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Review Article

Botulinum toxin use in neuro-rehabilitation to treat obstetrical plexus palsy and sialorrhea following neurological diseases: A review

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Abstract. In neuro-rehabilitation, botulinum toxin (BTX) as adjunct to other interventions can result in a useful therapeutic tool treating disabled people. Other than spasticity, numerous motor and non motor disorders can complicate clinical course and hamper rehabilitative process of neurological impaired patients. A review of BTX use in treating muscular imbalance of children with obstetrical brachial plexus palsy and in reducing sialorrhea following neurological diseases including amyotrophic lateral sclerosis (ASL), Parkinson disease and cerebral palsy (CP) is provided. Clinicians have to face unique and difficult to treat clinical conditions such as ulcers, sores and abnormal posture and movement disorders due to neurological affections. BTX effectiveness in treating some of these conditions is also provided. Since, neurologically disabled subjects can show complex dysfunction, prior to initiating BTX therapy, specific functional limitations, goals and expected outcomes of treatment should be evaluated and discussed with family and caregivers.

Keywords: Botulinum toxin, sialorrhea, obstetrical brachial plexus palsy, neuro-rehabilitation

1. Introduction

Botulinum toxins are some of the most potent poisons present in nature produced by the anaerobic bacterium called "*Clostridium botulinum*". Seven types of toxins have been harvested from clostridium, designated A through G, but only type A (BTX-A) and B (BTX-B) are commercially available and used in clinical practice. In last decades, the growing use of this drug in several neurological disturbances has made it one of the most important advancements in the therapeutics of movement disorders and in treating a wide range of disturbances including gastroenterological and urological diseases, as well as dermatological and cosmetic applications. In neuro-rehabilitation, BTX is predominantly used for the treatment of spasticity [36]. A bulk of papers have demonstrated the efficacy of BTX-A in reducing spasticity and recently, recommendations can guide and support physicians choosing dosage and muscles to inject [65]. Although spasticity is the most frequent motor disorder in patients requiring rehabilitation, a lot of disabling impairments and conditions can occur other than spasticity that have scarcely available therapeutic interventions. This paper will deal about the BTX use in treating children with obstetrical brachial plexus palsy (OBPP) and in reducing sialorrhea following some neurological diseases including amyotrophic lateral sclerosis (ASL), Parkinson disease and cerebral palsy (CP). Disturbances such as ulcers, pain and contracture can occur in neurological impaired patients producing unique conditions difficult to treat. BTX effectiveness in treating some of these conditions is provided. Since in clinical practice BTX-B is less used than BTX-A, and few researches studies have been

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published regarding its use, most of data presented concern BTX-A treatment.

1.1. Structure and type of BTX

The active BTX molecule is formed by two chains weighing ∼150.000 daltons, in which a heavy chain is linked by a disulfide bond to a light chain [16]. The heavy chain is responsible for neuron internalization, and the light chain binds to a specific target protein involved in the docking and fusion of acetylcholine-containing vesicles collectively referred as the SNARE complex. The BTX-A cleaves a protein termed SNAP-25, whereas BTX-B binds a different protein designed VAMP, also known as synaptobrevin [56] which are responsible for vesicle acetylcholine release. The derangement of this process at the neuro-muscular junctions cause clinical effects consisting in muscle weakness and paralysis. BTX-A and BTX-B are commercially available and used in clinical practice. To date, three formulation of BTX-A are commercialized and are marketed as Botox® (Allergan, Inc., Irvine, CA), Dysport® (Ipsen Ltd., Berkshire, United Kingdom) and Xeomin® (Merz, Frankfurt, Germany), respectively. The preparations are manufactured by different processes, have different formulations and potencies, which are determined by different biological assays based on their clinical use. BTX-B is marketed by Solstice Neuroscience (Malvern, PA) as MyoBloc in the United States and NeuroBloc (Elan Pharmaceuticals, San Diego CA) in Europe. It is important to note that the potency of a single unit varies greatly among the commercial types. Although the potency of 1 U of Botox® is roughly equal to 1 U of Xeomin®; 3 U of Dysport®, and 40 to 50 U of MyoBloc, it is very important to recognize that a simple ratio of dosing equivalencies cannot be applied [5]. For injections, botulinum toxins are diluted with 0.9% sodium chloride solution at variable volumes depending on the dose that the clinician plans to inject.

