Review

HAND
2019, Vol. 14(2) 150–154

DOI: 10.1177/1558944718760038
hand.sagepub.com

The Use of Botulinum Toxin Injection for Brachial Plexus Birth Injuries: A Systematic Review of the Literature

Patrick J. Buchanan[1], John A. I. Grossman[2], Andrew E. Price[3], Chandan Reddy[1], Mustafa Chopan[1], and Harvey Chim[1]

Abstract

Background: Most brachial plexus birth injuries (BPBIs) are caused by traction on the brachial plexus during a difficult delivery. Fortunately, the possibility of complete recovery from such an incident is relatively high, with only 10% to 30% of patients having prolonged and persistent disability. These patients have muscle imbalances and co-contractions typically localized around the shoulder and elbow. These imbalances and co-contractures cause abnormal motor performances and bone/joint deformities. Typically, physical/occupational therapies are the conventional therapeutic modalities but are often times inadequate. Botulinum toxin A (BTX-A) injections into targeted muscles have been used to combat the muscular imbalances and co-contractions. **Methods:** With compliance to PRISMA guidelines, a systematic review was performed to identify studies published between 2000 and 2017 that used BTX-A to treat neonatal brachial plexus palsies. **Results:** Ten studies were included, involving 325 patients. Three groups of indications for the use of BTX-A were identified: (1) internal rotation/adduction contracture of the shoulder; (2) elbow flexion lag/elbow extension lag; and (3) forearm pronation contracture. **Conclusions:** The included studies show an overall beneficial effect of BTX-A in treating co-contractures seen in patients with BPBI. Specifically, BTX-A is shown to reduce internal rotation/adduction contractures of the shoulder, elbow flexion/extension contractures, and forearm pronation contractures. These beneficial effects are blunted when used in older patients. Nevertheless, BTX-A is a useful treatment for BPBIs with a relatively low-risk profile.

Keywords: botulinum toxin, Botox, brachial plexus injury, brachial plexus, brachial plexus palsy

Introduction

A brachial plexus birth injury (BPBI) is a rare yet catastrophic event occurring in at least 1.5 per 1000 live births within the United States.[3,8,11] Fortunately, approximately two-thirds of these injuries are self-limiting and resolve spontaneously without lifelong deficits.[7] However, anywhere from 10% to 30% of infants will have permanent residual deficits that result in abnormal upper extremity development and function. BPBI is generally diagnosed upon birth, as the neonate demonstrates limitations in spontaneous upper extremity movement. This is confirmed clinically with a lack of Moro reflex on the affected side.

The brachial plexus is comprised of the C5 through T1 nerve roots. In neonatal injuries, the C5 and C6 nerve roots are the most commonly involved due to being more vertically oriented and vulnerable to traction injury.[1] The most common location of injury occurs in the upper trunk, more specifically at Erb's point. This injury is colloquially referred to as Erb's palsy and affects the suprascapular nerve as well as the anterior and posterior divisions of the upper trunk resulting in a medially rotated shoulder with an extended and pronated forearm. This position of the upper extremity provides little use to the patient, as they are unable to externally rotate the shoulder or flex the biceps which are two vital movements needed for feeding and self-care.

Many studies within the literature have sought to characterize the sequelae of permanent brachial plexus injuries. Incomplete nerve recovery results in worsening internal shoulder rotation as a result from an intact pectoralis major and subscapularis motor function. In addition,

[1]University of Florida Health, Gainesville, USA
[2]Nicklaus Children's Hospital, Miami, FL, USA
[3]NYU Hospital for Joint Diseases, New York City, USA

Corresponding Author:
Harvey Chim, Division of Plastic and Reconstructive Surgery, University of Florida College of Medicine, 1600 SW Archer Road, Gainesville, FL 32608, USA.
Email: harvey.chim@surgery.ufl.edu

glenohumeral dysplasia and shoulder internal rotation contracture occur.

Initially, BPBIs are treated conservatively using therapy with splints and range of motion exercises. For infants who fail to spontaneously regain function, microsurgical reconstruction is used when there is no return of biceps function after 3 to 9 months.

