Chapter 10

How Useful are Localization Techniques in Botulinum Toxin Injections for Dystonia and Spasticity Indications?

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Additional information is available at the end of the chapter

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Abstract

There is irrefutable evidence for the effectiveness of botulinum toxin (BoNT) in the treatment of various disorders associated with excessive muscle contraction or autonomic dysfunction. One of the earliest indications as well as the most common BoNT treated movement disorder is dystonia, predominantly its focal forms, including blepharospasm, oromandibular, spasmodic, cervical and limb dystonia. Spastic disorders comprise another area where BoNT treatment has proved beneficial. Optimal therapeutic results, however, depend on several factors, including the BoNT serotype, dose, concentration, injected volume, frequency of application, as well as precise localization of the muscles producing the abnormal movement. The accuracy in targeting muscle localization is considered to be a key factor for determining the outcome of BoNT injections, even more important than dilution volume and dose. Various techniques to find the best injection site for the delivery of BoNT have been described in the literature. An attempt was made to summarize in one place the available evidence, and when possible to compare and point out the advantages and disadvantages of different techniques for localization of BoNT injections. The widely applied clinical indications for dystonia and spasticity have been specifically chosen as our focus in this present work.

Keywords: dystonia, spasticity, BoNT, injection, localization, techniques

1. Introduction

Botulinum toxin (BoNT), the most potent biological toxin, has become a powerful therapeutic tool for a growing number of clinical indications. There are seven distinct serotypes of BoNT —A, B, C (C-1, C-2), D, E, F, and G—that have similar neurotoxic properties resulting in flaccid

muscle paralysis due to presynaptic blockage of acetylcholine release [1]. Double-blind placebo-controlled studies, as well as open-label clinical trials, provide evidence that when appropriate targets and doses are selected, BoNT temporarily ameliorates disorders associated with excessive muscle contraction or autonomic dysfunction [2]. BoNT/A and B are the most studied serotypes, commercially available and extensively used. Today BoNT/A is employed and considered safe and effective for treatment of movement disorders, with dystonia and spasticity being the most widely used indications. The BoNT serotypes, however, differ in their intracellular protein target, potency, and duration of action. These properties differ even between preparations that contain the same BoNT serotype due to variations in product formulations [3]. Recent changes to the established drug names were intended to reinforce these differences and prevent medication errors. The products and their approved indications include the following: onabotulinumtoxin A (Botox, Botox Cosmetic)—cervical dystonia (CD), severe primary axillary hyperhidrosis, strabismus, blepharospasm, upper and lower limb spasticity, overactive bladder, urinary incontinence, and migraine headache (Food and Drug Administration (FDA)). In the European Union (EU), it was approved also for the treatment of hemifacial spasm. Abobotulinumtoxin A (Dysport)—cervical dystonia, upper limb spasticity, moderate-to-severe glabellar lines (FDA), plus blepharospasm, hemifacial spasm, hyperhidrosis, strabismus, and cerebral palsy (EU). Incobotulinumtoxin A (Xeomin)—cervical dystonia, blepharospasm, upper limb spasticity, and glabellar lines. Rimabotulinumtoxin B (Myobloc, NeuroBloc)—cervical dystonia [4].

A retrospective long-term (10 year) BoNT/B study showed that although most patients required increased dosage, BoNT/B was an effective and safe treatment for a variety of movement disorders [5]. BoNT/F has been intensively tested, but due to its short-term effect, lasting about a month, it is not widely used in clinical practice [6].

The effectiveness of BoNT treatment depends on the proper selection of indications, protein content of the formulation, frequency of applications, dose, concentration, and injecting volume. It is also critically dependent on the appropriate localization of the intended target muscle(s), producing the abnormal movement, be it dystonic or spastic [7]. However, it is necessary not only to identify the proper muscles but also to localize the injection tip in a specific muscle area, namely the motor end-plate zone. A recent study compared low-dose BoNT injections applied into the end-plate zone with those injected at fixed distances from it at the same muscle. Injections only 1 cm apart reduced the effect of BoNT by 46%. Thus, precise end-plate-targeted injections increase the effect of BoNT and may reduce the required dosage, treatment costs, and also minimize side effects such as unwanted weakness of adjacent muscles [8]. However, motor end-plate zone location is not always easy to find. In order to facilitate its targeting, some efforts have been made for establishing the localization of the end-plate zone in different muscles in reference to external anatomical landmarks [9–11]. Another phenomenon that should be kept in mind is the diffusion of the toxin, after injection, because it may be a reason for the weakness of adjacent uninjected muscles. Diffusion may be influenced by the BoNT serotype and occur in direct proportion to the concentration of BoNT. Small size of target muscle and increased distance of needle tip from the neuromuscular junction can also result in increased diffusion of BoNT locally. This diffusion may be advan-

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tageous, however, when injecting muscles in children who may not be able to tolerate the pain associated with attempts to target the muscle. On the other hand, when treating dystonia or spasticity, diffusion of BoNT is clearly undesirable [12]. As BoNT diffusion correlates with dose, it once again favours injecting into the motor end-plate zone where administering a lower dose of the toxin provides satisfactory disease control with the possibility for less side effects. Not only higher doses but also the administration of injections in intervals shorter than 3 months is associated with the development of BoNT antibodies, leading to resistance to the specific BoNT serotype used [13]. Thus, there is a general consensus among experts that selection of the appropriate muscle and subsequent injection of the optimal dose are the most important determinants of the outcome of BoNT treatment [14].

A literature review was performed in order to summarize, and when possible, to compare and point out the advantages and disadvantages of different techniques for localization of BoNT injection. Revised techniques comprised clinically established specific sites of injecting commonly affected muscles in focal dystonia and spasticity, as well as several techniques facilitating the injection accuracy including electromyography (EMG): passive EMG (EMG guidance; EMG monitoring) and active EMG guidance (electrical stimulation), imaging, or endoscopic guidance.

2. Dystonia

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both. It results from involuntary concomitant contraction of agonist and antagonist muscles, with overflow of unwanted muscle contractions into adjacent muscles. Dystonia may be clinically classified according to its distribution as focal dystonia (affecting a single body part in isolation), segmental dystonia, hemidystonia, and generalized dystonia [15]. Primary dystonia is the most common type and primary focal dystonia is 10 times as common as primary generalized torsion dystonia. Primary focal dystonia occurs nearly always in adults and may involve the neck, face, or arm, whereas the leg is rarely involved [16].

Localized BoNT injections provide a symptomatic relief in primary and non-primary dystonia syndromes, as demonstrated by several randomized controlled trials and by a large number of uncontrolled studies. BoNT is the first-choice treatment for most types of focal dystonia and could be an effective treatment option for some segmental forms. The effect begins usually about a week after injections and lasts for about 3 months [4, 17].

2.1. Blepharospasm

Blepharospasm is the second most common form of focal dystonia. Blepharospasm describes dystonia in the orbicularis oculi and, optionally, its adjacent muscles, including the corrugator supercilii, procerus, nasalis, and levator labii superioris alaeque nasi muscles [7]. It usually affects both eyes and is characterized by noticeably increased frequency of blink rate, enduring

spasms of eyelids. It could significantly impair the voluntary eyelid opening which, in extreme cases, may render the patient functionally blind [18].

BoNT therapy is the treatment of choice for blepharospasm with a 90% efficacy rate of BoNT/A injections and is also safe during long-term treatment [19–23]. Evidence supported a Level A recommendation for BoNT/A, A/Inco, and A/Ona; a Level B recommendation for A/Abo; and a Level U recommendation for B/Rima [17, 24]. Adverse events include ptosis, tearing, blurred vision, double vision, dry eyes, and facial weakness [25]. Distant side effects are dose dependent and likely a result of toxin entering the circulatory or lymphatic system. Therefore, delivering the least effective amount of toxin in the most accurate manner decreases the risk of unwanted local and distant side effects as well as the risk of the development of neutralizing antibodies [23, 26, 27].

2.1.1. Anatomic/clinical muscle selection and localization of the injection needle

Although the beneficial effects of BoNT/A are self-evident, there are still several unresolved problems, referred to the optimal injection sites of BoNT [28].

The orbicularis oculi muscle consists of three portions: orbital portion, surrounding the orbital margin, including the brow, palpebral, and pretarsal portion [7]. The orbicularis oculi muscles lie immediately beneath the skin, and it is recommended that there is no need of EMG control during BoNT application [26, 29–31]. The muscle is readily accessible with a 27-, 30-, or 32-gauge needle [26, 30, 32]. Subcutaneous injections will readily spread into the underlying orbicularis muscle. A highly recommended injection strategy is the application of two injections into the upper lid near the canthus medially and laterally in order to avoid the bulk of the levator palpebrae muscle and consequent ptosis. Two lower lid injections are applied to the middle portion and to the lower lateral canthus, respectively. Avoiding the medial canthus spares the nasolacrimal apparatus [33]. A prospective trial compared four different patterns of injection sites: standard (medial and lateral aspects of the upper eyelid, and lateral and central portion of the lower eyelid), brow, inner orbital, and outer orbital. The inner orbital treatment produced significantly more episodes of ptosis (13%) and the standard the highest rate of epiphora and ocular irritation (18%). Thus, the further away from the eyelid margin the injection was, the lower risk of ocular side effects occurred [34]. Other studies summarized that the orbital portion of the orbicularis muscle should be injected at three to six sites peripherally to the orbital rim [30] and the periocular region might be injected at five to eight sites, depending on the severity and duration of the problem [35]. Mimic muscles adjacent to the orbicularis oculi, such as the procerus, the corrugator supercilii, and the nasalis muscles, may also be used as target muscles [7, 26].

Data of more special interest suggested that BoNT injections into the pretarsal portion of orbicularis oculi muscles increased the magnitude of the therapeutic response and decreased the number of unsuccessful treatments and ptosis [18, 32]. Aramideh et al. (1995) compared the response to BoNT/A according to a triple injection technique (two injections into the upper eyelid and one injection into the lower eyelid) and injections additionally applied into the pretarsal portion. The number of successful treatments with the additional pretarsal injections increased significantly from 81% to 95%, and ptosis occurred significantly less often [28].

Another study also confirmed the superior efficacy of pretarsal rather than orbital injections in 49 primary and secondary non-responders with blepharospasm [36]. A controlled study of 32 [37] and another study of 25 patients with blepharospasm [38] also revealed that pretarsal injections rather than preseptal injections were associated with better efficacy and significantly less ptosis. In 10 blepharospasm patients treated unsuccessfully with conventional bilateral periorbital injections, injecting BoNT into the pretarsal region proved to be highly effective, while the amount of toxin used was considerably less than that used in conventional methods [39].

2.1.2. Electromyography-controlled BoNT applications

Although EMG examination is not a routine strategy for localization of the injections [31, 32], a number of studies used EMG as a guide for accuracy in injecting BoNT into different portions of orbicularis oculi and in some other facial muscles [23, 28].

Besides, EMG studies of the levator palpebrae and orbicularis oculi muscles are instrumental in improving the understanding of the variable responses to BoNT application [26, 40, 41].

2.2. Oromandibular dystonia

Phenomenologically, there are seven types of oromandibular dystonia (OMD): jaw-closing dystonia (JCD), jaw-opening dystonia (JOD), jaw-deviation dystonia (JDD), lip and perioral dystonia, lingual dystonia, pharyngeal dystonia, and combinations. Most of the patients suffer from JCD [42]. Associated features may include protrusion or twisting of the tongue, as well as the involvement of facial, neck, and pharyngeal muscles [7].

OMD responds poorly to systemic therapy, yet a number of small open-label trials indicated significant improvement with BoNT/A injection [18]. Patients with JCD have a better response on BoNT therapy than patients with the other types of movements (JOD or JDD) [43]. JCD injections include the masseters and the temporal muscles; medial pterygoids may also be targeted. In JOD, the focus should be primarily on the lateral pterygoids. The submentalis complex (mylohyoid, geniohyoid, and anterior digastric muscles) has been targeted as well [33].

Palpation may be a helpful approach, but not all muscles are palpable. Another strategy may be to monitor muscle activity by EMG (passive EMG guidance) and inject those that showed increased activity during the particular abnormal movement or posture. However, this is not always possible because EMG recordings of all involved muscles during action dystonia, such as OMD, are technically difficult [42].

2.2.1. Anatomic/clinical muscle selection and localization of the injection needle

In a prospective study of 162 patients, the muscle selection was based on clinical observation and examination coupled with extensive, long-term experience. The masseters and submental muscles were injected with BoNT/A. With a moderate-to-marked improvement, responded 80% of the JCD; 40% of JOD, 33% of JDD, and 52% of the combinations. Complications such

as dysphagia and dysarthria were reported in 19% of the JCD and in 40% of the JOD patients. There was a poorer response and higher complication rate in the JOD than in the JCD [43]. Later on, the study group has modified its technique by directing the injection needle into the most anterior portion of the submental complex and administering the total dosage as a single bolus, which resulted in a marked reduction in dysphagia and other complications [42].