1.2. BTX and obstetrical brachial plexus palsy

Obstetric brachial plexus palsy (OBPP) can be a dramatic sequela of dystokia or complicated delivery. A recent study showed an incidence of 1.3 per 1000 live births in the United States [24]. A higher incidence, ranging from 3 to 4.6 per 1000 live births was found in Europe [5]. Severe brachial plexus palsies can result in disabling due to impairment and imbalance of the muscular contraction in the paretic limb. In spite of physical therapy, some children continue to experience contractures and abnormal posture that hamper complete recovery. In the last decade, an increasing number of reports on the treatment of BTX-A for OBPP have been published [8,17,18,28,29,48,52,59]. BTX-A has been used to improve muscular imbalance of the internal rotator-adductor muscles of the shoulder, limited active elbow extension, and triceps co-contraction in combination with conservative treatment, including long-term physiotherapy, occupational therapy, and functional orthopaedic or plastic surgery. Injected muscles and BTX dosage were variable depending on clinical pictures and muscular imbalance. Latissimus dorsi and pectoralis major muscles have been generally injected with a dosage ranging from 4 to 10 MU/kg and from 15 to 20 MU/kg of BTX-A when Botox® or Dysport® was used, respectively. A global dose of BTX-A (Dysport®) ranging from 200 to 400 MU has been used per single session [8,18]. In some trials, teres major, subscapolaris, elbow flexor and pronator muscles [18,59] were also injected. Two papers reported biceps and triceps muscle BTX injections, because co-contraction was detected to electromyographic (EMG) exam [31,52]. Heise et al. injected 2–3 MU/kg of BTX-A (Botox®) into both biceps and triceps muscles and observed improvement of elbow motion [31], whereas Rollnik et al. treated only triceps muscle with 40 MU of BTX-A (Dysport®) obtaining increase of elbow flexion-extension [52]. Main studies concerning the use of BTX in treating obstetrical brachial plexus palsy are reported in Table 1. BTX-A as adjunct to serial casting has been successfully used in children with OBPP to improve muscular contracture, arm position, elbow extension and dexterity in the paretic limb [8, 18]. Although functional and esthetic improvement has been described, a recent systematic review about the treatment indications of BTX-A in children with OBPP emphasized the need for randomized controlled trials to determine its benefits and efficacy in managing muscle imbalance and muscle co-contraction [28].

1.3. BTX in sialorrhea following neurological diseases

Sialorrhea is a common disorder in many neurological and systemic conditions. Since BTX also inhibits the release of pre-synaptic acetylcholine at the neuro-secretory junctions of the salivary glands, it has been proposed as a possible efficacious pharmacological treatment for hypersalivation and sialorrhea, which can occur and complicate the course and management

of some severe adult and child neurological diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and cerebral palsy (CP). In these disturbances, drooling is not caused by increased production of saliva, but by the inability to swallow secretions because of tongue spasticity, weakness of face, mouth and pharyngeal muscles, and loss of oropharyngeal co-ordination and function. Numerous studies have demonstrated that BTX-A and BTX-B are effective and safe for the reduction of drooling complicating neurological diseases. Neuro-toxin BTX-B is supposed to provide some advantages in the treatment of autonomic dysfunction when compared to BTX-A, owing to a more selective impact on vegetative symptoms, mainly due to the hypothesized affinity for postganglionic neurons containing M3 receptors (such as those responsible for salivation) [3]. BTX-B has a tendency to produce more autonomic side effects than BTX-A [21]. Indeed, BTX-B initially arise concerns about this action, which was sometimes observed far from the injection site (such as dry mouth) after treatment for axillary hyperhidrosis [20]. Recently, Guidubaldi et al. found that that BTX-B had a shorter latency than BTX-A and comparable duration [30]. The different latencies might be due to various characteristics of the two serotypes, perhaps diffusion and/or affinity for autonomic fibers.

1.3.1. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a disease of both upper and lower motor neurons and its incidence is 1–2 per 100,000 of the population [66]. In motor neuron disease, approximately 30% of people present with bulbar symptoms such dysphagia, dysarthria, hoarseness and hypophonia experiencing problems handling serous saliva and mucous nasal and bronchial secretions [1]. The prevalence of sialorrhea in patients with ALS is estimated from 50% to 70% [11]. Several studies has been published concerning the use of BTX to reduce drooling in patients with ALS. The doses of BTX injected into salivary glands were variable depending on neuro-toxin used and the clinician's experience. Doses ranging from 7.5 MU to 20 MU of BTX-A (Botox®) and from 5 MU to 75 MU of BTX-A (Dysport®) have been injected into salivary glands [26, 27,42,44,57,64]. A variable dose ranging from 500 MU to 1000 MU and from 250 MU to 750 MU of BTX-B has been injected into each parotid and submandibular glands, respectively [13,14,37]. The global dosage of BTX-B used for the treatment of drooling was 2500 MU (Table 2).