Despite the intervention performed, whether surgical or rehabilitative, studies have shown that residual muscle imbalances remain. These muscle imbalances develop when the brachial plexus injury weakens a certain muscular group more so than others. These muscle imbalances often times cause movement restriction by three mechanisms: (1) Differential muscular weakness perpetuates power imbalance; (2) during neuromuscular healing, agonist and antagonist muscle groups can develop aberrant co-contraction activity; (3) muscular imbalance can lead to structural joint deformities. These muscle imbalances lead to co-contractions causing impaired joint motion.[2,4,5,12,14,15] Co-contractions are identified clinically and confirmed using electromyographic studies. However, the pathophysiology of such co-contractions remains unclear. Nonetheless, multiple studies have reported positive improvements in shoulder and elbow motion following the use of botulinum toxin type A (BTX-A) in infants and children with BPBI.[5,6,15] Injecting BTX-A into antagonist muscle groups improves the synergistic muscle balance seen in BPBI.

BTX-A is a reversible neurotoxin used primarily in cosmetic surgery, ophthalmology, urology, and neurology. BTX-A has gained Food and Drug Administration (FDA) approval in the use of both upper and lower limb spasticity in adults; however, it has not yet been FDA approved for similar uses in the pediatric population.[4] The rationale for use is to temporarily weaken the antagonist muscles, which allows for better muscular balance via strengthening of the agonist muscles and promoting motor learning at the central nervous system level. Although BTX-A has a relatively short half-life of approximately 4 months, it is believed that the long-term benefits outlast its direct biological effect.

The aim of this study is to perform a systematic review to analyze previously published studies evaluating the use of BTX-A in treating BPBI.

Materials and Methods

Study Selection

Maintaining compliance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, 3 reviewers (P.J.B., M.C., and H.C.) conducted a systematic literature search within the MEDLINE, Embase, and Cochrane Central Register of Controlled Trial databases. All articles published between 2000 and 2017, with English as the primary language, were identified. Combinations of the following MeSH terms were used to conduct the search: "botulinum toxin," "birth palsy," "brachial plexus injury," and "brachial plexus palsy." The 3 reviewers independently performed each step in the study selection process. Cross-referencing initial articles found via the initial keyword searches allowed for the identification of additional articles. Ambiguous articles were sent to the senior author, H.C., for final determination for inclusion. Articles were included if they met the following criteria: (1) comparative retrospective studies, case reports, or prospective reports that reported clinical outcomes following BTX-A for BPBI; and (2) reported cases without additional history of trauma on the affected arm. Articles containing review articles, abstracts, cadaveric studies, editorials, and commentaries were excluded.

Data Extraction

From the included studies, the 3 reviewers independently assessed the quality and methodology of each study meeting the inclusion criteria. These articles were then further analyzed looking at patient population, interventions, and associated outcome/complications/recurrence rates. Baseline data including indication for treatment with BTX-A, muscles injected, functional improvement, and follow-up period for each study were collected. The level of evidence for each article was assessed using the standardized reporting scheme provided by the Oxford Centre for Evidence-Based Medicine (OCEBM).

Results

Search Results

Initial systematic search of the MEDLINE, Embase, and Cochrane Central Register of Controlled Trial databases using the aforementioned keywords yielded 23 articles. After the selection process using the inclusion and exclusion criteria detailed above, 10 studies were deemed eligible for inclusion in our systematic review. These 10 studies were comprised of 3 prospective cohort studies, 5 retrospective cohort studies, 1 case series, and 1 case report. There were a total of 325 patients. Table 1 summarizes the OCEBM levels of evidence for each included article.

Indications for the Use of BTX-A

Three groups of indications for the use of BTX-A were identified: (1) internal rotation/adduction contracture of the shoulder; (2) elbow flexion lag/elbow extension lag; and (3) forearm pronation contracture.

Internal Rotation/Adduction Contracture of the Shoulder

Eight articles were identified describing the indication for BTX-A on internal rotation/adduction contracture of the

Table 1. Study Design and OCEBM Level of Evidence for the Included Studies.