2.2.2. Electromyography-controlled BoNT applications

Brin et al. (1994) described their experience with 96 patients with OMD. Muscle selection was made using EMG and a relatively large number of muscles were considered for injection. EMG was always used to inject the pterygoids (preferentially the external pterygoids) and usually to inject the other muscles. If necessary, the digastrics and submentals were also injected. In all movement categories, patients' function improved from about 30% of normal function to about 74%. Adverse effects were seen in 14% of the patients. Only one case of dysphagia was severe enough to require a change in diet. Most cases of dysphagia were seen in the patients with JOD and were associated with injection of the digastrics [42, 44]. Because of different methods of muscle selection and different injection techniques (clinical and EMG) used by Tan et al. (1999) and Brin et al. (1994), as well as different methods of assessing severity, response, and adverse effects, it is impossible to compare the two studies; the overall results, however, appeared to be similar [42].

An open-label BoNT/A treatment trial of X-linked dystonia-parkinsonism reported 50 cases of OMD and 35 cases of lingual dystonia to be injected under EMG guidance. The OMD group included 32 cases with JOD, 12 cases with JCD, and 6 cases with JDD. The lingual dystonia group consisted of 27 cases with tongue protrusion and 8 cases with tongue curling. All the OMD types as well as lingual dystonias showed substantial improvement at week 4. Adverse events occurred in 19% of the JOD and in 17% of the JCD patients, as the most frequent of them were mouth dryness and dysphagia. The investigators observed higher rate of mouth dryness, particularly with percutaneous lateral pterygoid injections. On the other hand, they stated an opinion that the lateral pterygoid should be injected, as it was a major force producer in JOD, and the treated dystonia was severe, with associated pain. The bilateral intraoral approach under EMG guidance appeared to be safer, faster, and more convenient, rather than the percutaneous approach when treating JOD. The most common adverse event during the lingual dystonia treatment was dysphagia, which occurred in 19% of the tongue protrusion and in 13% of the tongue curling cases [45].

A study evaluated 45 patients treated with quantitative EMG-guided injections of BoNT for OMD: 11 patients with JCD, 7 with JOD, and 13 patients with OMD of mixed type. Marked effect was observed in 70% of the cases. Side effects occurred in 35.6%, most frequently as transient mild dysphagia, thus indicating quantitative EMG BoNT treatment was safe and effective [46]. A report of four cases with OMD that involved the lateral pterygoid muscles producing incapacitating protrusive and lateral jaw movements and displacements used graphic assessment of jaw movements by a magnetic tracking system. The EMG activity was recorded by needle electrodes applying an intraoral approach, whereas the activity of masseter muscles was recorded with surface electrodes. EMG-guided BoNT injections into the muscles

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led to marked reduction of the OMD severity, the mandibular movements, and the functional disturbances [47].

In general, the use of EMG has been suggested for muscles that are not superficially palpable, but it has not been validated [18]. Recently, some authors recommend all injections for OMD to be complemented with EMG guidance and performed with a hollow, 27-gauge, Teflon-coated, monopolar needle. To minimize the risk of contamination, the intraoral injections should be administered last [30, 48]. Other authors indicated that pterygoid muscle injections have to be performed with EMG guidance, as the muscles are not easily accessible to palpation. The EMG-guided approach was often helpful for other jaw muscles, such as the digastric, masseter, and temporalis [4].

In some forms of lingual dystonia, as with the case of tongue protrusion dystonia, because of the various muscles involved in tongue protrusion, as well as jaw opening, they could not be reliably differentiated either clinically or by EMG sampling. This, however, did not hamper the good results from BoNT injections in the 'submental muscles', although some swallowing difficulties could be triggered [42]. There are still unresolved issues concerning the best method of identifying and selectively injecting the most appropriate muscles, as well as the importance of EMG or ultrasound (US) in this process [42].

2.2.3. Ultrasound-guided BoNT injections

In 46 patients with temporomandibular disorders, the anterior temporalis, anterior masseter, deep masseter, anterior digastric, posterior digastric, and sternocleidomastoid muscles were measured bilaterally by US with satisfactory visualization [49]. In clinical practice, however, US guidance is not feasible for the pterygoid muscles and is only hardly feasible for the mimic and pharyngeal muscles, probably because of their direct accessibility. Supra- and infrahyoid as well as temporalis and masseter muscles can be visualized with US. However, guided BoNT injection in this area is rarely necessary [50, 51].

2.3. Laryngeal dystonia (adductor and abductor spasmodic dystonia)

Spasmodic dysphonia (SD) is a rare form of focal dystonia—laryngeal dystonia [52]. It results in irregular, uncontrolled contraction of the laryngeal musculature during phonation. SD is task specific and typically affects connected speech. It can be subdivided, based on the clinical signs and symptoms, into adductor, abductor, or mixed types [53].

The adductor type, caused by spasmodic activity of the vocal muscle (thyroarytenoid), is the most common type affecting 80–90% of SD patients. It induces hyperadduction of the vocal folds during speaking, producing a voice that is harsh, often tremulous, with inappropriate pitch or pitch breaks, breathiness, and glottal fry [4, 54]. The abductor, a less common type, is due to spasms of the posterior cricoarytenoid muscles (PCA), causing a prolonged, inappropriate abduction of vocal folds during voiceless consonants. This results in a breathy, effortful, hypophonic voice with abrupt termination of voicing and aphonic or whispered segments of speech [4].

BoNT/A, or BoNT/B, if there is resistance to type A, is considered the first-line treatment for SD [55]. Most investigators report a 75–95% improvement in voice symptoms and in quality of life [4, 56]. Adverse events include transient breathy hypophonia, hoarseness and occasional dysphagia, dyspnea, and stridor [57].

For adductor SD, the preferred treatment modality is the injection of BoNT into the intrinsic adductor muscle compartment of the larynx that includes most often the thyroarytenoid and, if a satisfactory effect was not observed, the lateral cricoarytenoid muscle as well [58]. Hillel et al. (2004) suggested that interarytenoid muscle may be an active dystonic muscle and should be treated in selected patients [59]. Treatment of abductor SD is challenging, because BoNT injections into the PCA often results in only partial symptom relief. This may be due to inaccurate placement into PCA. Meleca et al. (1997) described a transcricoid technique and compared it with the standard retrocricoid approach in six patients. Both practitioners and patients preferred the transcricoid method because of less discomfort, equivalent or better voice results, and fewer side effects [57, 60]. For treating abductor SD, the cricothyroid muscle can also be injected [4].

Unilateral or bilateral protocols have been proposed for treating both SD types [4, 61]. There are a variety of injection approaches to deliver BoNT into the intrinsic laryngeal adductor compartment, including EMG guidance, the 'point-touch' technique, a transnasal or transoral approach, and percutaneous fiberscopic guidance. No particular technique has been shown to be superior to another [53, 62].

2.3.1. Anatomic/clinical muscle selection and localization of the injection needle

The 'point-touch' technique is an injection method which relies on anatomical landmarks. It is cheaper, quicker and more accessible, but has not yet gained widespread acceptance due to concerns about patient satisfaction. In a prospective study of 37 patients with adductor SD, post-treatment results showed significantly improved swallowing [63]. A retrospective study compared the effectiveness of BoNT injection between EMG-guided and 'point-touch' techniques in the treatment of adductor SD for a period of 8 years. No endoscopic guidance or verification was utilized for injections using the 'point-touch' technique, as based purely on externally palpable laryngeal landmarks. Using a 1.5-inch 27-gauge needle, BoNT was introduced percutaneously into the laryngeal adductor compartment. Adequate needle positioning was guided by palpation and external landmark visualization alone. By the EMG-guided method a 37-mm 27-gauge monopolar, hollow-bore, Teflon-coated EMG needle was inserted percutaneously into the area of the thyroarytenoid muscle with the most active motor unit action potentials (MUAPs). There were no statistically significant differences in the rate of effective injections (94.4 and 93.2%, respectively; $p = 0.7$), need to alter dose, breathiness, or dysphagia. These results suggested that the BoNT treatment efficacy depends not only on the injection method used but also on the experience of the physician [53]. It seemed that the 'point-touch' technique can be well tolerated by the patient. But it is a true blind technique and visualization of the vocal folds may be required to confirm accurate placement of the needle tip in the thyroarytenoid muscle [62]. Another version of the 'point-touch' technique actually represented an anatomic approach to BoNT injection that requires only a flexible nasophar-

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yngeal endoscopy and careful evaluation of the anatomic landmarks. This technique has been used successfully by Green et al. (1992) on 13 patients with adductor SD [64].

2.3.2. Electromyography-controlled BoNT applications

Experienced clinicians suggested that there are several unique instances in which needle EMG guidance is necessary to achieve optimal results and avoid side-effects, and one of them is the percutaneous BoNT injections into vocal cords for the treatment of SD [14, 32]. It was even thought to be the 'gold standard' for adductor SD treatment [63]. In a double-blind treatment trial of BoNT versus saline, laryngeal EMG-guided injections into the thyroarytenoid muscle were beneficial [65]. Several studies confirmed that BoNT transcutaneous injections under EMG control into thyroarytenoid muscle represented a safe and effective treatment strategy [64, 66]. The results obtained, however, did not suggest inferiority of other techniques of non-EMG guided laryngeal BoNT delivery [53]. In a retrospective study of 25 patients with adductor SD, treated with EMG-guided BoNT injection into the thyroarytenoid muscle, substantial symptom relief was reported. However, a high percentage of side effects were observed, although transient and mild — breathiness (68%) and choking on fluid (56%) [54]. Based on the evidence, laryngeal EMG was recommended as possibly effective for the injection of BoNT into the thyroarytenoid muscle in the treatment of adductor SD [65]. A relative drawback of the method might be the need for EMG confirmation of needle placement [64].

EMG-guided BoNT injections are also used as a treating method in abductor type of SD. Blitzer et al. (1992) reported 32 patients who have been treated by sequential percutaneous EMG-guided injections of the PCA muscles and improved to an average of 70% of normal voice. Ten patients, however, required injection of the cricothyroid muscles and type I laryngoplasty [67]. A prospective randomized crossover trial compared two injection techniques—via either a percutaneous posterior-lateral approach (with EMG-guidance) or an endoscopic (transnasal fiberoptic) approach. Although patients perceived some benefits, blinded symptom counts did not substantiate significant reductions in the numbers of breathy breaks occurred with either techniques, and no differences were found between both techniques. Thus, BoNT/A injections into PCA muscle provided limited benefits to patients with abductor SD, demonstrating the need of a more effective therapy [68].

An advantage of EMG guidance is the confirmation of needle's placement within the muscles of the larynx by showing distinct MUAP with phonation, thus ensuring delivery of the exotoxin into the most active portion of the muscle, near the motor end plate [62]. Using a non-EMG-guided technique, placement of the needle into the vicinity of the muscle can be achieved, but it is not possible to confirm placement into the most active portion of the muscle. It is questionable whether BoNT needs to be delivered to the electrically most active portion, or if the EMG signal is just an aid to direct the needle into the correct muscle. On the one hand, it is assumed that more accurately placed dose in a particular muscle should reduce any side effects in an adjacent muscle. On the other hand, it has been demonstrated that BoNT easily passes through muscle fascia and can disseminate to the nearby muscles. It may be that once the needle is in the vicinity of the correct muscle, toxin delivered will dose the entire muscle regardless of needle tip proximity to the most active MUAP [53]. Some authors state that

injecting by EMG guidance is more precise and uses the lowest therapeutic dose [69]. Cited disadvantages include the possibility that EMG signal may be misleading, and the technique is more time consuming, redundant to anatomic localization, or even more uncomfortable due to additional needle positioning and manoeuvring. A few minor disadvantages to laryngeal EMG-guided BoNT administration may be related to a greater patient discomfort due to an inherent longer period of needle placement during the search for MUAPs [53]. Some authors suppose, however, that percutaneous injection with laryngoscopic guidance is less precise [69], although there is not clear evidence to support the superiority of any particular localization technique.

