes
	5	Latissimus dorsi and/or teres major		8mo, and from 8 to 11y					5 of 5 children with latissimus dorsi and/or teres major co-contractions: minor gains (no detailed results) Success rate: 0/5	
Michaud et al. 2007 ²⁶	9	Latissimus dorsi and pectoralis major (n=7), only pectoralis major (in combination with surgical transfer latissimus dorsi, n=2)	No information available	No information available	No information available	No information available	No information available		13 of 16 children improved post injections (no detailed results). Success rate: 13/16	Yes
Price et al. 2005 ²⁷	74	Pectoralis major only (n=10) or in combination with latissimus dorsi (n=64)	Primary nerve reconstruction and later muscle transfer for restoration of external shoulder rotation	No information available	44/74	10 units per kilogram	Gilbert and Miami Shoulder Scales		Shoulder function grades were significantly better Success rate: not applicable	Yes

Table II: Continued

Author/year of publication	Number of included patients for this indication	Muscles treated	Additional treatment	Age at the time of intervention	Neurosurgical intervention	Botulinum toxin dosage	Outcome assessment at the ICF level of body functions	Outcome assessment at the ICF level of activities	Results	Overall positive results
Price et al. 2007 ²⁸	13	Pectoralis major	Surgical release of the contracture. Physiotherapy for a minimum of 3mo after 6wks of cast immobilization.	Mean age 5.8y (range 2y 10mo–12y 11mo)	No information available	100 units	Modified Gilbert shoulder evaluation scale		Significant improvement on the Modified Gilbert Scale between the BoNT-A-treated group and the comparison group postoperatively ($p=0.012$) Success rate: not applicable	Yes
Stanton et al. 2002 ³¹	12	Subscapularis	A part of the population in combination with coracoidectomy. physiotherapy	Mean age 41 mo	No information available	No information available	Gilbert and Tassin	Subjective assessment by the children's parents	Average passive external rotation of the shoulder increased by 40°C. Subjective assessment by the parents of overall shoulder function was very encouraging. Success rate: not applicable	Yes

Indications of BoNT-A treatment for OBPI

Four groups of indications for BoNT-A treatment for children with OBPI could be identified: (1) internal rotation/adduction contracture of the shoulder; (2) limited active elbow flexion; (3) limited active elbow extension; and (4) pronation contracture of the lower arm.

Internal rotation/adduction contracture of the shoulder

Seven articles^{18–22,28,32} and five congress abstracts^{17,25–27,31} could be identified for the indication of internal rotation/adduction contracture of the glenohumeral joint. Table II gives an overview of the studies describing BoNT-A treatment for this indication. A total of 311 children were treated and the largest study included 74 children.²⁷ In most cases the treatment included the pectoralis muscle, often in combination with the latissimus dorsi muscle.^{17–22,26–28,32} Varying combinations involving the subscapularis, teres minor, and teres major muscles were also mentioned.^{20,25,31} Grossman et al.^{21,22} and Price et al.^{27,28} describe a combination of BoNT-A treatment with surgery, followed by immobilization with a plaster cast (contracture release and/or nerve reconstruction). Physiotherapy and/or occupational therapy were applied as an additional therapy in most of the studies.^{17–22,28,31} The age of the children at the time of treatment ranged from 8 months to 12 years 11 months, but most were under 6 years of age.

Limited active elbow flexion

Four articles^{19,23,24,29} and three abstracts^{25,26,30} could be identified for the indication of limited active elbow flexion caused by triceps co-contraction (Table SI, supporting information published online). Twenty-five children were treated, and the maximum number of children treated within one study was six. Most of the children were under 4 years of age at the time of BoNT-A treatment. Neurosurgical treatment of the brachial plexus of any kind was, if explicitly mentioned by the authors, provided for a large part of the study population.^{19,23,24,29} Additional physiotherapy^{23,24,29} or occupational therapy¹⁹ was not always mentioned.

Limited active elbow extension

Table SII (supporting information published online), describes the characteristics of three articles^{18,20,23} and three abstracts^{17,25,26} in which BoNT-A treatment was applied for limited active elbow extension caused by predominating biceps muscle activity^{17,18,20,23,26} and biceps/triceps co-contraction.²³ In 35 children, only the biceps brachii muscle was treated with BoNT-A. In 72 children, the brachialis and brachioradialis muscles were also treated.^{18,20} On average, the age of the children was 4 to 5 years in the Desiato and Risina²⁰ and Basciani and Intiso^{17,18} studies, and 2 years in the Heise et al.²³ and Johnstone et al.²⁵ studies. Neurosurgical treatment of the brachial plexus was only mentioned by Heise et al.,²³ with neurosurgical plexus neurolysis in two of four cases. Basciani and Intiso^{17,18} used a plaster cast as additional treatment. Physiotherapy, partly in combination with occupational

therapy^{17,18,23} and Vojta therapy²⁰ were other additional treatments.