Authors and years	Study design	OCEBM scale (level of evidence)
Basciani and Intiso, 2006[2]	Prospective cohort	Level III
DeMatteo et al, 2006[4]	Case series	Level IV
Desiato and Risina, 2001[5]	Prospective cohort	Level III
Price et al, 2007[14]	Retrospective cohort	Level IV
Rollnik et al, 2000[15]	Retrospective cohort	Level IV
Duijnisveld et al, 2017[6]	Prospective comparative	Level III
Greenhill et al, 2018[9]	Retrospective cohort	Level IV
Michaud et al, 2014[13]	Retrospective cohort	Level IV
Shin et al, 2014[16]	Case report	Level V
Hierner et al, 2001[11]	Retrospective cohort	Level IV

Note. OCEBM = Oxford Centre for Evidence-Based Medicine.

glenohumeral joint.[2,4-6,9,13,14,16] A total of 220 patients were treated with BTX-A within these 8 articles. The BTX-A was injected into the pectoralis muscle and often times in combination with the latissimus dorsi muscle.[2,4-6,9,13,14,16]

Shin et al performed a prospective case report of 4 patients whose shoulder abduction function was not improved by occupational therapy/physical therapy(OT/PT) alone. BTX-A was injected intramuscularly into the pectoralis major muscle and functional improvement monitored 1 and 6 months post injection. Three of the 4 patients experienced improvement in shoulder mobility. The last patient, who was the oldest (13 years 5 months), had no functional improvement from the BTX-A injection.[16]

Greenhill et al studied 49 patients who received BTX-A injections into the shoulder internal rotators, namely the latissimus dorsi/teres major complex, pectoralis major, and subscapularis muscles during closed glenohumeral reduction and casting. Passive external rotation improved in all patients during the study period. Age was not found to be a predictor of outcomes.[9]

Duijnisveld et al performed a prospective comparative study with a 5-year follow-up including 15 patients with internal rotation contracture treated with BTX-A injected into the subscapularis muscle. The passive external rotation increased 10 degrees after 3 months and no significant changes were seen after 1 or 5 years.[6]

Michaud et al performed BTX-A injection into the latissimus dorsi, pectoralis major, and upper subscapularis muscles followed by OT/PT. Fifty-one patients were included, and the mean age at injection was 30.4 months old. Six months after injection, they noted an average global shoulder external rotation improvement in 18 of the 51 patients (35.5%). They also found an average increase of 10° in shoulder external rotation in 22 of the 51 patients (43.1%).[13]

DeMatteo et al performed BTX-A injections into the latissimus dorsi and pectoralis major muscles in 3 patients. All 3 children had an increase in voluntary shoulder movement; however, this was not found to be statistically significant. Regardless, they found that the increase in shoulder movement was maintained at 4 months post injection.[4]

Basciani and Intiso performed BTX-A injection into the pectoralis major muscle in 22 patients followed immediately by plaster casting. These 22 patients previously failed serial casting. All but 4 patients showed significant improvement in shoulder mobility following a single BTX-A injection. These improvements persisted at 12 months post injection. The 4 patients who did not significantly improve were found to be of an older age, mean 7.5 years old.[2]

Price et al retrospectively reviewed 26 patients who underwent reconstruction for an internal rotation deformity of the shoulder via surgical release of the contracture using a subscapularis slide and transfer of the latissimus dorsi and teres major muscles into the rotator cuff. In 13 of these patients, BTX-A was injected into the pectoralis major muscle at the conclusion of the reconstructive surgery. The other 13 patients did not receive BTX-A injections following the surgery. The authors found a statistically significant improvement in shoulder mobility in the 13 patients who received the BTX-A injection versus their counterparts who did not.[14]

Desiato and Risina studied 50 patients and matched their results after BTX-A injections to the same patient's mobility results 1 month prior to entering the study. Each patient acted as his or her own control. The muscles injected included the pectoralis major and minor, teres major, subscapularis, and the latissimus dorsi. The authors noted a statistically significant increase in shoulder abduction and external rotation following BTX-A injection as compared with the preinjection measurements.[5]

Limited Active Elbow Flexion/Extension

Five articles were identified that utilized BTX-A for the treatment of biceps/triceps co-contractures.[2,4,10,13,15] A total of 60 patients with biceps/triceps co-contracture were

treated with BTX-A injections into the triceps musculature to help with meaningful elbow flexion.

