Chapter 5

Botulinum toxin injection for internal rotation contractures in obstetric brachial plexus injury A minimum 5-year prospective observational study

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ABSTRACT

Background: Obstetric brachial plexus injury (OBPI) is frequently associated with internal rotation contractures of the shoulder as a result of muscle imbalance. The purpose of this study is to assess the effect of botulinum toxin A (BTX-A) injection in the subscapular muscle on external rotation and the need for tendon transfer for external rotation of the shoulder.

Methods: A prospective comparative study was performed including 15 consecutive patients treated with BTX-A and a historic control group of 67 patients with mean age 30 months (SD 10). The BTX-A injection (2 IU/kg body weight) was performed immediately following MRI under general anesthesia in the subscapular muscle. Passive external rotation, the need for tendon transfer surgery, glenohumeral deformity and muscle degeneration were evaluated. The hazard ratio for no relapse of internal rotation contracture after BTX-A injection compared to no BTX-A injection was calculated.

Results: In the BTX-A group, the passive external rotation in adduction increased from -1° (95% CI -10 to 8) to 32° (95% CI 17 to 46) at 3 months and 6 patients were indicated for surgery compared to a decline from -2° (95% CI -7 to 3) to -11° (95% CI -17 to -6) in the control group with 66 indications for surgery. At 5 years follow-up, 10 patients in the BTX-A group were indicated for surgery with a hazard ratio of 4.0 (95% CI 1.9 to 8.4).

Conclusions: BTX-A injection in the subscapular muscle of OBPI patients can reduce internal rotation contractures and subsequently the need for tendon transfer surgery. At 5 years follow-up a relapse was seen in 67% of the patients treated with BTX-A. Since at MRI less SC degeneration was found in the good responders on BTX-A treatment, this group seems to be the best target group. Further research is needed on patient selection for BTX-A injection including glenohumeral deformity, subscapular degeneration as well as doses of BTX-A to be used.

Level of Evidence: Level II - prospective comparative study.

INTRODUCTION

Obstetric brachial plexus injury (OBPI) patients often develop internal rotation contractures with a prevalence of up to 39% depending on the extent and severity of the brachial plexus injury [1, 2]. Several theories on the origin of an internal rotation contracture in OBPI patients exist. The muscle imbalance theory states that OBPI leads to muscle imbalances around the shoulder, in which internal rotators are stronger resulting in an internal rotation contracture [3, 4]. But also posture by which the injured extremity is held close to the body to enable easier bimanual activities, will cause a contracture if this position is unopposed by active external rotation. Recently an animal study has shown that selective denervation of the subscapular muscle (SC) alone leads to SC atrophy and internal rotation contracture indicating that weakness of the external rotators are not solely responsible for the muscle imbalance causing internal rotation contracture [5]. Furthermore, excision of the external rotators in mice without brachial plexus injury caused no contractures or shortening of the SC muscle [6]. Previously, MRI studies have shown that upon brachial plexus injury the muscle degeneration was most prominent in the SC muscle [7].

Treatments of internal rotation contractures include surgical SC release. These techniques are combined with transfer of a latissimus dorsi and/or teres major tendon to the rotator cuff to create active external rotation to improve arm function and quality of life [8-10]. Disadvantages of SC release and/or tendon transfer include weaker adduction and potential partial power loss of internal rotation with a subsequent risk for an external rotation contracture of the shoulder. A less invasive method to address the internal rotation contracture is the injection of botulinum toxin A (BTX-A) [10-12]. There have been some reports on BTX-A injections but no clear conclusions can be drawn from these studies since the heterogeneity was large (ie number of BTX-A injections, variety of muscles, combination with tendon transfer surgery) [13-18].

Our hypothesis is that injection of BTX-A into the SC muscle alone could temporarily weaken its function to open a time window primarily for the treatment of the internal rotation contracture with intensive physical therapy, but also to give the external rotation movement time to get "learned" (i.e. cerebral plasticity) again during global movement of the upper extremity. There have been no reports on BTX-A injection in the SC to treat internal rotation contracture of OBPI children without tendon transfer surgery.