2.3.3. Endoscopy control

Although BoNT injection under EMG guidance is the standard for the thyroarytenoid muscle, in some instances, endoscopy-controlled BoNT placement could be an alternative [62]. Klap et al. (1991) reported satisfactory effect of direct BoNT injections into the thyroarytenoid muscle under fiberoptic visualization in six patients, followed for a period of 2 years [52]. In a retrospective study, a total of 426 BoNT injections were administered in 64 adductor CD patients under laryngoscopy guidance with satisfactory results, especially when BoNT injection was placed at the posterior portion of the thyroarytenoid and directed towards the lateral cricoarytenoid so that both muscle groups were affected [61]. A retrospective open trial investigated the effect of toxin preparation and injection monitoring on 15 patients with adductor SD. BoNT was administered into the vocalis muscle by 112 and 36 injections under EMG or laryngoscopy guidance, respectively. Failure rate did not differ, using EMG (28.6%) or laryngoscopy (30.5%) guidance. The treatment failure may occur regardless of the method of injection, possibly due to mislocalization of the vocal folds [70]. Thirty patients with adductor SD were randomly allocated into an EMG or a fiberscopy-guided BoNT treatment group. There were no significant differences in outcomes between the two groups in either the duration of effectiveness or complications such as breathy voice and aspiration. BoNT injection under fiberscopy guidance appeared to be a valuable alternative to EMG-guided treatment in adductor SD. The fiberscopy-guided percutaneous injections have demonstrated high reliability of confirming needle location. A source of discomfort may be the need of local anaesthesia to aid the insertion of the fiberscope [62]. There is, however, limited number of studies, comparing the endoscope-controlled injection placement with other guidance techniques, and additional investigations have to be performed in the field.

2.3.4. Ultrasound-guided BoNT injection

In laryngeal muscles, US guidance is hardly feasible. The laryngeal muscles (vocalis, PCA) can be injected transorally using endoscopic guidance, or transdermally. For transdermal injection, EMG guidance is crucial, either alone or, optionally, in combination with US [50].

2.4. Cervical dystonia

CD is the most common form of focal dystonia and is marked by deviation of the head around horizontal (torticollis), coronal (retrocollis, anterocollis), and vertical axis (laterocollis), often

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associated with reduced range of motion in the direction contralateral to the movement. Horizontal rotation is the most common abnormal movement, affecting 80% of the patients. It typically arises from activity of the sternocleidomastoid muscle contralateral to the turn and splenius capitis muscle ipsilateral to the direction of turn. Deeper muscles, including the longissimus capitis, splenius cervices, longus capitis, and obliquus capitis, can also be involved. Laterocollis is seen in 10–20% and ipsilateral splenius, sternocleidomastoid, and levator scapulae muscles are involved. Retrocollis and anterocollis are less frequent and involve bilateral posterior and anterior muscles, respectively. Often combinations of torticollis and laterocollis are presented. Shoulder involvement is present in approximately half of the patients. Associated pain is reported in 70–75% [7].

BoNT is the first-line treatment of idiopathic CD, and all commercially available BoNT brands have proven satisfactory symptom relief in more than 85% of the cases [22, 32, 71]. Adverse events are generally mild or moderate and transient, including pain at injection site, neck weakness, flu-like symptoms, hoarseness, dry mouth, and dysphagia. Systemic events include general fatigue and muscle weakness [4].

The most injected muscles are the sternocleidomastoid, splenius capitis, trapezius descendens/semispinalis capitis, trapezius horizontalis, levator scapulae, scalenii, and deep neck muscles [30, 50].

2.4.1. Anatomic/clinical muscle selection and localization of the injection needle

In the large and easily accessible muscles, typically treated in CD, clinical placement seems sufficient for the majority of patients [30, 32]. On physical examination, muscles should be palpated for hypertrophy, activity and contracture, or fibrosis. Areas of pain should be noted [30], as BoNT alleviates pain as well [72]. Manual application into the upper third of the sternocleidomastoid muscle is often sufficient to reduce dysphagia considerably [50].

2.4.2. Electromyography-controlled BoNT applications

The majority of electrophysiological techniques applied for BoNT treatment of CD implied polymiographic EMG for muscle detection and guidance of the injection needle [73]. Electric stimulation (ES) is considered not to be feasible because the response of neck muscles to the stimulus is not specific enough [74]. Only few EMG frequency analysis studies, with limited number of patients enrolled, are advocating some benefits in targeting more specifically the leading dystonic muscles [73]. The need of EMG guidance for CD patients remains an issue of controversy [26]. Although superficial muscles that may be readily palpated are usually involved, Barbano (2001) suggested that needle EMG exploration of the dystonic neck often revealed affecting of deeper muscles which are difficult to access. Furthermore, muscles with opposing actions are often in close proximity, making it possible to do more harm than good with poorly targeted injections [75]. Several studies reported benefits of EMG-guided BoNT injections. Speelman and Brans (1995) showed the benefits of EMG guidance when the accuracy of sternocleidomastoid localization in 139 EMG-guided injections was examined. They found that 83% of needle placement attempts reached the target muscles [76]. According to Wullf et

al. (1993), the EMG guidance proved to be helpful as it restricted the injections into muscles with EMG hyperactivity, thereby economizing the amount of toxin given. They conducted a study of 20 idiopathic torticollis patients, who received EMG-guided intramuscular BoNT/A injections. An overall improvement of 55%, in comparison to the status before treatment was found, and side effects were restricted to short-term dysphagia in two patients [77]. Based on the results of 84 patients, receiving injection under EMG guidance, Dubinsky et al. (1991) revealed treatment effectiveness in 78.7%. The complications included excessive neck weakness, which was observed in 16.0% and dysphagia—presented in 11.1% of the injection sessions [78]. Comella et al. (1992) randomized 52 CD patients into two groups. In the first one, both clinical and needle EMG examinations were used for muscle selection, and injections were performed by EMG assistance. In the second group, muscle selection was based solely on the clinical examination and manual needle location. The EMG assistance did not increase the number of patients improved, but the magnitude of improvement was significantly greater. Moreover, in particular patients with retrocollis, head tilt, and shoulder elevation, additional benefit with EMG-guided BoNT injection were noted [79]. In a prospective study, Lee et al. (2004) evaluated 15 CD patients. In those who underwent EMG-guided BoNT injection, there were fewer BoNT-related side effects due to injection of the adequate dose to the accurate site of hyperactive muscles. Besides, a greater clinical improvement due to confirmation of hyperactivity in target muscles and a better ability to reduce the amount of oral medication were reported. EMG-guided BoNT injections were considered to be useful for patients with retrocollis, for those who have had a suboptimal treatment response to non EMG-guided BoNT injections, and for those with increased concern of side effects or a concomitant goal of reducing oral medications [80]. In a recent, one-year prospective, randomized, and blinded study, Werdelin et al. (2011) evaluated 20 CD patients, comparing EMG-guided injections with chemodenervation after clinical evaluation alone. Quantitative EMG was performed simultaneously in the sternocleidomastoid muscles and the posterior neck muscles on both sides. In patients treated on EMG guidance, clinical outcome, evaluated by objective ratings, was better than in patients treated on clinical judgement alone. In a group blinded, 105 muscles were injected with BoNT, but 37 of those did not show dystonic EMG activity. EMG guidance by interference pattern analysis appeared to optimize BoNT treatment by more precise injection localization and may reduce the amount of the toxin used, side effects, and the risk of development of antibodies [81].

Although the advantages of EMG-guided BoNT application were reported, in most studies, EMG was used not only for injection guidance but also for muscle selection. Due to that reason, some authors advised that all these studies should be interpreted with caution [74]. A recent review, focused on identifying the best method for muscle selection in CD patients, compared EMG techniques with clinical examination and revealed that EMG-guided injections may improve the treatment outcome but did not show an overall better outcome compared to clinical muscle selection and anatomical needle placement [73]. In the presented pooled analysis of 28 studies of which 17 used clinical evaluation to identify dystonic muscles and 11 used EMG for selection and guidance, better results for the EMG approach regarding pain reduction (−40.3 vs.−32.5 %) were recorded. However, improvement was lower for EMG compared to clinical evaluation by rating scales like the Tsui score (−31.9 vs.−43.7%) [73].

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Some critical remarks also question the superiority of EMG-guided injections in routine treatment of CD. It has to be taken into account that positioning of the EMG needle is performed according to anatomic landmarks. The placement of the EMG needle tip into a specific muscle is thereby almost impossible to verify, as selective voluntary activation of neck muscles is not possible and might be additionally superimposed by dystonic activity of adjacent muscles. EMG therefore serves more as a 'functional' guidance than as an anatomical guidance. The assignment of EMG activity to specific muscles is flawed by the same anatomic inaccuracy as needle placement according to anatomical landmarks. Searching for dystonic EMG activity is associated with additional discomfort and pain for the patients. It is more time-consuming and requires some extra costs [74]. Besides, needle EMG does not differentiate between contractions produced by agonist versus antagonist muscles and may be misleading if the patient 'tenses' uninvolved muscles. If a muscle is obviously contracting or is hypertrophied, needle EMG is redundant. A strong argument implies that if the results of BoNT treatment without needle EMG are good, a small additional improvement does not justify the routine use of EMG [14].

On the other hand, based on clinical experience and an investigation of 20 CD cases, Cordivari et al. (2006) suggested that if a patient started to respond poorly to BoNT/A and resistance to the product was excluded, a re-examination and careful placement of injections under EMG guidance may improve the treatment outcome [82].

According to the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, the role of EMG has not been established for CD [17]. It may contribute for improving the outcome, especially in complex forms [32] or in secondary non-responders [82]. Still, evidence is limited and larger studies are needed [73].

2.4.3. Ultrasound-guided BoNT injections

Although BoNT/A has a favourable safety profile and is effective in the majority of patients with CD, in some cases, the treatment outcome is disappointing or side effects occur when higher doses are used. It is likely that in such cases either the target muscles were not injected accurately or unintended weakness of non-target muscles occurred [74]. Mezaki et al. (2000) described an US investigation of cervical muscles for 20 dystonic patients compared with healthy controls. They found contracting synergists responsible for the abnormal posture, a finding not presented in healthy controls. The investigators suggested US to be an accurate method for localizing the contracting muscles during injection, although the treating substance used was not BoNT, but lidocaine and pure ethanol [83]. US is of special value as the injected muscles differ in size, and the deep-seated muscles require a different approach compared to superficial ones [74]. Besides being a useful guidance, Mezaki (2011) suggested that it may be even superior to the EMG monitoring, especially when the obliquus capitis inferior muscle is targeted in rotatocollis, because the vertebral artery or upper cervical nerve root(s) may be injured when the needle penetrates the muscle [72]. Dysphagia is a common side effect after BoNT injections for CD, with an incidence of 10–40%, depending upon the study and dose used. Hong et al. (2012) examined the effects on swallowing using EMG guidance for BoNT injection and dysphagia occurred in 34.7%. Using US, combined with EMG guidance, there was no dysphagia across 27 injection sessions, possibly because of retaining the injected toxin

within the muscle [84]. Schramm et al. (2015) recently conducted a review of the relevance of sonography in CD and provided a statement from clinical experts for its use. In the authors' opinion, the routine use of US injection guidance could be recommended in general, as it facilitates anatomically precise and reproducible injections in specific muscles. Ordinary injected muscles are the splenius capitis, sternocleidomastoideus, semispinalis capitis, and levator scapulae muscles, as well as more difficult accessible, small, or deeply located muscles like the longus colli, longus capitis, scalene, and obliquus capitis inferior and superior muscles. This method might prevent unintended muscle weakness due to diffusion of BoNT, bearing in mind that injected neck muscles may be small or thin and lie in close proximity to each other. US is also indispensable when case-specific anatomic conditions are present such as obesity or very pronounced neck muscles, or even muscle atrophy, occurring in consequence of previous treatments. Furthermore, US helps in preventing injection in blood vessels and nerves. This might be of special importance in CD as injections in lateral cervical muscles bear a high risk for injuries of adjacent structures (carotid artery, thyroid truncus, internal and external jugular vein, vagal nerve, phrenic nerve, and brachial plexus). With injections in the dorsal neck region, the vertebral artery or the spinal canal may be erroneously injected. Moreover, US guidance offers the potential for dose reduction. That may decrease the risk of producing neutralizing antibodies and therefore ensure long-term efficacy of treatment. The combination of US and EMG could overcome the shortcomings of EMG regarding anatomic precision and would allow an accurate assignment of dystonic activity to specific muscles [74]. However, as there are only a few small randomized studies suggesting superiority of sonography guidance compared to conventional needle placement, US guidance should be investigated in future clinical studies [50].

2.4.4. Positron emission tomography/computer tomography control

Herting et al. (2004) reported a case of a patient, suffering from severe anterocollis, where repeated computer tomography (CT)-controlled injections of BoNT into the right longus colli muscle allowed a precise location of the needle and injection of the toxin, leading to an obvious improvement of symptoms [85].