Michaud et al cited a 67% improvement in elbow flexion after injection of BTX-A into the triceps.[13] DeMatteo et al performed BTX-A injections into the 3 heads of the triceps to facilitate elbow flexion with continuation of home OT. Three patients underwent BTX-A injection following reconstructive surgical attempts. All 3 of these patients were reported to have regained full spontaneous extension during play and during postural adjustments. Two patients underwent BTX-A injection into the triceps heads prior to reconstructive surgery. Unfortunately neither one of these patients showed any improvement in active extension/flexion and required reconstructive surgery at 9 months of age.[4]

Basciani and Intiso performed BTX-A injections in 22 patients who were previously unsuccessfully treated with serial casting. After BTX-A injection and plaster cast treatment, they cited a significant improvement in active elbow extension in all but 4 patients. They noted that the improvement persisted at 12 months despite further injections. They also noted that the 4 patients who did not respond were of an older age.[2]

Hierner et al performed BTX-A injections in 12 patients with severe biceps/triceps co-contractions. At the 18-month postinjection time point, all patients were free from co-contractions.[10]

Rollnik et al, like Hierner et al, enrolled 12 patients with co-contraction of the biceps/triceps. They noted an onset of response after an average of 8.5 days from the injection of BTX-A. They noted that 5 patients were able to perform hand-to-mouth motions without any clinical recurrence after a 1-year follow-up.[15]

Forearm Pronation Contracture

Two articles with a total of 45 patients evaluated the use of BTX-A in relief of forearm pronation contracture.[5,13] Michaud et al performed BTX-A injection into the pronator teres followed by OT/PT. Fifteen patients were included, and the mean age at injection was 17.1 months old. Four of the 15 patients previously underwent primary brachial plexus reconstruction. Fourteen of the 15 patients had no active supination past neutral prior to the BTX-A injection. After injection, 11 of the 15 patients regained some supination past neutral, and 2 patients were within functional limits of >50°.[13] Desiato and Risina performed repeated BTX-A injections in 30 patients. Injections were repeated before the muscular imbalance recurred. This muscular imbalance was identified via goniometry. Most of the repeated injections were performed at the end of the fourth and fifth months following the initial injection. It was noted that the youngest patients noted an awareness of their improved global motility of the affected arm after 2 to 5 days from BTX-A injection.[5]

Unfortunately, each individual study did not provide uniform data in terms of patient ages and length of follow-up post injection of BTX-A. Regardless, it can be concluded that patients over the age of 7.5, as noted in Basciani and Intiso, have a poorer recovery when injected with BTA.[2]

Discussion

This article provides a review of all available literature on the use of BTX-A in treatment of patients with BPBI. The majority of identified articles were retrospective in nature with no clear standardization of dosing (Table 1). Nevertheless, the available literature provides useful insight in the use of BTX-A for BPBI with positive results.

Overall, 3 indications for BTX-A treatment were identified. The use with adjunct interventions such as OT/PT, plaster casting, and reconstructive surgery to meet the treatment goals. These three indications represent the commonly encountered limitations in upper extremity range of motion caused by co-contractions of agonist and antagonist muscles in children born with brachial plexus injuries.

In regard to limited mobility of the shoulder, there are multiple muscles involved and often times require more sites of BTX-A injection. The vast majority of the current literature opted to inject only the pectoralis major; however, other muscles such as the latissimus dorsi, subscapularis, and teres major were injected in certain studies. For this reason, both co-contraction and muscle imbalance seemed to be indications for BTX-A injection. The use of BTX-A for pronation contracture is very limited within the current literature. In both studies, the use of BTX-A for this contracture provided beneficial results; however, it was used as part of a more comprehensive, global treatment of the upper extremity.

Overall, BTX-A injections are shown to provide a positive effect in combating the co-contractures of muscle groups seen in patients with BPBI. Specifically, the articles analyzed demonstrated an improvement in internal rotation/adduction shoulder contractures, elbow flexion/extension contractures, and forearm pronation contractures. However, caution must be taken when treating older patients (older than 7.5 years based on current available literature), as the degree of improvement likely will be minimal. Based on the included studies described above, the single most important criterion for using BTX-A in patients with BPBI is the clinical evidence of muscle group imbalance. As stated previously, BTX-A works to strengthen the agonist muscles by weakening the antagonist muscle groups. Therefore, it is imperative for every clinician to evaluate each patient and determine whether the cause of muscular imbalance is due to differential weakness or due to co-contraction of muscle groups.