Apart a case of recurrent mandibular luxation following bilateral injections of 5 MU of TBX-A (Dysport®) into both parotid glands [61], no serious adverse effect occurred in studies, in which BTX-A was used. On the other hand, viscous saliva, dry mouth, local pain, increased difficulty of chewing, severe xerostomia and thick secretions were frequently observed by using BTX-B. In treating sialorrhea of patients with ALS, one of the main concern is the risk worsening dysphagia and muscular weakness after salivary glands BTX injection. In this respect, the difficulty of swallowing was considered due to progressive course of disease. Furthermore, no study reported objective weakness in muscles distant from the injection site. All published studies, except one were case series and prospective open-label trials including small samples or few patients. A recent systematic review identified only one randomized controlled trial [37] in which BTX-B was injected into parotid and submandibular glands of 20 patients who showed positive results for four weeks. Although some evidence for use of BTX injections into salivary glands for the treatment of sialorrhea in patients with ALS, further well designed researches are required on this important symptom.

1.3.2. Parkinson disease

Studies have shown that patients with PD produce less saliva compared to healthy controls [49] and treatment with levo-dopa may worsen this disturbance. In PD patients, drooling is more likely caused by a decrease in swallowing reflexes and the flexed head posture. In advanced-phase of disease, drooling is a noteworthy symptom which negatively affects patient's quality of life both interfering with social participation and increasing care burden. It is estimated that up to 78% of PD patients experience sialorrhea [33]. Numerous studies concerning the BTX-A and B use for the treatment of sialorrhea in these patients have been published [13,19,25,38–40,42,43,45–47,50,53,60]. All salivary glands were generally treated in almost all studies. Doses ranging from 5 MU to 50 MU of BTX-A Botox® and from 125 MU to 150 MU of BTX-A Dysport®, have been injected into salivary glands. The mean global dosage of BTX-A (Botox®) and BTX-A (Dysport®) ranged from 55 MU to 200 MU [9] and from 250 MU to 450 MU [43,45]. A global dosage ranging from 2500 MU to 4000 MU of BTX-B has been used when all salivary glands were injected. Whereas, a dose ranging from 1000 to 2000 MU of BTX-B has been injected when alone parotid glands were treated. Only one research reported a method de-

Table 1

Main studies concerning botulinum toxin use in children with obsterical brachial plexus palsy

Study: author and year	Type of study	Botulinum dosage (SD)	Rehabilitation and additional physical therapy intervention	Patients; male/ female; mean age in years (SD)	Injected muscles	Primary outcome	Results
Desiato and Risina 2001 [18]	prospective case series	14.4 (5.3) MU/kg of BTX-A (Dysport); 311 (139) MU per single session	Vojta method	50 children; 26 M, 24 F; mean age 4.7 (3.4);	pectoralis major, pectoralis minor, teres major, subscapularis, latissimus dorsi, elbow flexor, biceps brachii, brachialis, brachioradialis, elbow pronator, pronator teres	active ROM; GCRS	all children but two showed a clinical improvement assessed by goniometry. Abduction and external rotation 50.1 $\pm$ 16 and 76.2 $\pm$ 19 ($p < 0.01$), respectively. GCRS: 70% showed step-like increments of function.
DeMatteo et al. 2006 [17]	prospective case series	4 MU/kg of BTX-A (Botox)	intensive occupational the therapy	3 children; 3 F; 1–2 yrs	latissimus dorsi and pectoralis major	Active Movement Scale (AMS); EMG and joint kinematics	AMS total score changed significantly. Parent report of change: generally positive
Basciani and Intiso 2006 [8]	prospective case series	22 (SD 5.1) MU/kg of BTX-A (Dysport); 200–400 MU per single session	physiotherapy and occupational therapy. Casting for 1 month with fixed elbow extension. The cast was lengthened each week for 2 wks.	22 children; 12 M, 10 F; mean age 5.7 (2.8);	pectoralis major	MRC, ROM (passive and active). Mallet scale. NHPT score	MRC values of deltoid, biceps, triceps were unchanged at 3, 6, and 12 mo of follow-up. NHPT scores improved significantly and persisted for 12mo. Little change in Mallet scores.
Price et al. 2007 [48]	retrospective case series study with historical control group	100 MU of BTX-A; commercial formulation n.r.	casting for 6 weeks and physiotherapy. Surgical release of the contracture	13 children; 6M, 7 F, mean age 5.8 (2.8 to 12.9);	pectoralis major	Modified Gilbert shoulder evaluation scale	Significant improvement on the modified Gilbert scale at a mean follow-up of three years ($p = 0.012$).
Grossman et al. 2003 [29]	retrospective case series	30 MU (latissimus dorsi); 70 MU of BTX-A (pectoralis major); commercial formulation n.r.	physiotherapy and occupational therapy. Neurolysis of the upper brachial plexus with bypass nerve grafting. Release of shoulder contracture by a subscapularis slide. Biceps/triceps co-contraction	19 children; mean age 16 mo (range 11–29) mo; gender ratio n.r.	pectoralis major, latissimus dorsi	Modified Gilbert; shoulder grading system	at the latest follow-up examination, all had improved by a mean of two grades.
Rollnik et al. 2000 [52]	prospective case series	40 MU of BTX-A (Dysport)	early microsurgical repair was performed in 3 children (no elbow flexion at the MRC)	6 F, age 2 to 4 yrs; mean age n.r.	triceps	MRC scale. ROM of elbow flexion	improvement score to MRC of biceps. Before treatment elbow flexion ranged from 40–60 deg. After BTX injection elbow ROM ranged from 80 to 120 deg ($p = 0.027$).
Heise et al. 2005 [31]	case series	2–3 MU/kg of BTX-A (Botox)	home- based physiotherapy	8 children; 1 M, 7 F; mean age 2.2 (1.1)	triceps (4 children) biceps (4 children)	MRC scale	improvement score to MRC of not injected muscle