As it is well known that glucose metabolism and 18F-FDG uptake are enhanced in contracting skeletal muscles, it was suggested that the degree of 18F-FDG uptake may be associated with the strength of contraction. Moreover, an integrated positron emission tomography/computer tomography (PET/CT) controlled method was found to provide both metabolic and anatomic information on hypermetabolic lesions [86, 87]. Sung et al. (2007) investigated six patients with idiopathic CD. BoNT injections into target muscles were performed with Teflon-coated monopolar needle electrode cannula guided by EMG. For deep cervical muscles adjacent to a major artery or the major nerve trunk (obliquus capitis inferior and longus colli muscles), BoNT was injected under CT or US guidance. All four patients who underwent PET/CT-guided injections experienced a significant improvement in symptoms, even though in three of these patients, previous BoNT therapy guided by clinical findings had failed [87]. Similar results were obtained by Lee et al. (2009), who conducted a study with 14 BoNT treated CD patients and compared different localization techniques. Muscles for BoNT injection were selected after

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considering abnormal posture type and EMG, and PET/CT findings. When selected muscles were located beyond the expected coverage of the EMG needle, near an important structure, imaging-guided injection was considered. A total of 13 BoNT injections in eight patients were performed under imaging guidance, and technical success was achieved in all cases. For injections into the longus colli muscle (poor sonic window due to the pharynx), the obliquus capitis inferior muscle, and the scalenus anterior, scalenus posterior, and levator scapulae muscles, CT guidance was chosen. Otherwise, US guidance was preferred because of its convenience. The results obtained using PET/CT and imaging guidance were superior to results obtained on the basis of physical examination or EMG [71]. Although CT provides a precise visualization of deep muscles of the neck and the surrounding structures, a disadvantage of the method is that its use is limited to a clinical setting where CT is accessible. Therefore, the use of CT has been recorded in a small number of patients. Moreover, CT is too expensive for frequent use in daily practice, it is not dynamic, and patients are exposed to radiation [50, 74].

PET has been used in two studies (mentioned above) to identify hypermetabolic and presumably dystonic muscles, whereas injection was performed under CT or US guidance [71, 87]. PET, therefore, rather represents a diagnostic method and not a method for injection control [74].

2.4.5. Fluoroscopy (electromyography combined with fluoroscopy)

While BoNT is the treatment of choice for CD, patients with anterocollis, who receive injections into the sternocleidomastoid and anterior scalene muscles, present a disproportionate number of treatment failures. Incomplete muscle selection may be one cause of treatment failures in anterocollis. Deep cervical muscles, such as the longus colli, are not routinely injected. Glass et al. (2009) described a technique for longus colli injection in three cases of anterocollis and reported the clinical outcomes of 10 such BoNT injections. The patients had previous treatment failures with sternocleidomastoid/anterior scalene injections or no activity was recorded during the needle EMG investigation of these muscles. All patients were injected into the longus colli under fluoroscopic and EMG guidance, which resulted in a significant symptomatic improvement (8 of 10 injections). Two patients reported mild dysphagia without serious complications after dose increased. It seems that fluoroscopic guidance allows safe and effective BoNT injections into deep cervical muscles [88]. However, fluoroscopy is associated with the application of considerable amounts of radiation and multiple intramuscular injections of iodinated contrast media, both of which can be potentially harmful [50].

2.4.6. Magnetic resonance imaging control

Magnetic resonance imaging (MRI) allows high-definition visualization of deep muscles, such as the longus colli and obliquus capitis inferior, glandular tissue and critical structures. Mixtures of BoNT and contrast medium allow documentation of the toxin placement. However, the visualization is not in real time, so that the relationship between the injection needle and the target tissue cannot be monitored continuously. Other disadvantages including costs and time prevent the routine use of this method [50].

2.5. Limb dystonia

Focal upper limb dystonia usually starts in the hand and is task specific; however, with progression, task specificity is gradually lost [89]. Other occupational hand dystonia and nontask-specific (fixed) dystonia are presented mainly by writer's cramp [17]. The upper extremity is affected more commonly than the lower, and most BoNT studies deal with the upper limb, and especially with writer's cramp [17, 18]. Writer's cramp is a task-specific dystonia characterized by involuntary, repetitive, or sustained contractions of finger, hand, or arm muscles that occur during writing and produce abnormal postures or movements that interfere with normal handwriting [90]. Injections for writer's cramp are usually focused on finger flexors and extensors in the forearm, but wrist pronators and flexors are often involved [18].

Foot dystonia is often presented with foot inversion, toe dorsiflexion, and/or ankle plantar flexion. The injected muscles may include tibialis posterior, extensor hallucis longus, gastrocnemius, and long toe flexors. Usually the treatment requires higher dose of the neurotoxin [4].

BoNT remains the first choice treatment, as there are no effective alternative medical or well-established surgical therapies. It is recommended as probably effective for treatment of focal upper extremity limb dystonia. BoNT treatment is considered to be possibly effective for lower extremity dystonia, but the presented data are insufficient to provide a recommendation [17, 91]. Therapeutic difficulties occur due to involving the subtle tuning of many muscles. Besides, it is difficult to obtain the requested quality of voluntary movement without weakness. Pain is the symptom most frequently improved, often independently of motor function [4]. In case of neutralizing antibodies against the A toxin, the treatment with BoNT/ B or BoNT/F is a possible alternative [32, 92]. The use of BoNT to treat limb dystonia requires thoughtful technique including customization of doses and muscle selection. The first step in treatment planning is to identify the muscles most severely affected, separating out dystonic from compensatory movements. After initial inspection, EMG- or US-guided muscle selection usually allows refining the choice of targets [89].

2.5.1. Anatomic/clinical muscle selection and localization of the injection needle versus electromyography-controlled BoNT applications: passive and active electromyographic guidance

As focal hand dystonia is a complex disorder, usually involving several muscles, and many of them are deep, not easily identified by surface landmarks and not palpable on examination, their localization is often challenging [50]. In some instances, however, physicians use their knowledge on surface anatomy and clinical examination to localize the target muscles but EMG guidance may be particularly important. In a trial, 40 patients with writer's cramp were randomized in a double-blind design to BoNT or an equivalent volume of saline placebo. Injected muscles were chosen based on clinical examination, but injections were performed under EMG guidance and a significant improvement was obtained [90]. In a prospective, double-blind crossover study of 17 patients with upper and lower limb dystonia, target muscles were identified either clinically on the basis of the abnormal posture and muscle contraction or by EMG guidance. The EMG method allowed the patient to perform the task that precipitated the cramp while EMG activity was recorded. Clinical and EMG identification

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usually correlated well, but on some occasions, muscles identified by clinical evaluation were not regarded as abnormal by EMG and vice versa. Received injections were EMG guided. Using a patient subjective scale, 82% reported benefit; however, physician rating did not reveal significant difference in the treatment outcome. The main side effect was focal weakness that emerged after 53% of BoNT injections [93]. In another placebo-controlled, double-blind, crossover trial in 20 patients with writer's cramp, muscle selection was determined by clinical examination. In eight patients, however, EMG was employed to guide selection of muscles. Twelve patients had improvement in pen control, but only four had significant improvement in writing. Focal weakness was the only adverse event and was severe enough to worsen pen control in one patient [94]. Molloy et al. (2002) compared the efficacy of EMG-guided versus non-guided injections for limb dystonia in a randomly chosen cohort of 14 consecutive patients. Only 37% of needle placement attempts reached the proper muscles in the absence of EMG guidance. Forty-seven percent were placed in an unintended muscle or fascicle and 16% were outside the muscle altogether. Individual finger fascicles of larger muscles such as flexor digitorum profundus or extensor digitorum communis were particularly difficult to isolate accurately without EMG [95]. EMG recording during the task associated with dystonia may be helpful to pinpoint muscle activation patterns [18]. Schuele et al. (2005) demonstrated benefits of EMG guidance in a study of 84 musicians with focal task-specific dystonia, treated with EMG-guided BoNT injections, where 69% of the patients experienced improvement from the injections and 36% reported a long-term benefit in their performance ability [96]. Sojer et al. (2001) even suggested that BoNT treatment of writer's cramp required EMG-guided injections in order to avoid side effects [32]. Because of the numerous small muscles located in a close proximity, some authors give priority to an active EMG muscle selection and needle localization, namely ES. It may be applied when a common muscular origin and innervation of different adjacent muscle exist, as with the extensor digitorum, flexor digitorum sublimis, and profundus. In such cases, passive EMG guidance appeared to be less useful, as it is difficult to flex or extend these digits without also causing similar movement in the adjacent ones. However, BoNT may spread to adjacent sites by diffusion, even with use of increasing target accuracy-guiding techniques [12]. Barbano (2001) also recommended ES for upper extremity dystonia, where an inappropriate toxin placement can worsen the functional outcome by weakening non-dystonic adjacent muscles, or in cases where it is important to weaken particular fascicles of individual muscles. Moreover, ES ensures the proper localization in sedated patients or in those who otherwise would have difficulty with fine motor control, such as children [75]. Due to the lack of consensus on the best way to localize muscles in the forearm for BoNT injection, Greenen et al. (1996) conducted a study comparing EMG with ES in 12 patients with the conclusion that localization by stimulation is probably at least as good as EMG. Weakness of 'non-target' muscles was present with both techniques [97]. In a critical expert review, based on long-term experience, Jankovic (2001) concluded that there are several unique instances in which needle EMG guidance is essential to achieve optimal results. These include BoNT treatment of certain task-specific dystonias, like in keyboard and string musician's cases, that are particularly difficult to treat because accurate and well-coordinated hand and finger movements are involved. However, even in patients with occupational cramps, such as dystonic writer's cramp or focal hand tremor, an injection into the forearm flexor muscles

(e.g., flexor carpi radialis and flexor carpi ulnaris) could be successfully performed by using well-defined anatomic landmarks. Benefits were obtained from local BoNT injections in patients with dystonic writer's cramp that were similar to the benefits seen when using complex EMG and fine-wire electrodes to localize bursts of muscle activation during the task and by injecting the toxin through a hollow EMG needle into the belly of the most active muscle [14, 98]. Therefore, if there is a minimal increase in improvement, the routine use of the EMG-guided approach does not justify the increased discomfort, time, and expense of this method, as compared with clinical examination. Moreover, it is known that BoNT diffuses outside of the target muscles even when these muscles are localized by ES [14].

In one series of patients with upper limb dystonia, weakness of uninjected muscles, adjacent to the injected, was found in 63% of the patients which was the primary cause of a suboptimal response in 15% of them [99]. The treatment of focal limb dystonia with BoNT is challenging, particularly in achieving sufficient neuromuscular blockade to alleviate dystonic movements without causing excessive muscle weakness. While many clinicians advocate EMG or ES to optimize needle localization for injection, further data are needed to establish this recommendation [17].

2.5.2. Ultrasound-guided BoNT injections

Active EMG guidance or US guidance (or a combination of both) has been found to be most helpful when targeting the forearm muscles especially for task-related dystonia [100]. In many patients with writer's cramp, the BoNT dose could be reduced when switching from manual application to US guidance [50]. US is feasible for proximal and distal arm muscles, intrinsic hand muscles, and leg muscles. For forearm and leg muscles, US visualization may protect sensitive adjacent structures (nerves, large vessels). The usefulness of US is low, however, in shoulder, proximal arm, and superficial axial muscles, because of their size and accessibility [50].

3. Spasticity

Central nervous system disorders with upper motor neuron dysfunction often produce spasticity and hypertonia of the limb that is dependent both on velocity and on range of motion. Besides increased tone, spasticity presents typically with increased muscle stretch reflexes, muscle spasms and clonus, weakness (spastic paralysis), and impairment of voluntary movements. Spasticity may occur in diffuse or focal pathological disorders of the brain and spinal cord. In adults, spasticity results from diverse aetiologies, including stroke, traumatic brain injury, multiple sclerosis, and neoplasm involving the central nervous system. The most common cause of spasticity in children is cerebral palsy (CP) [4, 18, 101]. In the upper extremities, the shoulder adductors, elbow flexors, wrist pronators, finger, and thumb flexors are frequently involved. In the lower extremities, hip adductors, knee extensors, and ankle plantar flexors and inverters may have increased spastic tone [18].

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Treatment is aimed at prevention of contractures and improved functional outcome, without worsening weakness. Non-pharmacologic treatment options often do not provide long-term relief, and systemic interventions can have intolerable side effects [102]. BoNT efficacy is better established for spasticity in the upper rather than lower limb [4, 18]. BoNT doses used in spasticity are higher than those used in other movement disorders. The treatment effect is maintained for approximately 3–5 months [4]. Adverse events are rare, often benign and of short duration, as the majority of the self-reported adverse events include local muscular weakness or fatigue [103].

Several localization techniques are available to physicians that allow identification of the selected target muscles. These methods include anatomic localization in isolation or in conjunction with EMG guidance, ES guidance, or US guidance [102].