Pronation contracture of the lower arm

Table SIII (supporting information published online), gives an overview of BoNT-A treatment for pronation contracture. Two articles^{18,20} and one abstract¹⁷ could be identified for the indication of pronation contracture. Desiato and Risina²⁰ mentioned 59 injections of the pronator teres muscle in 20 children, and 50 children were treated in the studies by Basciani and Intiso.^{17,18} In all studies the pronator teres muscle was treated in combination with shoulder and elbow muscles. The mean age of the children at the time of treatment was around 5 years. No information about neurosurgical treatment of the brachial plexus was given in the publications. Additional treatment consisted of physiotherapy,^{17,18} occupational therapy,¹⁸ and Vojta therapy.²⁰

Effectiveness of BoNT-A treatment for OBPI

The effects of BoNT-A for children with OBPI are described for each indication separately. The 16 articles and congress abstracts describe the treatment results of 14 studied populations of children with OBPI.

Internal rotation/adduction shoulder contracture

Positive results were reported by nine of 12 studies,^{20–22,25,26,28,31,32} and in four cases there was improvement on the modified Gilbert shoulder grading system.^{21,22,28} No significant improvement on the Active Movement Scale shoulder score was reported by DeMatteo et al.¹⁹ (Table II). No detailed description of the effects was given by Michaud et al.²⁶ or Price et al.²⁷ Further, Basciani and Intiso^{17,18} did not evaluate the shoulder separately. Aiming to achieve further gains, some children were given repeated BoNT-A injections, some with a higher dose.²⁵ The children had a follow-up of 3 to 12 months,^{17–20,31} but in some studies there was a follow-up of more than 2 years.^{21,22,27,28} The most commonly used methods of evaluation were the Gilbert evaluation scale^{21,22,27,28,31} and the range of motion of the shoulder.^{17,18,20}

The (non-)occurrence of adverse events was explicitly mentioned in a few studies,^{18,20,28} with no complications reported in the study by Price et al.²⁸ A transient weakness of the adductor/internal rotator muscles, in one case lasting 10 days, was mentioned by Desiato and Risina,²⁰ and a dose of 11.7 mouse units (m.u.)/kg was used for the second injection session. Basciani and Intiso¹⁸ described adverse events, but these were most certainly caused by the plaster cast and not by the BoNT-A injections (articular pain after removing the plaster cast in two children).

Limited active elbow flexion

All five studies^{19,23–26,29,30} reported improvement after BoNT-A treatment, assessed with different measurement instruments, although Michaud et al.²⁶ reported no specific results for this indication. For the study population of Rollnik/Hierner/Schubert,^{24,29,30} as well as for the study

populations of Heise et al.²³ and DeMatteo et al.,¹⁹ improvement was reported persisting for the time of follow-up, varying from 3 to 18 months. Repeated injections were given in the study by Rollnik/Hierner/Schubert^{24,29,30} to achieve stable elbow flexion. The follow-up time ranged from 4 to 18 months. Electromyography (EMG) evaluation of all children before and after treatment was described for one study population, as well as the non-occurrence of adverse events.^{24,29,30} The most frequently used methods for the evaluation of treatment were the MRC muscle strength grading scale^{23,24,29,30} and the hand-to-mouth movement test^{23,24,29} (Table SI).

Limited active elbow extension

Three of six studies^{17,18,20} reported improvement in active elbow extension after treatment with BoNT-A treatment. Two studies reported no benefits or only minor benefits^{23,25} (Table SII). No description of the results for this indication was given by Michaud et al.²⁶ If the improvement was not sustained, repeated injections were given up to three times in the study by Basciani and Intiso,¹⁸ and in almost two-thirds of the cases in the study by Desiato et al.²⁰ The follow-up period in these studies varied from 3 to 12 months. Only two studies mentioned the (non-)occurrence of adverse events.^{18,20} A transient weakness of the adductor/internal rotator muscles of the shoulder, as described above, was probably caused by simultaneously treated shoulder muscles, rather than by treatment in the biceps muscle.²⁰ As mentioned earlier, Basciani and Intiso¹⁸ described adverse events that were most certainly caused by the plaster cast (articular pain after removing the plaster cast in two children). A diversity of outcomes was measured, with range of motion^{17,18,20} and the MRC muscle strength grading scale^{17,18,23} being the most frequently reported measures.