Legend: SD = standard deviation; ROM= range of motion; MRC = Medical Research Council scale; GCRS = Global clinical rating scale; NHPT = nine hole peg test; n.r. = not reported.

Table 2

Main researches concerning BTX-A and BTX-B use in patients with ALS. Studies with a sample size less than 4 subjects were excluded

Amyotrophic lateral sclerosis		BTX-A						
Study: author and year.	Type of study	Number patients; Sex ratio M/F; mean age (SD)	Botulinum dosage (SD)	Injected glands	Drooling measurements	Results	Duration of effect	Adverse events
Giess R et al. 2000 [26]	case-healthy control	5 pts; 3M, 2F 63.8 (1.7)	mean dosage of 46 (16.9) MU (range 30–72) of BTX-A (Botox); 6–20 MU for each parotid; additional 5 MU for each submandibular gland was injected if parotid treatment resulted ineffective	parotid glands in all and submandibular in 2 subjects	number of one brand of paper handkerchiefs used each day. Improvement of QoL	not significant reduction of number of used paper handkerchiefs each day at 4 wks after BTX-A injection. Improvement in QoL in 3 subjects	3 mo	no adverse event
Lipp et al. 2003* [42]	double-blind, placebo-controlled dose-finding trial	32 pts: 12 with ALS; 23M, 9F; age n.r.	18.7, 37.5, or 75 MU of BTX-A (Dysport) for each parotid	parotid glands	weight of dental rolls before and after keeping them for 5 min in the mouth; mechanical counter once a week for a 12-hour; 6-item questionnaire once per month; ALSFRS	saliva reduction of 50% and significant improvement of counter measurement in group treated with 75 MU of BTX;	3 mo	n.r.
Manrique et al. 2005 [44]	case series	5 pts; 2M, 3F; age 45 to 59 yrs	20 MU of BTX-A (Botox) for each parotid in two sites; 30 MU for each submandibular glands	parotid and submandibular glands	questionnaire concerning 4 points. The questions were: need to eliminate saliva from the mouth, participation in the family group during the meals, embarrassment in public places because of sialorrhea, physical contact on the face with family and close friends	authors reported significant improvement of questionnaire after BTX treatment.	3 mo, (4 mo in 3 subjects)	no adverse events
Scott et al. 2005 [57]	case series	6 pts; sex ratio and age n.r.	10 MU of BTX-A (Botox) into each parotid gland. Repeated injection with 20 MU into each parotid after 12 weeks	parotid glands	patient log book of daily tissue use. Single item from ALSFRS assessing salivation. Single item from MQOL regarding overall QoL.	no change in mean daily tissue use in three of six patients after 10 MU injection (2 subjects). No subjective clear effect on ALSFRS or on QoL using MQOL	12 weeks	no adverse effects
Verma and Steele 2006 [64]	case series	10 pts; 4M, 6F; 69.5 (3.7)	7.5 MU of BTX-A (Botox) for each parotid gland. If response insufficient (VAS less than 25% from baseline) over first 4 weeks, a second dose of 15 MU was injected into each parotid	parotid glands	count of the number of one brand of paper tissue used daily. Subjective assessment by VAS and DIS.	significant reduction of the number of paper tissue at 4 wks: 82 ± 26 vs 58 ± 17 ($P < 0.02$). Significant improvement of DIS at 4 wks ($p < 0.001$).	2–3 mo in 5 subjects	no adverse effect