3.1. Anatomic/clinical muscle selection and localization of the injection needle

BoNT/A injections given by manual intramuscular needle placement in the lower extremity under general anaesthesia is an established treatment and standard of care in managing spasticity in CP children [104]. Most clinicians do so using manual technique without radiologic or EMG guidance to aid needle placement [105, 106]. This procedure is usually performed by finding the largest bulk of the muscle and injecting the toxin into several sites at mid-belly [105]. In a placebo-controlled, double-blind, randomized multicentre study, Mall et al. (2006) evaluated BoNT/A effect on adductor spasticity in 61 CP children, concluding that in large and easily accessible muscles, that are typically treated in adductor spasticity, clinical placement seems sufficient for the majority of patients [107]. However, Chin et al. (2005) investigated the accuracy of the 'free hand' intramuscular needle placement guided by anatomic landmarks, palpation, and passive stretching of the muscles with ES-guided method for upper and lower limb spasticity in 226 CP children. The accuracy of manual needle placement compared with ES was acceptable only for the gastrocnemius and soleus muscles (75%). It was unacceptable for all the other muscles investigated—the hip adductors (67%), medial hamstrings (46%), tibialis posterior (11%), biceps brachii (62%), and forearm and hand muscles (13–35%). The authors recommended using ES or other guidance techniques to aid injection preciseness [106]. In a prospective study, the accuracy of manual needle placement of 272 injections in gastrocnemius muscles of 39 children with spastic CP was checked against US. The needle was accurately inserted into gastrocnemius muscles in 78.7% of the cases. Accuracy was acceptable for gastrocnemius medialis (92.6%), but not for gastrocnemius lateralis (64.7%) [108]. A randomized controlled trial compared the efficacy of BoNT/A injection guided by ES or palpation, and 2 weeks of physiotherapy, to treat spasticity of the ankle plantar flexors in 65 children with spastic CP. The ES-guided injection group plus physiotherapy showed greater improvement in the spasticity and functional performance, than the other two groups (the BoNT/A group guided by palpation injection plus physiotherapy and the physiotherapy-only group) [109]. Some critical evaluation of the largest studies applying manual needle placement in the spastic lower extremity of CP children was performed. Warnink-Kavelaars et al. (2013) pointed as a main disadvantage of the studies the lack of a standardized injection protocol, which interfered with a correct base for accurate statistical analysis. Besides, methodological

methods used did not allow the calculation of positive and negative predictive values, sensitivity, and specificity, which obscured the outcome [104]. Thus, Warnink-Kavelaars et al. (2013) developed a detailed protocol for manual intramuscular needle placement checked by passive stretching and relaxing of the target muscle (PSRM). It was developed for each individual muscle injection location of the adductor brevis, adductor longus, gracilis, semimembranosus, semitendinosus, biceps femoris, rectus femoris, gastrocnemius lateralis, gastrocnemius medialis, and soleus muscles. PSRM is a rapid intramuscular needle localization technique, useful for larger muscles, especially in the lower extremity, which can be performed without sophisticated equipment. Manual intramuscular needle placement would be assessed as a PSRM-positive verification when the needle moves upon passive stretching and relaxing of the intended muscle, or a PSRM-negative verification when there is no movement or only a small straight motion of the needle upon passive stretching and relaxing of the muscle. This needle location protocol would be verified then by means of ES [104].

Several clinical trials compared the efficacy of BoNT treatment in adults with spastic upper or lower limbs, when injections were placed only by clinical and anatomic landmarks, with those guided by ES or US. Still, Childers et al. (1996) suggested researches comparing more precise localization methods for BoNT/A injections might further establish the importance of EMG guidance [110]. A very recent randomized controlled study compared manual needle placement with ES- and US-guided techniques for BoNT injection of 60 adults with arm (wrist and finger) spasticity. One month after injection, the outcome measurement instruments used revealed greater improvement in the ES group than in the manual needle placement group. Furthermore, patients improved more in the US group than in the manual needle placement group. No difference was found between the US and the ES groups. These results implied that instrumental guidance may improve the outcome of BoNT injections into the spastic forearm muscles of stroke patients [111]. Another recent controlled trial compared the three localization techniques, mentioned above, but this time for the gastrocnemius of adults with spastic equinus after stroke. Forty-seven patients were randomized into three groups, and each patient received the same dose of BoNT/A into the lateral and medial head of the gastrocnemius muscle of the affected leg. One month after injection, the modified Ashworth scale recorded greater improvement in the US group than in the manual needle placement group. The ankle passive range of motion improved better in the US group than in the ES and the manual needle placement groups. No difference was found between groups for the Tardieu scale. A superiority of the US-guided injection technique was shown and the authors concluded that it could improve the clinical outcome of BoNT injections into the gastrocnemius of adults with spastic equinus [112]. Henzel et al. (2010) also compared US localization with surface landmark localization of BoNT injection targets for forearm muscle spasticity in 18 patients. Flexor pollicis longus, flexor carpi radialis, pronator teres, and flexor digitorum superficialis were identified by these separate localization techniques. Significant differences were observed between surface and ultrasound proximodistal and lateral coordinates for several flexor muscles. It seemed that US could improve the accuracy of toxin placement and help to avoid injection into vascular and nerve structures, so that it should be considered as an adjunct for localization in patients with upper limb spasticity [113].

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Schnitzler et al. (2012) evaluated the accuracy of manual needle placement in the gastrocnemius muscles guided only by anatomical landmarks and palpation. One-hundred twenty-one practitioners were evaluated. Fifty-two injections were successful (43%) and 69 failed (57%), showing a poor success rate, regardless of the injector experience. Therefore, muscle palpation and anatomical landmarks were insufficient to ensure the accuracy of BoNT/A injections, even for large, superficial muscles [114]. In clinical practice, however, clinical landmarks and palpation are still often used for injecting superficial limb muscles.

3.2. Electromyography-controlled BoNT applications

The use of EMG or the motor point stimulation method is recommended to identify muscles targeted for injection, particularly for the smaller muscles in the forearm and hand [105]. Several case series and small studies reported a satisfactory treatment outcome when identification of the target muscles in the affected hand and forearm of post-stroke adults was made by passive EMG that was used also to guide the injection needle [115–117]. However, EMG was successfully applied also in the BoNT treatment of large, superficial, as well as deep muscles in the lower extremity. Statistically significant improvement in gait parameters were noted in the treatment of 12 chronic hemiparetic patients with pronounced lower limb extensor spasticity. The soleus, tibialis posterior, and gastrocnemius muscles of the affected side were injected using a 21-gauge Teflon-coated needle, which was also used as an EMG electrode. Injections were made at two sites close to the motor point, which was identified by standard neurophysiological techniques. The toxin was injected only when either a continuous or stretch-induced EMG activity was recorded, otherwise another injection site in the vicinity was checked [118]. An open BoNT/A effectiveness study comprised 40 patients, with moderate to severe spasticity of the upper (13) or lower limbs (27) refractory to conventional physical and medical treatments. To ensure precise muscle selection, the authors localized the target muscle primarily on clinical assessment, and after that recorded muscle activity using EMG and injected targeting the middle third of the muscle belly. The initial dosage of BoNT/A varied with individual muscles and the degree of their involvement as judged clinically and as confirmed by EMG. Thirty-four patients (85%) derived worthwhile benefit, with improved limb posture and increased range of passive motion in 31, pain reduction in 28 of 31 with pain, and improved function in 16. Side effects were limited to local and usually mild discomfort from the injections (19), symptomatic local weakness (1), and local infection (1) [119].

Active EMG guidance may be applied when treating spasticity, where it is difficult to accurately target the muscle using voluntary contraction. Following injection, however, BoNT may spread to adjacent sites by diffusion, even with the use of special guidance techniques to increase the accuracy of targeting [12]. Quantitative EMG criterion (turn/amplitude analysis) may also be a valuable tool for selection of target muscles, determining benefits of single and subsequent BoNT applications in the treatment of spasticity [120].

In CP children, several studies reported some benefits from BoNT injections after ES localization of appropriate muscles [121, 122]. ES is easy to perform, does not require formal EMG training, and does not prolong the procedure significantly [105]. Although the passive [123] as well as the active EMG-guided techniques have shown to be more accurate in needle

placement than the manual technique, they are of limited use in children because the procedure is painful [124] and time-consuming, and requires the cooperation of the patient. Thus, it does require the patient to have sedation or mask anaesthesia. However, these techniques are used in needle placement, but it remains uncertain whether the effort to improve the BoNT injection accuracy would lead to a better response to the toxin [105].

In general, it seems that the importance of EMG or ES for guiding BoNT injections in limb muscles to treat dystonia or spasticity appeared to be based more on theoretical and preclinical data than on controlled clinical trials. Questions remain about the preferred administration of BoNT for these conditions. Future clinical researches are necessary to demonstrate a clear functional benefit of any particular injection localization method [125].

3.3. Ultrasound-guided BoNT injections

As BoNT/A is a first-line treatment for post-stroke focal spasticity, and the accuracy in delivering the toxin to the target muscles may influence the treatment outcome, a randomized clinical trial compared the reduction of upper limb spasticity using US guidance and manual needle placement (two groups of 15 stroke patients each). After one month of follow-up, the scores of the modified Ashworth scale and the finger position at rest were significantly improved in both treatment groups, although these clinical outcomes were significantly better in patients treated under US guidance [126]. In the above-mentioned randomized controlled study, manual needle placement was compared to ES- and US-guided BoNT injections into spastic forearm muscles and both US- and ES-guided techniques revealed better results than manual needle placement, but no difference was found between the two instrumental guided groups [111]. Henzel et al. (2010) compared US localization with surface landmark localization of BoNT injection in the forearm muscles in 18 spasticity patients and significant differences were observed between surface and ultrasound proximodistal and lateral coordinates for several flexor muscles, assuming that ultrasound can improve accuracy of toxin placement [113]. Another controlled trial (described more detailed above) compared manual needle placement versus ES and US guidance, but this time for the gastrocnemius muscle with better results obtained in the US group than in the ES and manual needle placement groups [112]. Ding et al. (2015) very recently explored the effectiveness of colour Doppler US-guided BoNT/A injection combined with an ankle foot brace for treating lower limb spasticity after a stroke. They found that the colour Doppler US-guided BoNT/A injection could be a safe and precise technique and a useful adjunct to the ankle foot brace treatment method [127]. US feasibility is intermediate in superficial leg muscles. It is high in forearm muscles, intrinsic hand muscles, and deep leg muscles, unless spasticity is massive and functionality is not an issue [50].

As the US-guided BoNT injection technique is easy, quick and painless, many authors suggested it might be a suitable method for use in children [105]. Moreover, according to the European consensus statement, children with CP should generally receive BoNT injections using EMG guidance or US guidance [128]. Kown et al. (2010) recently compared the clinical outcomes of ES- and US-guided localization techniques for BoNT/A gastrocnemius injections for the treatment of spastic equinus in CP children. Subscales of the physician's rating scale significantly improved in the US-guided group, but no statistical differences were noted in the

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modified Ashworth scale, the modified Tardieu scale, and the selective motor control. According to the authors, visual feedback by US could improve the accuracy of selective neuromuscular blocking of the gastrocnemius [129]. Besides, this guidance is preferable in children due to a better tolerability [50]. Another study compared manual needle placement with US-guided technique for BoNT injections into affected lower extremities in CP children. For the lower limb spasticity, the deep-located tibialis posterior muscle, although potentially difficult to inject, needle insertion is often performed using anatomic landmarks for guidance. Accordingly, the US anatomy of the lower leg was investigated in 25 subjects. B-mode, real-time US was performed using a 5 – 12 MHz linear array transducer. During anterior and posterior approaches, safety window width and depth were measured at the upper third and at the midpoint of the tibia. Considering the safety window width, this study suggested needle placement at the upper third of the tibia for the anterior approach and at the midpoint for the posterior approach to be safe and useful in BoNT injections [130].

US guidance of BoNT injections, however, was not solely used for limp spasticity. Chen et al. (2010) aimed to evaluate the effects of a single transrectal US-guided transperineal injection of BoNT/A to the external urethral sphincter for treating detrusor external sphincter dyssynergia in 18 patients with suprasacral spinal cord injury. There were significant reductions in integrated EMG and static and dynamic urethral pressure, but not in detrusor pressure and detrusor leak-point pressure after treatment. Postvoiding residuals also significantly decreased in the first and second month after treatment. The technique had beneficial effects in treating detrusor external sphincter dyssynergia [131]. Later on another study compared the results of a transrectal US-guided BoNT injection (18 cases) with those of a cystoscopy-guided method (20 cases) to the external urethral sphincter. Although there were no significant differences between the groups in all of the outcome measures, the study demonstrated that transrectal US-guided transperineal BoNT injection may be an alternative to a cystoscopy-guided injection. This alternative procedure provided clinicians with an innovative and less invasive method that is performed without requiring anaesthesia or cystoscopy [132]. In a non-controlled clinical trial on 19 men with sphincter hypertonia due to spinal cord injury, BoNT was injected through the transperineal way in the external urethral sphincter under EMG and transrectal US guidance, and that appeared to be an effective and safe therapeutic option [133].

It appears that although at present it is not possible to identify a golden standard among injection techniques, US guidance may be very useful in precise targeting of injections, and may help to avoid BoNT application into fat, fibrosis, vascular, and nerve structures, minimizing the spread of the toxin outside the targeted muscle belly, thus improving clinical outcomes [126]. As it is a non-invasive method, providing a relatively quick and painless muscle selection, the US-guided BoNT injection has been recommended as a standard procedure in treatment of lower leg spasticity in children with CP [50].