Pronation contracture of the lower arm

In three studies BoNT-A injections were given to reduce the pronation contracture (Table SIII). In the study by Desiato and Risina,²⁰ BoNT-A resulted in an improvement in active supination. Basciani and Intiso¹⁸ described a reduction in pronation contracture for the same children whose active elbow extension also improved significantly. The follow-up period was 9 to 12 months after treatment. No other adverse effect was described, other than those mentioned earlier.^{18,20} The outcome measures were range of motion, the MRC muscle strength grading scale, the Mallet score,³³ the nine-hole peg test, video-taped recordings to document spontaneous movements, and functional assessment as perceived by the parents.

DISCUSSION

In this article we have reviewed the available literature on BoNT-A treatment for children with OBPI. We included 16 studies of 14 populations published by researchers from four different continents, indicating the worldwide use of, and interest in, BoNT-A treatment for this group of children. The identified articles were mostly retrospective case series. The lack of prospective, randomized controlled trials shows that

BoNT-A treatment for children with OBPI is still at an experimental stage. Nevertheless, the literature that has been published so far provides us with useful information about different aspects of BoNT-A treatment for children with OBPI.

Indications

Overall, four indications for BoNT-A treatment could be identified. The treatment goal was partly achieved in combination with other therapeutic interventions, for example physiotherapy, plaster cast, neurosurgery, or orthopaedic surgery. Nevertheless, identifying these four different indications makes it possible to give a better overview and comparison of BoNT-A treatment. The four indications represent common limitations in active range of motion in children with OBPI caused by the imbalance or co-contraction of agonistic and antagonistic muscles.

The exact indication criteria that were applied for treatment with BoNT-A were not clearly stated or defined by the authors, and no clear inclusion or exclusion criteria were found, probably because of the experimental state of BoNT-A treatment for children with OBPI.

However, for the limited range of motion of the elbow, caused by co-contraction of triceps and biceps muscles, surface EMG of the affected muscles seems to be a relatively easy way to confirm the presence of co-contraction. After BoNT-A injections, surface EMG can be used to evaluate the reduction in co-contraction of elbow muscles. Because co-contraction was only found once in our review as a reason to apply BoNT-A treatment for limited active elbow extension, EMG evaluation was not used for this indication.

The shoulder joint has more degrees of freedom, with more muscles involved than the elbow joint. This means that there is often more than one agonist and antagonist for each of the six possible anatomical movements. Consequently, many different muscles and combinations of muscles are often treated with BoNT-A for the same indication. Both muscle imbalance and co-contraction are a reason for BoNT-A treatment of shoulder muscles. In those cases in which co-contraction is the reason for treatment, surface EMG is not able to provide us with information about deeper-lying muscles, such as the subscapularis muscle. Needle electrodes would be required to obtain a useable EMG signal from deeper-located muscles. Because the patients are usually young at the time of the treatment, this is not feasible, so it is difficult to prove co-contraction for this indication. In addition, in most of the studies we reviewed, BoNT-A treatment for the shoulder muscles was given in combination with other types of treatment, such as surgical reconstruction of an already structural joint limitation, or muscle transfer, to improve the muscle balance. The pronation contracture seems to be a less common indication for BoNT-A treatment, and was part of more comprehensive BoNT-A treatment of the upper extremity.

Effectiveness

The quality of this systematic literature review was highly influenced by the low methodological quality of the individual

articles and abstracts included. Therefore, the structure of our review slightly deviates from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for studies that evaluate health-care interventions.³⁴ It should be noted that the low internal validity of the included studies caused biased results in the summarized effects of BoNT-A in OBPI. In general the results of the (mainly level IV) studies of BoNT-A treatment for children with OBPI are positive and longer lasting than the pharmacologically expected duration of the effect of BoNT-A, with a follow-up period that often lasts for more than 1 year. BoNT-A treatment of the triceps muscle, exclusively for the indication of co-contraction, seems to be more successful than treatment of the biceps muscle. However, the absence of randomized controlled trials and the poor methodology of the studies we reviewed lead us to conclude that the evidence is at best weak. More than a third of the included studies are congress abstracts, representing nearly a quarter of the included children. For the indication of limited elbow flexion and pronation contracture, 40% of the children have been included through abstracts. Without the inclusion of congress abstracts, the overall results of BoNT-A treatment for the indication of limited elbow extension would be more positive. As can be learned from experience with BoNT-A treatment for the upper extremity in children with cerebral palsy (CP), even with studies of high methodological quality, it remains difficult to find evidence of the effect of BoNT-A on range of motion.³⁵