The primary objective of the present study was to assess the efficacy of BTX-A injection in the SC on the passive external rotation (PER) in children with OBPI. Because of a potential increase of PER, the need of tendon transfer could decrease after BTX-A treatment. Therefore the second objective was to assess the effect of BTX-A injection on the number of indications for tendon transfer surgery. The

third objective was to investigate whether patient or MRI characteristics influence BTX-A treatment.

METHODS

Patients

A prospective comparative study was performed with at least five year follow-up on 15 OBPI patients with an internal rotation contracture treated with BTX-A in the SC muscle. Clinical outcome of these BTX-A OBPI patients were compared to a historic prospective control group of 67 patients with an internal rotation contracture. BTX-A was used after written informed consent was obtained from the parents.

Between 1997 and 2009 all patients with OBPI were seen at the outpatient clinic of the Leiden University Medical Center. Only those patients with a progressive internal rotation contracture were included in the present study, regardless whether the OBPI lesion was initially treated conservatively or by nerve surgery. From 2007 onwards, all patients younger than 48 months old were injected with 2 IU/kg BTX-A (Botox ®, Allergan Inc.) in the two parts of the SC muscle. Patients treated before 2007 were used as a historical control group. Management of all patients, both the historical control group and the BTX-A group, consisted of daily stretching exercises supervised by a trained physical therapist for at least 3 months. A progressive internal rotation contracture was defined as an external rotation in adduction of less than 30 degrees. In all patients, the passive external rotation (PER) range of motion was reduced to 30° or less, and the Mallet functional shoulder score was 3 or less for the subsets hand-to-mouth and/or hand-to-head movement [19]. A standardized MRI of the shoulder was performed under anesthesia, which is part of the preoperative work-up for children eligible for an external rotation tendon transfer in our clinic [7]. In the control group, all patients eligible for MRI were considered to have a surgical contracture release and a tendon transfer after the MRI. The time elapsed between MRI and surgery depended on the surgical waiting list.

To reduce any potential sources of bias, consecutive patients were included. Furthermore, in both the historical patient group and the BTX-A group, patients were excluded if a complete posterior dislocation of the humeral head was present at MRI. A complete dislocation was defined as a smaller than 10% part of the humeral head being anterior to the longitudinal axis of the scapula (PHHA) [20]. These dislocated shoulders were considered to be beyond the point of a correctable joint. Patients with prior secondary orthopedic surgery or Raimondi hand function scale less than 3 were excluded as well [21].

The affected side, severity of the lesion according to Narakas, type of primary treatment and age at nerve surgery was recorded [22]. All patients were evaluated at 3 months and yearly after the BTX-A injection at the outpatient clinic. All patients completed 5 year follow-up and were included in the data analysis. If a tendon transfer was not indicated, then patients were scheduled for clinical follow-up. The medical ethical review board of the Leiden University Medical Center approved for the prospective database of orthopedic interventions of OBPI patients.

Clinical assessment

The PER of the glenohumeral joint was assessed in adduction and 90° abduction using a hand held goniometer. The passive external rotation range of motion was measured with the elbow flexed to 90° and with the hand of the examiner holding the scapula (i.e. the acromion). True glenohumeral external rotation range was measured at the position where the first sign of resistance (i.e. movement of scapula with respect to the humeral bone) while external rotating the arm was felt. No force was exerted on the arm in order to avoid a shift of the scapula which introduces a thoracoscapular component in the total external rotation range. Negative degrees denote internal rotation from neutral position. Furthermore, the passive glenohumeral abduction was measured and the passive internal rotation was measured in 90° abduction. The Mallet score was used to assess global active shoulder function [19].

