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

Nikolina Ilkova Semerdjieva

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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-
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 supercili, 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 supercili, 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
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