Table 2, continued

Amyotrophic lateral sclerosis		BTX-A						
Study: author and year.	Type of study	Number patients; Sex ratio M/F; mean age (SD)	Botulinum dosage (SD)	Injected glands	Drooling measurements	Results	Duration of effect	Adverse events
Gilio et al. 2010 [27]	Prospective open label	26 pts; 14M, 12F; mean age 64.4 (15.3)	BTX-A (Botox 10–20 MU and Dysport 30–60 MU) was injected into each parotid gland without USG	parotid glands	weight of dental rolls before and after keeping them for 5 min in the mouth.	VAS	n.r.	dry mouth 2
			BTX-B					
Contarino et al. 2007 [13]	case series	9 patients; 3 M, 6 F 68.4 (13.6)	global dosage of 2500 MU of BTX-B (Neurobloc); 1000 MU of BTX-B for each parotid and 250 into each submandibular gland	parotid and submandibular glands	weight of 5 cotton rolls before and after keeping them for 5 min in the mouth. DSS, DFS and VAS	significant reduction of saliva production at 1 week. Significant reduction of DSS, DFS and VAS score at 1 week.	3.4 ± 0.5 mo	viscous saliva 7; dry mouth 2
Costa et al. 2008 [14]	case series	16 patients 9M,7F; 69.2 (8.0)	global dosage of 2500 MU of BTX-B (Neurobloc); 1000 MU of BTX-B for each parotid and 250 into each submandibular gland	parotid and submandibular glands	weight of cotton rolls before and after keeping them for 5 min in the mouth. Improvement of at least 50% on a 10 cm VAS. DSS, DFS.	significant reduction of VAS, DSS and DFS at 4 wks.	3 mo	viscous saliva 5, local pain 4, Increased difficulty of chewing 3, respiratory infection 2, facial paresis 1, burning tingling of the eyes 1, severe xerostomia 1
Jackson et al. 2009 [37]	double-blind, randomized, placebo-controlled	20 patients; 7 M, 13F 67 (6.8)	global dosage of 2500 MU of BTX-B (Myobloc); 500 MU for each parotid and 750 for each submandibular gland	parotid and submandibular glands	change in volume of saliva produced over 5 min (measured with funnel and tube); visual analog scale from 0–100 mm that rated the thickness of the saliva (thin to thick) and the severity of the saliva problem (no problem to serious problem)	significant reduction of saliva production in BTX-B group vs placebo at 4 wks ($p < 0.05$).	n.r.	dry mouth 2, thick saliva 1

Legend: ALS = amyotrophic lateral sclerosis; VAS = Visual Analogue Scale; DSS = Drooling Severity Scale; DFS = Drooling Frequency Scale; MQOL = McGill quality-of-life questionnaire; ALSFRS = ALS functional rating score; QoL = quality of life; DIS = Drooling impact score; n.r. = not reported; USG = ultrasound guidance.
*Heterogeneous population including ASL, PD, multiple system atrophy (SMA) and cortical basal degeneration patients; & sample including PD and ALS patients.

sign, in which 250 MU of BTX-B were injected in each submandibular glands (Table 3).

Since BTX-B has been supposed to work more than BTX-A on the autonomic nervous system, a recent research study compared BTX-A and BTX-B in controlling sialorrhea of ASL and PD patients [30]. The authors reported that either 250 MU BTX-A (Dysport®) (100 MU for each parotid and 25 MU for each submandibular gland) or 2500 MU BTX-B (Neurobloc) (1000 MU into two sites in each parotid and 250 MU into a single site in each submandibular gland) had similar effectiveness and safety [30]. Evidence from 4 randomized controlled trials showed that botulinum toxin type A injections were generally well tolerated [19,39, 42,43] and no serious side effects were observed. BTX-B injections also appear to be generally well tolerated, even if the treatment was associated with mild adverse events including viscous saliva, dry mouth, weakness of chewing and local pain [13,40,46,50].