BTX-A injection

The BTX-A injection was performed immediately following the MRI under general anesthesia in fifteen patients. In one patient the BTX-A injection was performed two months after the MRI was performed under general anesthesia. Patients were put in the lateral decubital position with the affected arm in maximum internal rotation and adduction to reach winging of the medial edge of the scapula. A flacon of 100 IU BTX-A was diluted in 10 ml 0.9% NaCl. In total, 2 IU per kg was injected per patient. A nine cm 22 gauge slightly bowed needle was inserted anterior of the medial scapular edge at one- and at two-thirds of the distance between the angulus superior and inferior of the scapula to block the motor endplates of the upper subscapular and the lower subscapular nerves. When the needle touched the scapular bone, the needle was retracted a few millimeters to ensure that the BTX-A was injected in the SC [23]. Slightly bowing the needle did never result in breaking. Furthermore, neurovascular injury or pneumothorax did not occur. After BTX-A injection parents were instructed to continue the daily stretching exercises just as before the BTX-A injection supervised by a trained physical therapist. Throughout the study there were no changes in the BTX-A injection or physical therapy instructions.

MRI

The MRI images were acquired using a 1.5 Tesla magnet (Philips Healthcare Inc.). T1 images were made in the transverse plane of the shoulder. For all sequences, the slice thickness was 4.0 mm with a 0.4 mm spacing gap. The degree of glenoid version and PHHA were measured in a transverse plane of the shoulder at midglenoid level, as previously described [7, 20, 24]. The degree of SC degeneration was measured on a 3-point visual scale. The SC was graded as normal if the diameter of the SC of the affected and the contra lateral shoulder were similar. The SC was graded as atrophic if the diameter was smaller. If fatty streaks were also present, the SC was graded as atrophic with fatty degeneration [7]. To measure the interobserver variability, 2 independent observers evaluated the PHHA and glenoid version of 15 patients (R.G.H.H.N. and B.J.D.) and the SC degeneration of 50 patients (S.H. and B.J.D.). One investigator (B.J.D.) repeated the scoring at an interval of two weeks to measure the intraobserver variability. The interobserver variability of the MRI variables was excelled for glenoid version (ICC 0.87), PHHA (ICC 0.96) and SC degeneration (kappa 0.77) as was the intraobserver variability for glenoid version (ICC 0.92), PHHA (ICC 0.96) and SC degeneration (kappa 0.79).

Statistical analysis

Statistical differences were tested by the Pearson's Chi-Square test for nominal categorical variables, the Fisher's exact test for nominal categorical variables if more than 20% of the cells had an expected value of less than 5 and the Mann-Whitney test was used for ordinal categorical variables. The Student independent sample t-test was used for continuous variables with 95% confidence intervals (CI). Differences in Mallet scores were tested using the Wilcoxon Signed Ranks test. Kaplan Meyer analysis was used to calculate survival probability of conservative therapy with 95% confidence interval of the BTX-A patient group. The interclass correlation coefficient (ICC) was calculated for reliability testing of the PHHA and glenoid version, using the 2-way random model with absolute agreement [25]. The linear weighted kappa was calculated for reliability testing of SC degeneration [26]. For interpretation, the criteria formulated by Cichetti and Sparrow were used: 0.00 to 0.39, poor; 0.40 to 0.59, fair; 0.60 to 0.74, good; or 0.75 to 1.00, excellent [27]. For statistical analysis a SPSS software package was used (SPSS Inc., version 20.0, Chicago, Illinois). For the Kaplan Meier analysis R was used (The R foundation for statistical computing, version 3.1.2, Austria). All analyses were two tailed and *p*-values < 0.05 were considered significant.

RESULTS

Range of motion

The individual characteristics of patients treated with BTX-A and the control group are summarized in Table I. No significant differences were found between gender, age, affected side, Narakas type and type of primary treatment. No adverse events were observed following BTX-A injection. The results of the PER and indications for tendon transfer surgery for both groups are summarized in Table II. At baseline, the mean PER in adduction was -1° (95% CI -10 to 8) in the BTX-A group and -2° (95% CI -7 to 3) in the control group. In the BTX-A group, the mean PER in adduction was increased to 32° (95% CI 17 to 46) after 3 months follow-up. In the control group, who eventually had surgery, the follow-up time was determined by the waiting list for surgery. All patients were assessed at the day before surgery again. The mean follow-up time of the control group was 5.7 (SD 2.2) months. These patients showed a further decline with a mean PER in adduction to -11° (95% CI -17 to -6).