Child characteristics

When we look at the mean age of treatment, children with a limited active range of motion in the elbow are treated earlier (usually from about 2 to 4 years of age) than children with a shoulder contracture. Two studies explicitly mentioned the correlation between young age at the time of BoNT-A treatment and the best results.^{18,20} Explanations could be that contractures are more likely to be reversible, and less osseous deformities are present at a younger age. Spontaneous neurological recovery and recovery after neurosurgical treatment are also more likely to occur at a younger age. The suggestions that central nervous mechanisms can be a reason for age-related success, and can, even more so, be a possible general explanation for the long-lasting effect of BoNT-A treatment on OBPI, is a subject of intense debate.^{36–38} Although there is no evidence that BoNT-A acts directly on structures of the central nervous system, several studies suggest that BoNT-A affects the functional organization of the central nervous system indirectly through peripheral mechanisms.³⁷ Brown et al.³⁶ suggest that, although OBPI is a peripheral nerve injury, the resulting impairment is, at least partly, a form of developmental apraxia caused by disturbed motor programming in early infancy. Contrary to this theory, Van Dijk et al.³⁸ argue that the suggested motor apraxia can be explained through aberrant outgrowth as a matter of axonal repair. At the same time, Van Dijk et al.³⁸ do not exclude the involvement of central nervous mechanisms. Deafferentation due to OBPI, as well as feedback from the movement of co-

contracting muscles innervated by split axons, might affect central motor programming. Although these mechanisms are usually hard to document, the observation that children with OBPI neglect their affected limb during certain activities also suggests central nervous involvement in OBPI.³⁸

Dose

In children with CP, BoNT-A has already been used for a long time to reduce spasticity-associated co-contractions of the lower and upper extremity,³⁹ and this has provided experience and information about dosages.^{40–42} The dosages of Botox (Allergan, Irvine CA, USA) recommended for children with CP are far lower than those given to children with OBPI.^{6,17–32} The dosages recommended for the upper extremity muscles of children with CP range from 0.5 to 3 units per kilogram per muscle, whereas the dosages reported for children with OBPI are usually 4 to 10 units per kilogram per muscle. Whether the choice of higher dosages for children with OBPI was based on the personal experience of the authors or other reasons was not described in the articles included in our review. We did not find such differences between the dosage of Dysport (Ipsen, Brisbane, CA, USA) used for children with OBPI^{18,20} and the most commonly used dosage for the treatment of children with chronic muscle spasticity.⁴³ Details describing the application of BoNT-A (electro-stimulation, EMG guidance) to ensure treatment of the desired muscles were very scarce. EMG guidance was mentioned twice^{29,30} and electro-stimulation only once.³¹ General anaesthesia during BoNT-A treatment can be assumed in those cases in which BoNT-A was applied in combination with a shoulder operation; otherwise, it was only mentioned once.³¹

Outcome measures

The most commonly used outcome measures were the joint range of motion and the MRC muscle strength grading scale. Eight other measures were used, each being used in one or two studies. This can be explained to a certain extent by the use of specific tests for different muscle groups, e.g. the modified Gilbert score for the shoulder. If used for the same indication, the large variation in outcome measures makes it difficult to compare the results of the various studies. Applying the ICF¹⁴ model, most outcome measures could be classified as measuring at the level of body functions and structures. Hardly any methods were used to measure the influence of BoNT-A on the level of activities (e.g. hand to mouth). Depending on the content documented, 'parent report of change' could be a change in activity. The Mallet score³³ is often mistakenly classified as measuring at the level of activities, but it actually measures body functions and structures. Considering the fact that the aim of rehabilitation treatment should be to improve the performance of age-appropriate daily activities, almost solely measuring changes in body functions and structures does not seem to record the targeted effect.

The effect of BoNT-A treatment should preferably be evaluated by measuring a combination of body functions and structures, including strength (e.g. with the MRC muscle strength grading scale, Gilbert and Tassin, Active Movement Scale) and

passive and active joint range of motion, and evaluating the influence on activities involving the arm and hand. The difficulty, though, is specifically to measure the influence of BoNT-A treatment on the level of activity. Instruments such as the Paediatric Evaluation of Disability Inventory and the Vineland Adaptive Behavior Scale measure compensation strategies to perform activities of daily life with the non-affected arm rather than the actual improvement of the treated side.

Recommendation

This systematic review summarizes the state of the art for the treatment indications of BoNT-A in children with OBPI. For the effectiveness of BoNT-A in OBPI, our review was limited by the small number of studies available, the absence of randomized controlled trials, and the low quality of the remaining studies. A well-established, multicentre randomized clinical

trial, with well-defined and objectified inclusion criteria and primary treatment goals of BoNT-A in these children, preferably with a functional child-related outcome measure, is clearly needed to determine the benefits and efficacy that would support continued use of this intervention in managing muscle imbalance and muscle co-contraction in children with OBPI.

ONLINE MATERIAL

The following tables from this article are published online only:

Table SI: limited elbow flexion (five study populations with 25 children)

Table SII: limited elbow extension (six studies, 107 children)

Table SIII: Elbow/wrist: pronation contracture (three studies, 70 children)

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