1.3.3. Cerebral palsy

In children with CP, drooling and sialorrhea have an incidence of 10 to 37% [4]. These symptoms can have a devastating effect on the family's social relationships and the patient's quality of life. Several studies have demonstrated that BTX-A can be used with success in controlling sialorrhea in children with CP [2, 51]. A mean dose of BTX-A (Botox®) ranging from 2 to 22.5 MU/kg of body weight per single gland has been injected [10,22,41]. A total dose ranging from 30 MU to 100 MU of BTX-A (Botox®) and from 100 to 140 MU of BTX-A (Dysport®) into salivary glands has been injected. In all studies salivary glands were treated bilaterally. Lin et al. used a different method design. They injected 2 MU/kg of BTX-A (Botox® into one parotid and the contralateral submandibular gland under ultrasound guidance (USG) obtaining alike reduction of sialorrhea [41]. Few data has been published concerning the use of BTX-B for the treatment of drooling in these children. A recent randomized trial comparing three doses of 1500 MU, 3000 MU and 5000 MU of BTX-B injection into the salivary glands with USG reported that the 3000 MU of BTX-B significantly improved the frequency and severity of sialorrhea in those children [6]. The lower dosage was ineffective, and the higher dosage produced no greater benefit and more side effects. Currently, there is an emerging body of literature regarding the use of BTX for saliva control in children with CP, but few randomized trials have been performed.

1.4. BTX use in unique rehabilitative clinical conditions

Neurologically disabled subjects can present with complex dysfunction and clinicians have to face unique and difficult to treat clinical conditions. BTX can be a useful therapeutic tool in some of these conditions. Anecdotal reports have been published concerning the use of BTX-A in specific rare conditions such as sustaining posture after surgery in patients with cervical disk herniation, secondary to dystonic cerebral palsy [7] or reducing involuntary movement after fracture [12]. BTX-A has been used to hasten the healing of lower lip ulcers due to oro-mandibular dyskinesia in a subject in a vegetative state following a severe sub-arachnoid hemorrhage [34]. Likewise, BTX-A treatment was used to hasten the healing of a buttock pressure sore in a subject with severe spastic paraplegia following a traumatic spinal cord lesion. In this last case, several therapeutic agents were applied without success since all efforts at healing the ulcer by topical medication were hampered by recurrent spasms involving the gluteal muscles and the ulcer region [35]. Gluteal injections of 660 MU BTX-A (Dysport®) reduced the movement disorder and improved buttock ulcer healing.

Pisa syndrome is a rare type of trunk dystonia characterized by abnormal and severe axial lateral flexion of the trunk accompanied by contraction of the trunk musculature with marked flexion of the thoracolumbar spine. It is generally idiopathic, but can occur in neurodegenerative diseases or in PD patients. The use of BTX-A adjunct to rehabilitation treatment may be useful to reduce this postural abnormality [55]. Furthermore the use of BTX-A solved focal hand dystonia in a patient who underwent surgical treatment for thumb duplication [54] and resulted effective in reducing facial synkinesis after facial nerve palsy [63].

2. Adverse events and neutralizing antibodies

Before performing BTX-A injections for therapeutic purposes, the expected risks and benefits for each patient must be carefully considered. Reported adverse events associated with BTX are infrequent in treating OBPP. In drooling following neurological disease, they are mild to moderate and transient concerning predominantly the BTX-B formulation. In a previously mentioned paper, 28.5% of CP children who were injected with 5000 MU of BTX-B for sialorrhea developed generalized weakness and severe dysphagia requiring hos-