The PER in abduction in the BTX-A group increased from 55° (95% CI 45 to 65) to 65° (95% CI 55 to 80, $p = 0.014$) after three months. No significant changes were observed after 1 or 5 years. The median passive abduction was 90 degrees (interquartile range 90-90) and did not change during follow-up. The passive internal rotation in abduction increased from 45° (95% CI 35 to 55) to 65° (95% CI 50 to 85, $p = 0.005$) after 5 years follow-up. The Mallet score did not significantly change for the BTX-A or the control group at follow-up.

Tendon transfer surgery

At follow-up after the BTX-A injections, patients were indicated for tendon transfer surgery if the internal rotation contracture persisted (PER in adduction 30° or less) in presence of no active external rotation, both indicating a Mallet functional shoulder score of 3 or less for the subsets hand-to-mouth and/or hand-to-head movement. Survival probability of conservative therapy is shown in the Kaplan Meier curve of figure 1. In the BTX-A group, six patients (40%) were indicated for tendon transfer after 3 months. Nine patients showed an improvement in PER in adduction and were therefore not indicated for tendon transfer surgery. In contrast, only one patient in the control group showed (spontaneous) good clinical function at follow-up and 66 patients (99%) were indicated for tendon transfer surgery. At 5 years follow-up, 10 patients (67%) in the BTX-A group showed an internal rotation contracture relapse and were therefore indicated for tendon transfer surgery. The hazard ratio for no relapse after BTX-A injection compared to no BTX-A injection was 4.0 (95% CI 1.9 – 8.4).

Table I Baseline characteristics

Number	Age*	Sex	Side	Narakas type	Primary treatment	Glenoid version†	PHHA	SC score#
BTX-A Group								
1	12	Female	Right	C5-C6	Conservative	-21	48	3
2	14	Male	Left	C5-C7	Nerve surgery	-28	17	3
3	16	Male	Right	C5-T1	Nerve surgery	-16	44	2
4	17	Male	Left	C5-C6	Conservative	-21	37	1
5	18	Male	Left	C5-C7	Nerve surgery	-38	40	3
6	21	Male	Left	C5-C6	Nerve surgery	-28	38	2
7	23	Male	Right	C5-C6	Conservative	-30	44	2
8	24	Male	Left	C5-C7	Nerve surgery	-29	16	3
9	41	Male	Left	C5-C6	Conservative	-22	39	1
10	42	Female	Left	C5-C6	Nerve surgery	-14	42	3
11	42	Male	Right	C5-C6	Neurolysis	-21	38	3
12	43	Male	Left	C5-C7	Nerve surgery	-9	46	3
13	44	Female	Right	C5-C6	Nerve surgery	-17	44	3
14	47	Female	Left	C5-C7	Nerve surgery	-18	39	3
15	51	Female	Right	C5-C6	Nerve surgery	-12	46	3
Control Group								
67 patients	30 (8.7)‡	30 male	40 right	34 C5-C6 27 C5-C7 1 C5-C8 5 C5-T1	14 conservative 3 neurolysis 50 nerve surgery	-21 (7.9)‡	32 (10.7)‡	5 score 1 15 score 2 47 score 3

*Age is given in months. † Glenoid version is given in degrees. # SC = subscapularis muscle was scored as 1: normal, 2: atrophic or 3: atrophic with fatty degeneration. ‡ The values are given as mean and standard deviation. MRI = magnetic resonance imaging, BTX-A = botulinum toxin A, PHHA = the percentage of the humeral head anterior to the transverse axis of the scapula.