3.4. Endoscopy control (esophagoscopy and electromyographic guidance)

Since dysphagia and deglutition problems combined with aspiration are often caused by spasticity, hypertonus, or delayed relaxation of the upper esophageal sphincter, Schneider et al. (1994) replaced the conventional treatment including lateral cricopharyngotomy by

localized BoNT injections into the cricopharyngeal muscle in a series of seven patients. For precise localization, injections were performed under general anaesthesia after location of the cricopharyngeal muscle by direct esophagoscopy and EMG guidance. Injections were administered into the dorsomedial part and on both sides into the ventrolateral parts of the muscle. All but two patients experienced complete relief or marked improvement of their complaints. There were no severe side effects or postoperative complications. This method seemed to be an effective alternative treatment to invasive procedures for patients with isolated dysfunction of the upper esophageal sphincter, and also for patients with more complex deglutition problems combined with aspiration [134].

3.5. Magnetic resonance imaging/computer tomography/fluoroscopy

MRI-, CT-, and fluoroscopy-guided procedures are typically performed by interventional radiologists [101, 135]. Because most clinicians who perform BoNT injections are not typically radiologists, US guidance of the injection is the imaging localization method routinely used. Moreover, it has several advantages in comparison with the other imaging methods, including lack of radiation, low cost, and higher accessibility, whilst providing comparable results with the mentioned imaging guiding techniques [50, 74].

4. Summary

All the studies reviewed in this chapter were quite heterogeneous regarding the characteristics of subjects and dosage, study methodology, clinical outcome measurements, and these differences hinder the possibility of performing an exact comparison or statistical analysis. Most of the studies either exploring an injection localization technique or comparing different guiding methods enrolled a small number of patients that did not allow a general unflinching recommendation to be made. The heterogeneity of muscles affected by dystonia or spasticity also contributes to the latter. However, there were some randomized, controlled clinical trials presented, but the most frequent conclusion was that there is still need of more studies in the field, so that a solid proof of the superiority of a certain localization method for BoNT injection in each specific condition can be offered.

There is informal agreement on the practicalities of BoNT injections for dystonia. The clinical examination is the simplest and most commonly applied method for localization of an overactive muscle. Based predominantly on palpation and surface anatomy, the clinical examination is usually sufficient to target a superficial muscle when not lying in close proximity to antagonistic muscles, such as most facial and some cervical muscles. Thus, it is routinely applied in the treatment of blepharospasm, some types of CD, and in many JCDs [4, 26, 106]. In these regions, EMG and imaging-guided targeting provide a second-line approach whenever refinement of muscle selection is needed or when treating a complex form [4, 71].

Although it might be beneficial, EMG is not necessary for large, superficial, easily visible muscles but is advisable for smaller and deep muscles, not readily accessible to palpation [18]. This would be the case of SD and JOD [26]. In the case of some task-specific dystonias, EMG

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guidance is believed to provide optimal treatment results [14]. Barbano (2001) pointed that the main advantage of needle EMG guidance is precision of toxin placement, which allows a lower dose to produce an equivalent effect. Furthermore, lower toxin doses will decrease the chance of developing neutralizing antibodies and may also allow the injection of more muscles in patients with more widespread disease [75]. However, passive EMG guidance requires selective activation of the target muscle, which is difficult to perform for patients with higher degree disturbances. In patients with dystonia and sometimes also in patients with spasticity, the co-activation of adjacent muscles may superimpose the target muscle activity. EMG guidance may be improved by ES via the injection electrode [50]. ES is the technique of choice when attempting to precisely target small muscles sited adjacent to muscles for which no BoNT effect is desired, as it is in the forearm and foot muscles. Passive EMG guidance is preferably used when injecting patients with CD or SD [12]. The disadvantages of EMG guidance include increased discomfort due to larger size of EMG needles and the lack of identification of critical structures, such as nerves and vessels and the lack of control of the applied BoNT [50]. Moreover, needle EMG is relatively invasive and may cause complications, such as bleeding and infection, and presents electrical hazards [87]. Jankovic (2001) pointed that if there is an obvious benefit of non-guided EMG BoNT treatment, a small additional improvement does not justify the routine use of EMG [14]. It is presumed that quantitative EMG-guided injections of BoNT for OMD and CD may provide treatment benefits, but very few studies, exploring the methodology, are available [46, 73]. Surface recording electrodes have been used in some trials but their recordings are limited to superficial muscles. Fine-wire electrodes have also been used, mainly for simultaneous recordings of several muscles. All these techniques are more appropriate in the research setting [26].

Recently imaging-guided BoNT injections become more popular and practiced. B-mode US allows immediate and high-resolution imaging of the injection needle position within the target region. Visual identification of muscles and depth control of needle placement are the key features of US-guided injection that lead to improved targeting and safety of BoNT applications [50, 74]. Some physicians also used the color Doppler technique in addition to the real-time B-mode scanning in order to visualize more accurate adjacent blood vessels. An emerging application is the US-guided BoNT injection into deep cervical and nuchal muscles in patients with CD, such as the scalene muscles, the longissimus cervicis muscle, and the obliquus capitis inferior muscle [50]. The use of US for locating both superficial and deep muscles is growing, as it is safe, non-invasive, and less distressing than EMG. US guidance is extremely useful when injecting muscles, adjacent to large blood vessels, or nerves, as is the case with deep cervical, forearm, and leg muscles injections [18]. The method, however, is not feasible for the pterygoid muscle and hardly feasible for the most mimic, pharyngeal, and laryngeal muscles.

Other imaging techniques, including CT or PET/CT, MRI, and fluoroscopy, are used to help accurate selection when affected muscles are deeply located (as with CD); however, these techniques are of limited value due to high costs, radiation exposure, or non-availability in daily clinical routine [71, 74].

Endoscopy-controlled BoNT injections in the terms of fiberscopy or laryngoscopy, for the treatment of SD, or as esophagoscopy in spasticity, may lead to a satisfactory treatment outcome, but often require a multidisciplinary approach that limits to some extend its use in the clinical practice [62].

Manual needle placement is still often applied in the BoNT treatment of limb spasticity. It might be sufficient in some instances when targeting large and easily accessible muscles [107], although contradictory data exist, suggesting poor success rate [114]. Thus, most studies in this area deal with electrophysiological or US techniques to optimize muscle localization for injection. Another common approach is to perform ES or EMG targeting. Similarly to focal limb dystonia, EMG is advisable for smaller and deep muscles, and it is particularly applicable in forearm and lower leg muscles and hip flexors (psoas major) [18]. Due to the listed advantages, US is considered as a valuable adjunct for muscle localization in patients with spasticity and could improve the accuracy of BoNT placement, as well. Moreover, US is already widely applied in neuropaediatric care for CP patients, as it was associated with less pain [74].

The preference of a specific localization BoNT injection method also depends on the clinical expertise of the performer, the profound knowledge on anatomy and clinical landmarks, as well as the experience in the field of EMG, US, or other more specialized disciplines as radiology and laryngology. Besides, the guiding injection technique used is not so much important in some instances as is the expertise of the physician in the field. In clinical practice, the injection guidance usage also depends on the facilities and trained personal available, as well as on the expenses incurred.

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References

[1] Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev. 1981;33(3):155–88

[2] Jankovic J. Botulinum toxin in clinical practice. J Neurol Neurosurg Psychiatry. 2004;75(7):951–7

[3] Aoki KR, Guyer B. Botulinum toxin type A and other botulinum toxin serotypes: a comparative review of biochemical and pharmacological actions. Eur J Neurol. 2001;8(Suppl 5):21–9

[4] Guidubaldi A, Bentivoglio AR, Albanese A. Clinical use of botulinum neurotoxin: neuromuscular disorders. In: Foster KA, editor. Clinical Applications of Botulinum Neurotoxin. New York: Springer; 2014. p. 51–94

[5] Wan XH, Vuong KD, Jankovic J. Clinical application of botulinum toxin type B in movement disorders and autonomic symptoms. Chin Med Sci J. 2005;20(1):44–7

[6] Dauer WT, Burke RE, Greene P, Fahn S. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. Brain. 1998;121(Pt 4):547–60

[7] Warner T, Bressman S, editors. Clinical diagnosis and management of dystonia. London; Boca Raton, FL: Informa Healthcare; Distributed in North and South America by Taylor & Francis; 2007.

[8] Lapatki BG, van Dijk JP, van de Warrenburg BP, Zwarts MJ. Botulinum toxin has an increased effect when targeted toward the muscle's endplate zone: a high-density surface EMG guided study. Clin. Neurophysiol. 2011;122(8):1611–6. DOI: 10.1016/j.clinph.2010.11.018

[9] Amirali A, Mu L, Gracies JM, Simpson DM. Anatomical localization of motor endplate bands in the human biceps brachii. J Clin Neuromuscul Dis. 2007;9(2):306–12. DOI: 10.1097/CND.0b013e31815c13a7

[10] Van Campenhout A, Molenaers G. Localization of the motor endplate zone in human skeletal muscles of the lower limb: anatomical guidelines for injection with botulinum toxin. Dev Med Child Neurol. 2011;53(2):108–19. DOI: 10.1111/j.1469-8749.2010.03816.x

[11] Ye JF, Lee JH, An XC, Lin CH, Yue B, Han SH. Anatomic localization of motor entry points and accurate regions for botulinum toxin injection in the flexor digitorum superficialis. Surg Radiol Anat. 2011;33(7):601–7. DOI: 10.1007/s00276-011-0779-9

[12] Lim EC, Seet RC. Botulinum toxin: description of injection techniques and examination of controversies surrounding toxin diffusion. Acta Neurol Scand. 2008;117(2):73–84. DOI: 10.1111/j.1600-0404.2007.00931.x

[13] Jankovic J, Albanese A, Atassi MZ, Dolly JO, Hallett M, Mayer NH. Preface. Botulinum Toxin. Philadelphia: W.B. Saunders; 2009. pp. ix–x. DOI: http://dx.doi.org/10.1016/B978-1-4160-4928-9.00041-X

[14] Jankovic J. Needle EMG guidance is rarely required. Muscle & Nerve. 2001;24(11):1568–70. DOI: 10.1002/mus.1186

[15] Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. Brain. 1998;121(Pt 7):1195–212

[16] Tarsy D, Simon DK. Dystonia. N Engl J Med. 2006;355(8):818–29. DOI: 10.1056/NEJMra055549

[17] Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-

based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1699–706. DOI: 10.1212/01.wnl.0000311389.26145.95

[18] Ney JP, Joseph KR. Neurologic uses of botulinum neurotoxin type A. Neuropsychiatr Dis Treat. 2007;3(6):785–98

[19] Jost WH, Kohl A. Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm. J Neurol. 2001;248(Suppl 1):21–4

[20] Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. Clin Experiment Ophthalmol. 2014;42(3):254–61. DOI: 10.1111/ceo.12165

[21] Costa J, Espirito-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev. 2005(1):CD004900. DOI: 10.1002/14651858.CD004900.pub2

[22] Balash Y, Giladi N. Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. Eur J Neurol. 2004;11(6):361–70. DOI: 10.1111/j.1468-1331.2004.00845.x

[23] Rollnik JD, Matzke M, Wohlfarth K, Dengler R, Bigalke H. Low-dose treatment of cervical dystonia, blepharospasm and facial hemispasm with albumin-diluted botulinum toxin type A under EMG guidance. An open label study. Eur Neurol. 2000;43(1): 9–12. DOI: 8121

[24] Hallett M, Albanese A, Dressler D, Segal KR, Simpson DM, Truong D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon. 2013;67:94–114. DOI: 10.1016/j.toxicon.2012.12.004

[25] Dashtipour K, Chen JJ, Frei K, Nahab F, Tagliati M. Systematic literature review of abobotulinumtoxinA in clinical trials for blepharospasm and hemifacial spasm. Tremor Other Hyperkinet Mov (N Y). 2015;5:338. DOI: 10.7916/D8CJ8CVR

[26] Barbano RL. Anatomic Principles for Botulinum Toxin Injection. In: Stacy MA, editor. Handbook of dystonia. New York: Informa Healthcare; 2007. p. 317-40

[27] Vogt T, Lussi F, Paul A, Urban P. [Long-term therapy of focal dystonia and facial hemispasm with botulinum toxin A]. Nervenarzt. 2008;79(8):912–7. DOI: 10.1007/s00115-008-2486-2

[28] Aramideh M, Ongerboer de Visser BW, Brans JW, Koelman JH, Speelman JD. Pretarsal application of botulinum toxin for treatment of blepharospasm. J Neurol Neurosurg Psychiatry. 1995;59(3):309–11

[29] Bogucki A. [Botulinum toxin injections under electromyographic guidance]. Neurol Neurochir Pol. 1998;32(Suppl 1):85–93

[30] Blitzer A, Benson BE, Guss J, editors. Botulinum neurotoxin for head and neck disorders. New York: Thieme; 2012.