It is unclear whether the aforementioned long-term effects of BTX-A are strictly age related. However, Desiato and Risina, as well as Basciani and Intiso, reported better long-term results in younger-aged patients.[2,5] The most likely explanation for this finding is highly complex neuroplasticity that is more prevalent in the young. Children are more adept at changing neurologic pathways than adults.

Although the included studies did not adequately describe their protocol for BTX-A injections, it is common for patients to undergo deep sedation or general anesthesia to increase the probability of correct site injection and decrease the risk of complications such as pneumothorax. Nevertheless, given the low profile risk of BTX-A in conjunction with the proven benefit, using BTX-A in BPBI is a worthwhile treatment and should be considered in all patients, under the age of 7.5 years, who fail early conservative and/or microsurgical interventions.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Informed consent was not required for this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Abid A. Brachial plexus birth palsy: management during the first year of life. *Orthop Traumatol Surg Res*. 2016;102(suppl 1):S125-S132.
2. Basciani M, Intiso D. Botulinum toxin type-A and plaster cast treatment in children with upper brachial plexus palsy. *Pediatr Rehabil*. 2006;9(2):165-170.
3. Chauhan SP, Rose CH, Gherman RB, et al. Brachial plexus injury: a 23-year experience from a tertiary center. *Am J Obstet Gynecol*. 2005;192(6):1795-1800; discussion 1800-1802.
4. DeMatteo C, Bain JR, Galea V, et al. Botulinum toxin as an adjunct to motor learning therapy and surgery for obstetrical brachial plexus injury. *Dev Med Child Neurol*. 2006;48(4): 245-252.
5. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients with brachial plexus birth palsy. *Pediatr Rehabil*. 2001;4(1):29-36.
6. Duijnisveld BJ, van Wijlen-Hempel MS, Hogendoorn S, et al. Botulinum toxin injection for internal rotation contractures in brachial plexus birth palsy. A minimum 5-year prospective observational study. *J Pediatr Orthop*. 2017;37(3):e209 -e215.
7. Foad SL, Mehlman CT, Foad MB, et al. Prognosis following neonatal brachial plexus palsy: an evidence-based review. *J Child Orthop*. 2009;3(6):459-463.
8. Foad SL, Mehlman CT, Ying J. The epidemiology of neonatal brachial plexus palsy in the United States. *J Bone Joint Surg Am*. 2008;90(6):1258-1264.
9. Greenhill DA, Wissinger K, Trionfo A, et al. External rotation predicts outcomes after closed glenohumeral joint reduction with botulinum toxin type A in brachial plexus birth palsy. *J Pediatr Orthop*. 2018;38:32-37.
10. Hierner R, Rollnik JD, Berger AC, et al. Botulinum toxin type A for the treatment of biceps/triceps co-contraction in obstetrical brachial plexus injuries. *Eur J Plast Surg*. 2001;24:2-6.
11. Hoeksma AF, ter Steeg AM, Nelissen RG, et al. Neurological recovery in obstetric brachial plexus injuries: an historical cohort study. *Dev Med Child Neurol*. 2004;46(2):76-83.
12. Kozin SH, Zlotolow DA. Advanced imaging and arthroscopic management of shoulder contracture after birth palsy. *Hand Clin*. 2012;28(4):541-550.
13. Michaud LJ, Louden EJ, Lippert WC, et al. Use of botulinum toxin type a in the management of neonatal brachial plexus palsy. *PM R*. 2014;6(12):1107-1119.
14. Price AE, Ditaranto P, Yaylali I, et al. Botulinum toxin type A as an adjunct to the surgical treatment of the medial rotation deformity of the shoulder in birth injuries of the brachial plexus. *J Bone Joint Surg Br*. 2007;89(3):327-329.
15. Rollnik JD, Hierner R, Schubert M, et al. Botulinum toxin treatment of cocontractions after birth-related brachial plexus lesions. *Neurology*. 2000;55(1):112-114.
16. Shin YB, Shin MJ, Chang JH, et al. Effects of botulinum toxin on reducing the co-contraction of antagonists in birth brachial plexus palsy. *Ann Rehabil Med*. 2014;38(1):127-131.