Table II Clinical outcome of BTX-A injection vs. control group

Number	Passive external rotation in adduction (degrees)				Mallet score at final follow-up						Tendon transfer surgery at final follow-up (months)*
	Baseline	3 months	1 year	5 years	Abduction	External rotation	Hand - head	Hand - back	Hand - mouth	Aggregate	
BTX-A Group											
1	-10	60	25		4	1	4	4	2	15	36
2	-10	-15									3
3	30	65	20	40	4	3	4	4	3	18	None
4	0	40	40	25	4	2	4	4	4	18	None
5	0	10									3
6	10	50	30		4	1	4	4	3	16	36
7	10	20			4	1	3	3	3	14	3
8	-10	0			3	1	2	2	3	11	3
9	0	80	30	20	4	2	4	4	4	18	None
10	-40	40	-20		4	1	3	4	3	15	12
11	0	15			4	1	4	3	3	15	3
12	-10	20	0	10	3	1	3	3	3	13	None
13	15	25			4	1	3	2	3	13	3
14	0	45	35	25	4	1	4	2	3	14	None
15	0	20	0		2	1	2	3	2	10	24
Control group											
67 patients	0 (20)#	-10 (20)#			3 (1-4) †	3 (1-4) †	3 (1-4) †	3 (1-4) †	3 (1-4) †	3 (1-4) †	66 patients

Clinical outcome of the BTX-A group and the control group as baseline and follow-up. In the control group the mean follow-up time was 6 months which was the time elapsed between MRI and surgery depended on the surgical waiting. *Patients with relapse of internal rotation contracture were indicated for tendon transfer surgery. #Values are given as mean with standard deviation. †Values are given as median with range. BTX-A = botulinum toxin A.

MRI and patient characteristics

MRI characteristics of the BTX-A and the control group are shown in Table I. The glenoid version, PHHA and SC degeneration were not different between the groups. Of the 5 patients in the BTX-A group with still a good response after 5 years follow-up, the SC score was normal in 2 patients (40%), atrophic in 1 patient (20%) and atrophic with fatty degeneration in 2 patients (40%). Whereas in the 10 patients who were indicated for tendon transfer surgery, the SC score was normal in none of the patients, atrophic in 2 patients (20%) and atrophic with fatty degeneration in 8 patients (80%), however this was not significantly different (p = 0.08). No significant differences were found in age, gender, Narakas type, primary treatment, baseline PER, glenoid version or PHHA between the good responder group and the patients indicated for tendon transfer surgery.

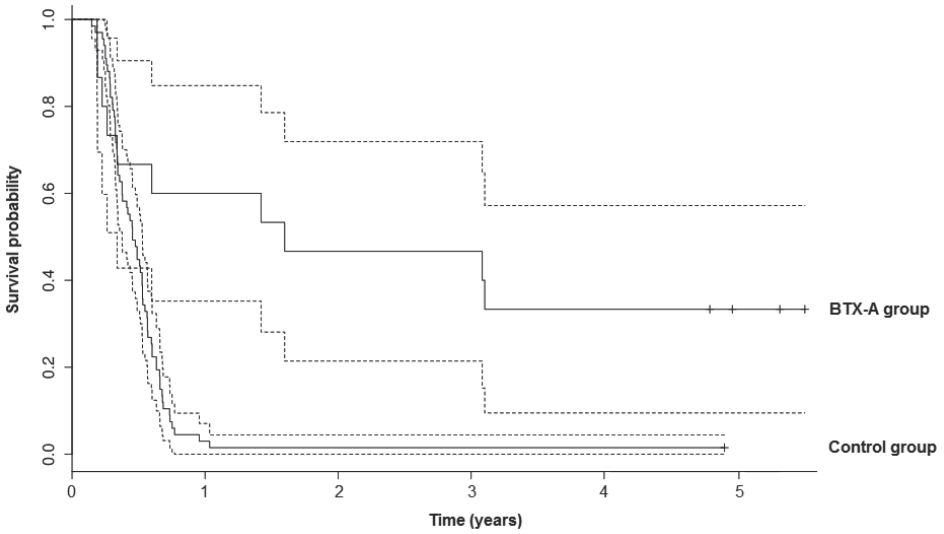

Figure 1: Survival after BTX-A treatment versus control group
Kaplan Meyer curve with survival probability of conservative therapy with 95 % confidence interval of the botulinum toxin A (BTX-A) and control group. Tendon transfer surgery was indicated if at follow-up the passive external rotation (PER) range of motion persisted at 30° or less and the Mallet functional shoulder score was 3 or less for the subsets hand-to-mouth and/or hand-to-head movement.