[31] Van den Bergh P, Francart J, Mourin S, Kollmann P, Laterre EC. Five-year experience in the treatment of focal movement disorders with low-dose Dysport botulinum toxin. Muscle Nerve. 1995;18(7):720–9. DOI: 10.1002/mus.880180708

[32] Sojer M, Wissel J, Muller J, Poewe W. [Treatment of focal dystonia with botulinum toxin A]. Wien Klin Wochenschr. 2001;113(Suppl 4):6–10

[33] Bhidayasiri R, Cardoso F, Truong DD. Botulinum toxin in blepharospasm and oromandibular dystonia: comparing different botulinum toxin preparations. Eur J Neurol. 2006;13(Suppl 1):21–9. DOI: 10.1111/j.1468-1331.2006.01441.x

[34] Price J, Farish S, Taylor H, O'Day J. Blepharospasm and hemifacial spasm. Randomized trial to determine the most appropriate location for botulinum toxin injections. Ophthalmology. 1997;104(5):865–8

[35] Anwar MS, Zafar H. Efficacy of botulinum toxin in benign essential blepharospasm: desirable & undesirable effects. Pak J Med Sci. 2013;29(6):1389–93

[36] Albanese A, Bentivoglio AR, Colosimo C, Galardi G, Maderna L, Tonali P. Pretarsal injections of botulinum toxin improve blepharospasm in previously unresponsive patients. J Neurol Neurosurg Psychiatry. 1996;60(6):693–4

[37] Jankovic J. Apraxia of lid opening. Mov Disord. 1995;10(5):686–7

[38] Cakmur R, Ozturk V, Uzunel F, Donmez B, Idiman F. Comparison of preseptal and pretarsal injections of botulinum toxin in the treatment of blepharospasm and hemifacial spasm. J Neurol. 2002;249(1):64–8

[39] Mackie IA. Riolan's muscle: action and indications for botulinum toxin injection. Eye (Lond). 2000;14(Pt 3A):347–52. DOI: 10.1038/eye.2000.86

[40] Patel BC, Anderson RL. Blepharospasm and related facial movement disorders. Curr Opin Ophthalmol. 1995;6(5):86–99

[41] Valls-Sole J, Tolosa ES, Ribera G. Neurophysiological observations on the effects of botulinum toxin treatment in patients with dystonic blepharospasm. J Neurol Neurosurg Psychiatry. 1991;54(4):310–3

[42] Tintner R, Jankovic J. Botulinum toxin type A in the management of oromandibular dystonia and bruxism. In: Brin M, Hallett M, Jankovic J, editors. Scientific and Therapeutic Aspects of Botulinum Toxin. Philadelphia: Lippincott Williams & Wilkins; 2002. pp. 343–50

[43] Tan EK, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. Neurology. 1999;53(9):2102–7

[44] Brin M, Blitzer A, Herman S, Steward C. Oromandibular dystonia: treatment of 96 cases with botulinum A. In: Jankovic J, Hallett M, editors. Therapy with Botulinum Toxin. New York: Marcel Dekker; 1994. pp. 429–35

[45] Rosales RL, Ng AR, Delgado-Delos Santos MM, Fernandez FF. The Broadening application of chemodenervation in X-linked dystonia-parkinsonism (Part II): an open-label experience with botulinum toxin-A (Dysport R) injections for oromandibular, lingual, and truncal-axial dystonias. Int J Neurosci. 2011;121:44–56. DOI: 10.3109/00207454.2011.558260

[46] Erdal J, Werdelin LM, Prytz S, Fuglsang-Frederiksen A, Moller E. [Botulinum toxin treatment of patients with oromandibular dystonia]. Ugeskr Laeger. 2000;162(48): 6567–71

[47] Moller E, Bakke M, Dalager T, Werdelin LM. Oromandibular dystonia involving the lateral pterygoid muscles: four cases with different complexity. Mov Disord. 2007;22(6): 785–90. DOI: 10.1002/mds.21304

[48] Odderson IR, editors. Botulinum toxin injection guide. New York: Demos Medical Pub.; 2008.

[49] Emshoff R, Bertram S, Strobl H. Ultrasonographic cross-sectional characteristics of muscles of the head and neck. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(1):93–106

[50] Walter U, Dressler D. Ultrasound-guided botulinum toxin injections in neurology: technique, indications and future perspectives. Expert Rev Neurother. 2014;14(8):923–36. DOI: 10.1586/14737175.2014.936387

[51] Song JH, Cho ES, Kim ST, Ahn HJ. Change of distribution and timing of bite force after botulinum toxin type A injection evaluated by a computerized occlusion analysis system. Yonsei Med J. 2014;55(4):1123–9. DOI: 10.3349/ymj.2014.55.4.1123

[52] Klap P, Marion MH, Perrin A, Fresnel-Elbaz E. [Treatment of spasmodic dysphonia with botulinum toxin]. Ann Otolaryngol Chir Cervicofac. 1991;108(8):477–82; discussion 82–3

[53] Fulmer SL, Merati AL, Blumin JH. Efficacy of laryngeal botulinum toxin injection: comparison of two techniques. Laryngoscope. 2011;121(9):1924–8. DOI: 10.1002/lary.21966

[54] Srirompotong S, Saeseow P, Taweesaengsuksakul R, Kharmwan S, Srirompotong S. Botulinum toxin injection for treatment of spasmodic dysphonia: experience at Srinagarind Hospital. J Med Assoc Thai. 2006;89(12):2077–80

[55] Blitzer A. Botulinum toxin A and B: a comparative dosing study for spasmodic dysphonia. Otolaryngol Head Neck Surg. 2005;133(6):836–8. DOI: 10.1016/j.otohns.2005.09.008

[56] Morzaria S, Damrose EJ. A comparison of the VHI, VHI-10, and V-RQOL for measuring the effect of botox therapy in adductor spasmodic dysphonia. J Voice. 2012;26(3):378–80. DOI: 10.1016/j.jvoice.2010.07.011

[57] Rosow DE, Parikh P, Vivero RJ, Casiano RR, Lundy DS. Considerations for initial dosing of botulinum toxin in treatment of adductor spasmodic dysphonia. Otolaryngol Head Neck Surg. 2013;148(6):1003–6. DOI: 10.1177/0194599813484685

[58] Sulica L. Contemporary management of spasmodic dysphonia. Curr Opin Otolaryngol Head Neck Surg. 2004;12(6):543–8

[59] Hillel AD, Maronian NC, Waugh PF, Robinson L, Klotz DA. Treatment of the interarytenoid muscle with botulinum toxin for laryngeal dystonia. Ann Otol Rhinol Laryngol. 2004;113(5):341–8

[60] Meleca RJ, Hogikyan ND, Bastian RW. A comparison of methods of botulinum toxin injection for abductory spasmodic dysphonia. Otolaryngol Head Neck Surg. 1997;117(5):487–92

[61] Inagi K, Ford CN, Bless DM, Heisey D. Analysis of factors affecting botulinum toxin results in spasmodic dysphonia. J Voice. 1996;10(3):306–13

[62] Kim JW, Park JH, Park KN, Lee SW. Treatment efficacy of electromyography versus fiberscopy-guided botulinum toxin injection in adductor spasmodic dysphonia patients: a prospective comparative study. ScientificWorldJournal. 2014;2014:327928. DOI: 10.1155/2014/327928

[63] Morzaria S, Damrose EJ. The point-touch technique for botulinum toxin injection in adductor spasmodic dysphonia: quality of life assessment. J Laryngol Otol. 2011;125(7):714–8. DOI: 10.1017/S0022215111000739

[64] Green DC, Berke GS, Ward PH, Gerratt BR. Point-touch technique of botulinum toxin injection for the treatment of spasmodic dysphonia. Ann Otol Rhinol Laryngol. 1992;101(11):883–7

[65] Sataloff RT, Mandel S, Mann EA, Ludlow CL. Practice parameter: laryngeal electromyography (an evidence-based review). Otolaryngol Head Neck Surg. 2004;130(6):770–9. DOI: 10.1016/j.otohns.2004.04.003

[66] Zielinska M, Selmaj K. [A case of laryngeal adductor dystonia treated with transcutaneous injections of botulinum toxin]. Neurol Neurochir Pol. 1998;32(5):1273–80

[67] Blitzer A, Brin MF, Stewart C, Aviv JE, Fahn S. Abductor laryngeal dystonia: a series treated with botulinum toxin. Laryngoscope. 1992;102(2):163–7. DOI: 10.1288/00005537-199202000-00011

[68] Bielamowicz S, Squire S, Bidus K, Ludlow CL. Assessment of posterior cricoarytenoid botulinum toxin injections in patients with abductor spasmodic dysphonia. Ann Otol Rhinol Laryngol. 2001;110(5 Pt 1):406–12

[69] Persaud R, Garas G, Silva S, Stamatoglou C, Chatrath P, Patel K. An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions. JRSM Short Rep. 2013;4(2):10. DOI: 10.1177/2042533312472115

[70] Galardi G, Guerriero R, Amadio S, Leocani L, Teggi R, Melloni G, et al. Sporadic failure of botulinum toxin treatment in usually responsive patients with adductor spasmodic dysphonia. Neurol Sci. 2001;22(4):303–6

[71] Lee IH, Yoon YC, Sung DH, Kwon JW, Jung JY. Initial experience with imaging-guided intramuscular botulinum toxin injection in patients with idiopathic cervical dystonia. AJR Am J Roentgenol. 2009;192(4):996–1001. DOI: 10.2214/AJR.08.1535

[72] Mezaki T. [Clinical application of botulinum toxin]. Brain Nerve. 2011;63(7):785–94

[73] Nijmeijer SW, Koelman JH, Kamphuis DJ, Tijssen MA. Muscle selection for treatment of cervical dystonia with botulinum toxin--a systematic review. Parkinsonism Relat Disord. 2012;18(6):731–6. DOI: 10.1016/j.parkreldis.2012.04.005

[74] Schramm A, Baumer T, Fietzek U, Heitmann S, Walter U, Jost WH. Relevance of sonography for botulinum toxin treatment of cervical dystonia: an expert statement. J Neural Transm (Vienna). 2015;122(10):1457–63. DOI: 10.1007/s00702-014-1356-2

[75] Barbano RL. Needle EMG guidance for injection of botulinum toxin. Needle EMG guidance is useful. Muscle Nerve. 2001;24(11):1567–8

[76] Speelman JD, Brans JW. Cervical dystonia and botulinum treatment: is electromyographic guidance necessary? Mov Disord. 1995;10(6):802. DOI: 10.1002/mds.870100619

[77] Wulff CH, Dupont E. [Torticollis treated with botulinum toxin]. Ugeskr Laeger. 1993;155(5):284–9

[78] Dubinsky RM, Gray CS, Vetere-Overfield B, Koller WC. Electromyographic guidance of botulinum toxin treatment in cervical dystonia. Clin Neuropharmacol. 1991;14(3): 262–7

[79] Comella CL, Buchman AS, Tanner CM, Brown-Toms NC, Goetz CG. Botulinum toxin injection for spasmodic torticollis: increased magnitude of benefit with electromyographic assistance. Neurology. 1992;42(4):878–82

[80] Lee LH, Chang WN, Chang CS. The finding and evaluation of EMG-guided BOTOX injection in cervical dystonia. Acta Neurol Taiwan. 2004;13(2):71–6

[81] Werdelin L, Dalager T, Fuglsang-Frederiksen A, Regeur L, Karlsborg M, Korbo L, et al. The utility of EMG interference pattern analysis in botulinum toxin treatment of torticollis: a randomised, controlled and blinded study. Clin Neurophysiol. 2011;122(11):2305–9. DOI: 10.1016/j.clinph.2011.04.012

[82] Cordivari C, Misra VP, Vincent A, Catania S, Bhatia KP, Lees AJ. Secondary nonresponsiveness to botulinum toxin A in cervical dystonia: the role of electromyogram-

guided injections, botulinum toxin A antibody assay, and the extensor digitorum brevis test. Mov Disord. 2006;21(10):1737–41. DOI: 10.1002/mds.21051

[83] Mezaki T, Matsumoto S, Sakamoto T, Mizutani K, Kaji R. [Cervical echomyography in cervical dystonia and its application to the monitoring for muscle afferent block (MAB)]. Rinsho Shinkeigaku. 2000;40(7):689–93

[84] Hong JS, Sathe GG, Niyonkuru C, Munin MC. Elimination of dysphagia using ultrasound guidance for botulinum toxin injections in cervical dystonia. Muscle Nerve. 2012;46(4):535–9. DOI: 10.1002/mus.23409

[85] Herting B, Wunderlich S, Glockler T, Bendszus M, Mucha D, Reichmann H, et al. Computed tomographically-controlled injection of botulinum toxin into the longus colli muscle in severe anterocollis. Mov Disord. 2004;19(5):588–90. DOI: 10.1002/mds.10704