Table 3

Main studies concerning BTX-A and BTX-B use in patients with Parkinson disease

Parkinson disease		BTX-A						
Study: author and year.	Type of study	Number patients; Sex ratio M/F; mean age (SD)	Botulinum dosage (SD)	Injected glands	Drooling measurements	Results	Duration of effect	Adverse events
Jost et al. 1999 [38]	case series	5 pts; 3M, 2 F; 59.6	total dose of 10 MU of BTX-A (Botox); 5 MU of BTX-A for each parotid glands	parotid glands	rating by the patient and his or her spouse	good 2 (normal salivation), moderate 2 (decreased salivation), no change 1	4–5 mo	no increased swallowing problems or xerostomia
Pal et al. 2000 [47]	case series	9 pts; 6M, 3F; 75.2 (8.1)	7.5 MU of BTX-A (Botox) and 8 weeks later 15 MU	parotid glands	questionnaires comprising rating scales for severity and frequency of drooling. Dental rolls placed in the mouth for 5 min.	all patients except one had an objective reduction in saliva secretion. There was an approximately 35% reduction in mean value of salivary production at the study's completion	n.r.	dry mouth
Friedman et al. 2001 [25]	open label case-control study	11 pts; 8M, 3F; 63.3 (8)	5 MU of BTX-A for each parotid glands	parotid glands	weight of dental rolls placed in the mouth for 2 min	significant reduction in saliva production at 1 week ($p < 0.0001$ vs baseline)	6 wks	no side effects
Lipp A et al. 2003* [42]	double-blind, placebo-controlled dose-finding trial	32 pts; 12 with ALS; 23M, 9F; age n.r.	18.7, 37.5, or 75 MU BTX-A for each parotid of BTX-A (Dysport)	parotid glands	weight of dental rolls before and after keeping them for 5 min in the mouth; mechanical counter once a week for a 12-hour; 6-item questionnaire once per month; ALSFRS	saliva reduction of 50% and significant improvement of counter measurement in group treated with 75 MU of BTX;	3 mo	n.r.
Mancini et al. 2003^ [43]	double-blind randomized placebo study	7 pts with PD and 3 with MSA; 6M, 4F; 69.6 (6.1)	global dose of 450 MU of BTX-A (Dysport). 146.2 MU for each parotid and 78.7 MU for each submandibular gland using USG	parotid and submandibular glands	DSS and DFS	significant reduction in DSS at 1 week ($p = 0.005$ vs PL)	1 mo	no adverse events
Dogu et al. 2004 [19]	randomized controlled study	15 pts; 10 M, 5F; 67.3 (7.3)	30 MU of BTX-A for each parotid glands; 8 and 7 pts with without USG, respectively	parotid glands	dental roll weight placed in the mouth for 5 min, VAS	significant reductions in saliva production at 1, 4 and 12 wks ($p = 0.001$ vs baseline) in group treated by USG. Significant reductions from baseline in VAS scores.	4.4 (1.2) mo (range 2–6) in both groups	dry mouth in 2 pts
Lagalla et al. 2006 [39]	double-blind randomized placebo controlled study	16/32 pts; 69.4 (5.5)	50 MU of BTX-A (Botox) for each parotid glands without USG	parotid glands	dental roll weight retained in the mouth for 5 min, VAS-D, VAS-FD, VAS-FS	significant reduction in saliva production, VAS-D, VAS-FD and VAS-FS scores at 4 wks	n.r.	transitory swallowing difficulties 1

Table 3, continued

Parkinson disease		BTX-A						
Study: author and year.	Type of study	Number patients; Sex ratio M/F; mean age (SD)	Botulinum dosage (SD)	Injected glands	Drooling measurements	Results	Duration of effect	Adverse events
Su et al. 2006£ [60]	case series	15 pts; 9M, 6F; 71.8 (7.1)	total dose of 40 MU of BTX-A (Botox); 15 MU for each parotid and 5 MU for each submandibular glands	parotid and submandibular glands	weight of dental rolls placed into the mouth and retained for 10 min; DSS, DFS	significant reduction in saliva production at 4 wks ($p < 0.01$). Significant reduction of DSS score.	16.3 (5.7) wks	mild dry mouth for less than 6 in 2 pts
Nobrega et al. 2006 [45]	case series	21 pts; 18M, 3F; 70 yrs (55–84)	global dose of 250 MU of BTX-A (Dysport). A dose of 125 MU for each parotid glands by USG	parotid glands	DSS and DFS	significant Improvement of drooling severity score at 4 weeks	n.r.	dry mouth 2
Santamato et al. 2008 [53]	consecutive case series	18 pts; 14M, 4F; 71 (7.1)	global dose from 60 to 100 MU of BTX-A (Botox) (mean 82 ± 14.49). A dose from 20 to 50 MU (mean 36 ± 11.4 MU) for each parotid glands by USG	parotid glands	DSS and DFS	significant improvement of subjective scale at 4 wks	4.2 mo	no serious side effects
		BTX-B						
Racette et al. 2003 [50]	Open-label, case series	9 pts; sex ratio n.r. Mean age 71.8 (13.1)	1000 MU of BTX-B for each parotid	Parotid glands	VAS from 0 to 4, where 0 indicated no drooling and 4 indicated worst drooling. Change in weight of the pads provided a quantified 5-minute saliva measurement	improvement corresponded to a 2.4-point reduction on the VAS ($P = 0.000005$).	13 wks (range 8–20)	one subject experienced excessive dry mouth but this resolved within 1 month
Ondo et al. 2004 [46]	double-blind placebo controlled study	8/16 pts; 13M, 3F; mean age 70.4 (11.4)	global dosage of 2500 MU of BTX-B (Myobloc); 1000 MU of BTX-B for each parotid and 250 into each submandibular gland	parotid and submandibular glands	Drooling Rating Scale and DSS and DFS; VAS	improvement on the VAS ($p < 0.001$); Drooling Rating Scale ($p < 0.05$), and DSS and DFS ($p < 0.001$)	n.r.	dry mouth 3, worsened gait 2, diarrhea 1, and neck pain 1
Contarino et al. 2007 [13]	open-label study	9 ps; 8M, 1F; 72.7 (6.6)	global dosage of 2500 MU of BTX-B (Neurobloc); 1000 MU of BTX-B for each parotid and 250 MU into each submandibular gland by USG	parotid and submandibular glands	weight of 5 cotton rolls before and after keeping them for 5 min in the mouth. DSS, DFS, VAS.	Significant reduction of saliva production at 1 week. Significant reduction of DSS, DFS and VAS score at 1 week.	4.8 (0.8) mo	viscous saliva 1, dry mouth 2