DISCUSSION

The purpose of the present study was to assess the efficacy of BTX-A injection in the SC to improve the PER in children with OBPI. No adverse events were observed, therefore BTX-A injection can be considered to be safe and feasible in this patient group with a mean age of 2.5 years old. The results of this study show that BTX-A injection increases PER in adduction compared to the control group. Addressing internal rotation contracture of the shoulder is important since progressive glenohumeral joint deformity occurs after persisting internal rotation contracture in OBPI [7, 20]. The reason to focus on the SC muscle to treat the contracture was that the SC muscle is the main constrained in adduction of the arm and source of internal rotation contracture. The results of this study are clinically relevant since the improvement of PER was sufficient to postpone tendon transfer surgery for at least five years and prevent tendon transfer surgery in 33% of patients in the BTX-A group. These good responders on BTX-A injection showed less SC muscle degeneration. This difference did not reach statistical significance, most probably due to the low number of patients treated. Lack of effect on BTX-A injection in degenerated muscle (fibrosis or fatty degeneration) could be a result of absence of a target for the BTX-A, since no or little muscle fibers are present.

In previous studies many different muscles were injected (pectoralis major and minor, teres major, SC and latissimus dorsi), in a variety of number of injections (1 to 4) and patients with a variety of ages (range 0.3 to 13.5 years old) [13-17]. In a recent study Michaud et al. found a mean increase of 6° in PER after BTX-A injections in the muscles which altered the surgical plan in 4 of the 18 patients, however also multiple muscles were injected (pectoralis major, SC and / or latissimus dorsi) in patients with variable ages (range 0.5 to 10 years) with short follow-up of 1 year [18]. The present study is the first controlled study on BTX-A injections in the SC of OBPI patients to correct internal rotation contractures.

In this study the improved clinical effect outlasted the therapeutic time window of BTX-A. This phenomenon could be explained by the time window opened by the BTX-A injection which causes relaxation of the SC muscle during which physical therapy could be more effective. Furthermore, relaxation of the SC muscle reduce afferent signals to the brain and gives time for cortical recruitment for the injured nerves leading to an altered balance between afferent input and motor output [15, 28].

Limitations of this study include the lack of long term (beyond five years) effects on PER and the need for tendon transfer surgery in the future remain unknown at this moment. Because glenohumeral joint morphology and SC degeneration affect shoulder functional outcome, we measured the PHHA, glenoid version and the SC degeneration of the affected and normal shoulder on MRI. As previously observed, we found a significant difference in glenoid version and PHHA of the affected

shoulder compared to the normal shoulder [7, 20]. This study excluded patients with severe glenohumeral deformity and/or complete posterior dislocation of the humeral head, since it was considered that this deformity was beyond a passively correctable joint. Finally, this study is a non-randomized study, thus confounders might be present for example the willingness of the parents to practice the external rotation.

In conclusion, this prospective observational study demonstrates that BTX-A injections in the SC of OBPI children with an internal rotation contracture reduces the internal rotation contracture and could potentially postpone and in some cases prevent external rotation tendon transfer surgery. The beneficial effect of BTX-A injection due to relaxation of the SC muscle opens a time window for both intensive exercises of external rotation, as well as teaching the child to make this movement part of its global movement of the extremity (i.e. cerebral plasticity). Both pathways will reduce the internal rotation contracture resulting in a new balance between the external and internal rotators of the shoulder. This is however not valid in all patients since at minimum 5 years follow-up a relapse of internal rotation contracture was seen in 67% of the patients treated with BTX-A. Since at MRI less SC degeneration was found in the good responders on BTX-A treatment, this group seems to be the best target group. BTX-A injection in multiple injection sites of the subcapular muscle could optimize the effectiveness of BTX-A treatment as anatomic studies showed variability of the subscapular innervations [29, 30]. This study focused on patients of 4 years old or younger as young patients may have more reinnervation potential and more cerebral plasticity to strengthen the external rotators. Future research could focus on patients older than 4 years to investigate whether or not the indication for BTX-A treatment could be extended to older patients with OBPI. Further research is needed on patient selection for BTX-A injection including glenohumeral deformity, SC degeneration as well as doses of BTX-A to be used and whether repeating the BTX-A injection could further reduce the internal rotation contracture.

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