[86] Pappas GP, Olcott EW, Drace JE. Imaging of skeletal muscle function using (18)FDG PET: force production, activation, and metabolism. J Appl Physiol (1985). 2001;90(1):329-37

[87] Sung DH, Choi JY, Kim DH, Kim ES, Son YI, Cho YS, et al. Localization of dystonic muscles with 18F-FDG PET/CT in idiopathic cervical dystonia. J Nucl Med. 2007;48(11):1790–5. DOI: 10.2967/jnumed.107.044024

[88] Glass GA, Ku S, Ostrem JL, Heath S, Larson PS. Fluoroscopic, EMG-guided injection of botulinum toxin into the longus colli for the treatment of anterocollis. Parkinsonism Relat Disord. 2009;15(8):610–3. DOI: 10.1016/j.parkreldis.2009.01.006

[89] Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. Mov Disord. 2004;19(Suppl 8):S116–9. DOI: 10.1002/mds.20025

[90] Kruisdijk JJ, Koelman JH, Ongerboer de Visser BW, de Haan RJ, Speelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatry. 2007;78(3):264–70. DOI: 10.1136/jnnp.2005.083170

[91] Sherman AL, Willick SP, Cardenas DD. Management of focal dystonia of the extensor hallucis longus muscle with botulinum toxin injection: a case report. Arch Phys Med Rehabil. 1998;79(10):1303–5

[92] Chen R, Karp BI, Hallett M. Botulinum toxin type F for treatment of dystonia: long-term experience. Neurology. 1998;51(5):1494-6

[93] Yoshimura DM, Aminoff MJ, Olney RK. Botulinum toxin therapy for limb dystonias. Neurology. 1992;42(3 Pt 1):627–30

[94] Tsui JK, Bhatt M, Calne S, Calne DB. Botulinum toxin in the treatment of writer's cramp: a double-blind study. Neurology. 1993;43(1):183–5

[95] Molloy FM, Shill HA, Kaelin-Lang A, Karp BI. Accuracy of muscle localization without EMG: implications for treatment of limb dystonia. Neurology. 2002;58(5):805–7

[96] Schuele S, Jabusch HC, Lederman RJ, Altenmuller E. Botulinum toxin injections in the treatment of musician's dystonia. Neurology. 2005;64(2):341–3. DOI: 10.1212/01.WNL.0000149768.36634.92

[97] Geenen C, Consky E, Ashby P. Localizing muscles for botulinum toxin treatment of focal hand dystonia. Can J Neurol Sci. 1996;23(3):194–7

[98] Cohen LG, Hallett M, Geller BD, Hochberg F. Treatment of focal dystonias of the hand with botulinum toxin injections. J Neurol Neurosurg Psychiatry. 1989;52(3):355–63

[99] Ross MH, Charness ME, Sudarsky L, Logigian EL. Treatment of occupational cramp with botulinum toxin: diffusion of toxin to adjacent noninjected muscles. Muscle Nerve. 1997;20(5):593–8

[100] Lim EC, Quek AM, Seet RC. Accurate targeting of botulinum toxin injections: how to and why. Parkinsonism Relat Disord. 2011;17(Suppl 1):S34–9. DOI: 10.1016/j.parkreldis.2011.06.016

[101] Mokhtari S, Hugeron C, Roffi F, Thibaut JB, Le Breton C, Mompoint D, et al. [Spasticity: clinical and imaging features]. J Radiol. 2010;91(12 Pt 2):1387–97

[102] Walker HW, Lee MY, Bahroo LB, Hedera P, Charles D. Botulinum toxin injection techniques for the management of adult spasticity. PM R. 2015;7(4):417–27. DOI: 10.1016/j.pmrj.2014.09.021

[103] Muller F, Cugy E, Ducerf C, Delleci C, Guehl D, Joseph PA, et al. Safety and self-reported efficacy of botulinum toxin for adult spasticity in current clinical practice: a prospective observational study. Clin Rehabil. 2012;26(2):174–9. DOI: 10.1177/0269215511412799

[104] Warnink-Kavelaars J, Vermeulen RJ, Becher JG. Study protocol: precision of a protocol for manual intramuscular needle placement checked by passive stretching and relaxing of the target muscle in the lower extremity during BTX-A treatment in children with spastic cerebral palsy, as verified by means of electrical stimulation. BMC Pediatr. 2013;13:129. DOI: 10.1186/1471-2431-13-129

[105] Park ES, Rha DW. Botulinum toxin type A injection for management of upper limb spasticity in children with cerebral palsy: a literature review. Yonsei Med J. 2006;47(5):589–603. DOI: 10.3349/ymj.2006.47.5.589

[106] Chin TY, Nattrass GR, Selber P, Graham HK. Accuracy of intramuscular injection of botulinum toxin A in juvenile cerebral palsy: a comparison between manual needle placement and placement guided by electrical stimulation. J Pediatr Orthop. 2005;25(3):286–91

[107] Mall V, Heinen F, Siebel A, Bertram C, Hafkemeyer U, Wissel J, et al. Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebo-controlled study. Dev Med Child Neurol. 2006;48(1):10–3. DOI: 10.1017/S0012162206000041

[108] Yang EJ, Rha DW, Yoo JK, Park ES. Accuracy of manual needle placement for gastrocnemius muscle in children with cerebral palsy checked against ultrasonography. Arch Phys Med Rehabil. 2009;90(5):741–4. DOI: 10.1016/j.apmr.2008.10.025

[109] Kaishou X, Tiebin Y, Jianning M. A randomized controlled trial to compare two botulinum toxin injection techniques on the functional improvement of the leg of children with cerebral palsy. Clin Rehabil. 2009;23(9):800–11. DOI: 10.1177/0269215509335295

[110] Childers MK, Stacy M, Cooke DL, Stonnington HH. Comparison of two injection techniques using botulinum toxin in spastic hemiplegia. Am J Phys Med Rehabil. 1996;75(6):462–9

[111] Picelli A, Lobba D, Midiri A, Prandi P, Melotti C, Baldessarelli S, et al. Botulinum toxin injection into the forearm muscles for wrist and fingers spastic overactivity in adults with chronic stroke: a randomized controlled trial comparing three injection techniques. Clin Rehabil. 2014;28(3):232–42. DOI: 10.1177/0269215513497735

[112] Picelli A, Tamburin S, Bonetti P, Fontana C, Barausse M, Dambruoso F, et al. Botulinum toxin type A injection into the gastrocnemius muscle for spastic equinus in adults with stroke: a randomized controlled trial comparing manual needle placement, electrical stimulation and ultrasonography-guided injection techniques. Am J Phys Med Rehabil. 2012;91(11):957–64. DOI: 10.1097/PHM.0b013e318269d7f3

[113] Henzel MK, Munin MC, Niyonkuru C, Skidmore ER, Weber DJ, Zafonte RD. Comparison of surface and ultrasound localization to identify forearm flexor muscles for botulinum toxin injections. PM R. 2010;2(7):642–6. DOI: 10.1016/j.pmrj.2010.05.002

[114] Schnitzler A, Roche N, Denormandie P, Lautridou C, Parratte B, Genet F. Manual needle placement: accuracy of botulinum toxin A injections. Muscle Nerve. 2012;46(4):531–4. DOI: 10.1002/mus.23410

[115] Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. Am J Phys Med Rehabil. 2000;79(1):44–7

[116] Palmer DT, Horn LJ, Harmon RL. Botulinum toxin treatment of lumbrical spasticity: a brief report. Am J Phys Med Rehabil. 1998;77(4):348–50

[117] Richardson D, Edwards S, Sheean GL, Greenwood RJ, Thompson AJ. The effect of botulinum toxin on hand function after incomplete spinal cord injury at the level of C5/6: a case report. Clin Rehabil. 1997;11(4):288–92

[118] Hesse S, Lucke D, Malezic M, Bertelt C, Friedrich H, Gregoric M, et al. Botulinum toxin treatment for lower limb extensor spasticity in chronic hemiparetic patients. J Neurol Neurosurg Psychiatry. 1994;57(11):1321–4

[119] Dunne JW, Heye N, Dunne SL. Treatment of chronic limb spasticity with botulinum toxin A. J Neurol Neurosurg Psychiatry. 1995;58(2):232–5

[120] Finsterer J, Fuchs I, Mamoli B. Automatic EMG-guided botulinum toxin treatment of spasticity. Clin Neuropharmacol. 1997;20(3):195–203

[121] Wallen MA, O'Flaherty S J, Waugh MC. Functional outcomes of intramuscular botulinum toxin type A in the upper limbs of children with cerebral palsy: a phase II trial. Arch Phys Med Rehabil. 2004;85(2):192–200

[122] Speth LA, Leffers P, Janssen-Potten YJ, Vles JS. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy. Dev Med Child Neurol. 2005;47(7):468–73

[123] Autti-Ramo I, Larsen A, Taimo A, von Wendt L. Management of the upper limb with botulinum toxin type A in children with spastic type cerebral palsy and acquired brain injury: clinical implications. Eur J Neurol. 2001;8(Suppl 5):136–44

[124] Bayon-Mottu M, Gambart G, Deries X, Tessiot C, Richard I, Dinomais M. Pain during injections of botulinum toxin in children: influence of the localization technique. Ann Phys Rehabil Med. 2014;57(9–10):578–86. DOI: 10.1016/j.rehab.2014.09.010

[125] Childers MK. The importance of electromyographic guidance and electrical stimulation for injection of botulinum toxin. Phys Med Rehabil Clin N Am. 2003;14(4):781–92

[126] Santamato A, Micello MF, Panza F, Fortunato F, Baricich A, Cisari C, et al. Can botulinum toxin type A injection technique influence the clinical outcome of patients with post-stroke upper limb spasticity? A randomized controlled trial comparing manual needle placement and ultrasound-guided injection techniques. J Neurol Sci. 2014;347(1–2):39–43. DOI: 10.1016/j.jns.2014.09.016

[127] Ding XD, Zhang GB, Chen HX, Wang W, Song JH, Fu DG. Color Doppler ultrasound-guided botulinum toxin type A injection combined with an ankle foot brace for treating lower limb spasticity after a stroke. Eur Rev Med Pharmacol Sci. 2015;19(3):406–11

[128] Heinen F, Desloovere K, Schroeder AS, Berweck S, Borggraefe I, van Campenhout A, et al. The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. Eur J Paediatr Neurol. 2010;14(1):45–66. DOI: 10.1016/j.ejpn.2009.09.005

[129] Kwon JY, Hwang JH, Kim JS. Botulinum toxin a injection into calf muscles for treatment of spastic equinus in cerebral palsy: a controlled trial comparing sonography and electric stimulation-guided injection techniques: a preliminary report. Am J Phys Med Rehabil. 2010;89(4):279–86. DOI: 10.1097/PHM.0b013e3181ca24ac

[130] Rha DW, Park ES, Jung S, Lee SC, Suh M, Choi HS. Comparison of ultrasound-guided anterior and posterior approaches for needle insertion into the tibialis posterior in hemiplegic children with spastic cerebral palsy. Am J Phys Med Rehabil. 2014;93(10):841–8. DOI: 10.1097/PHM.0000000000000170

[131] Chen SL, Bih LI, Chen GD, Huang YH, You YH, Lew HL. Transrectal ultrasound-guided transperineal botulinum toxin a injection to the external urethral sphincter for treat-

ment of detrusor external sphincter dyssynergia in patients with spinal cord injury. Arch Phys Med Rehabil. 2010;91(3):340–4. DOI: 10.1016/j.apmr.2009.11.006

[132] Chen SL, Bih LI, Chen GD, Huang YH, You YH. Comparing a transrectal ultrasound-guided with a cystoscopy-guided botulinum toxin a injection in treating detrusor external sphincter dyssynergia in spinal cord injury. Am J Phys Med Rehabil. 2011;90(9): 723–30. DOI: 10.1097/PHM.0b013e31821a72a3

[133] Romero-Culleres G, Conejero-Sugranes J, Gonzalez-Viejo MA, Bruno-Montoro J, Lopez-Guillen P, Abenoza-Guardiola M. [Efficacy and safety of botulinum toxin in external urethral sphincter by transperineal way guided transrectal ultrasound and electromyography on chronic urinary retention due to spinal cord injury]. Med Clin (Barc). 2011;137(8):346–8. DOI: 10.1016/j.medcli.2010.10.025

[134] Schneider I, Thumfart WF, Pototschnig C, Eckel HE. Treatment of dysfunction of the cricopharyngeal muscle with botulinum A toxin: introduction of a new, noninvasive method. Ann Otol Rhinol Laryngol. 1994;103(1):31–5

[135] Brant CQ, Siqueira ES, Ferrari AP, Jr. Botulinum toxin for oropharyngeal dysphagia: case report of flexible endoscope-guided injection. Dis Esophagus. 1999;12(1):68–73

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