Table 3, continued

Parkinson disease		BTX-A						
Study: author and year.	Type of study	Number patients; Sex ratio M/F; mean age (SD)	Botulinum dosage (SD)	Injected glands	Drooling measurements	Results	Duration of effect	Adverse events
Lagalla et al. 2009 [40]	Double-blind randomized study	18/36 pts; 14M, 4F, 71.9 (5.9)	Global dosage of 4000 MU of BTX-B (Neurobloc) in parotid glands without USG	Parotid glands	Weight of dental rolls retained in the mouth for 5 minutes. DSS, DFS. Familial (VAS-FD) and social VAS (VAS-SD).	Significant reduction of drooling at 4 wks ($p < 0.0001$) and significant improvement of all subjective measurements: DS-FS, FD-VAS, S-VAS	6 mo 19.2 (6.3) wks	No relevant adverse effect. 2 subjects: one transient dysphagia, 1 transient mild weakness of chewing

Legend: VAS-D = visual analogue rating of drooling frequency, patient embarrassment within the familial (VAS-FD) and social (VAS-SD) context. VAS = Visual Analogue Scale; DSS = Drooling Severity Scale; DFS = Drooling Frequency Scale; USG = ultrasound guidance; n.r. = not reported.
*heterogeneous population including ASL, PD, multiple system atrophy (MSA) and cortical basal degeneration patients; & sample including PD and ALS patients; ^ sample including PD and MSA patients; £ sample including PD dementia with Lewy bodies or MSA.

pitalization and naso-gastric tube feeding [6]. A recent review of cases described in the literature indicate that risk of developing systemic effects does not seem to be related to dose based on body weight [15]. It may be more likely that risk for this condition is related to the total injection dose and injection frequency. BTX-A effects can be abolished by the development of neutralizing antibodies (NAbs). Antibody formation against BTX proteins is one of the reasons for therapy failure, particularly in treating spasticity and dystonia. The development of NAbs are facilitated if repeated injections and high dosages of BTX are used, independently from the treated disturbances. The development of NAbs has been also observed in subjects who underwent BTX injections for non-motor disorders such as sialorrhea. Although, no BTX-A resistance in the treatment of sialorrhea has yet been reported, this disappointing phenomenon has recently been described for BTX-B after repeated injection into the salivary glands [9].

3. Limitation in the use of BTX

Although a growing use of BTX in clinical practice, information to guide the choice of toxin remains limited. Currently, dosages are largely titrated by the practitioner based on expert opinion, clinical experience, as well as the formulation of botulinum toxin being used and the individual patient's response. It need to keep in mind that BTX-A and BTX-B have different effects at the cellular level, different pharmacokinetics, and different adverse event profiles. Target selection is a key feature for the efficacy of BTX treatment and the infiltration modalities are a further source of heterogeneity requiring a trained physician. BTX injections are more efficacious if the designed structures are targeted by needle EMG or USG. A drawback for BTX therapy is its high cost and the transient nature of the toxin. Since, BTX have a duration of effect that lasts from a few weeks to 7 months, it requires less frequent administration than other medications. In this respect, recent papers have reported that the clinical benefits of BTX-A treatment outweigh the apparent high costs of this intervention, showing it to be a cost-effective treatment in post-stroke spasticity [23,58]. However no data has been reported on this issue in treating other disturbances.

4. Conclusions

Botulinum toxin types A and B are valuable agents in the multiple therapeutic strategies that clinicians carry out in a neuro-rehabilitation setting. Since neurologically disabled subjects can show complex dysfunction, prior to initiating BTX treatment, specific functional limitations, goals and expected outcomes of treatment should be evaluated. It is important to strive to attain the best clinical and functional benefit that improves the quality of care of patients undergoing rehabilitation. BTX strategies should be viewed as adjunct measures to other rehabilitative interventions in achieving the best functional outcome. Although BTX-A treatment has been demonstrated safe and effective in managing OBBP and sialorrhea due to some neurological diseases, further well designed researches are required in order to support the continued use of this intervention.

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