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Letter to the Editor: New Observation

Optimizing Botulinum Toxin Injections by Minding the Muscle Architecture and Its Innervation Zone: The "Seeding" Technique

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Intramuscular application of BoTX has been used to treat muscle hyperactivity (e.g. spasticity and dystonia) in patients with certain neuromuscular disorders. Although, innervation zone (IZ)-targeted and ultrasound-guided injections are generally recommended to increase the effectiveness of the toxin,[1,2] a specific and detailed injection technique has not been described. Accordingly, we aimed to illustrate a technique based on the muscle architecture and BoTX distribution in the tissue.

It is well known that BoTX molecules delivered to neuromuscular junctions (NMJs) are bound and internalized very rapidly from the presynaptic membranes into the cytosol of nerve terminal – in which they act by cleaving SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) protein.[3] Therefore, during IZ-targeted application of BoTX, suggested injection technique should ensure that the BoTX molecules come into contact with the presynaptic membrane before they are distributed to the other parts of the muscle – which contain fewer or no NMJ at all. Of note, the IZ – in which NMJs are clustered – is not an area but a three-dimensional volume (Figure 1) and the toxin diluted with saline is distributed via applying pressure to the syringe. Transport of BoTX molecules in muscle tissue is dependent on pressure gradient (causing flow) and concentration gradient (causing diffusion). Since muscle tissue is not a homogenous medium and changes considerably according to its architectural feature, which is determined by the arrangement of the muscle fibers, the distribution of the BoTX will also be different at the IZ.[1,4]

Some studies investigating the distribution of BoTX in skeletal muscles exist in the literature; however, to our best knowledge, the transport of BoTX within the three-dimensional concept has not been evaluated. In only one magnetic resonance imaging study, the distribution of BoTX in the sagittal plain was estimated according to the alignment of the muscle fibers in healthy and spastic biceps brachii muscles. Supero-inferior distribution along the muscle fibers was found to be 5.3 and 3.2 cm, while antero-posterior distribution perpendicular to the muscle fibers was only 0.5 cm for and 0.7 cm, respectively.[5] Although medio-lateral distribution of BoTX was not measured, it would be probably similar to that of the antero-posterior axis – since they are both perpendicular to the muscle fibers' alignment. The restricted distribution of BoTX through the axes perpendicular to the muscle fibers are probably due to the high density of connective tissue (e.g. endomysium and perimysium) in between. Likewise, the dense fibrous structures and ground substance molecules in the interstitium (rather than the cells) were found to be the main determinants of tissue resistance to fluid flow in high cellular tissues such as skeletal muscle.[6]

The IZ of the skeletal muscle lies perpendicular to the muscle fibers' alignment through which the distribution is significantly restricted. Moreover, the IZ of a skeletal muscle may have a band-like shape – for example, in biceps brachii, it is 5–10 mm wide (supero-inferior) and 4–6 cm long (medio-lateral).[7] Therefore, to ensure that BoTX molecules are homogeneously distributed through the IZ, the needle should be inserted into the hyperactive skeletal muscle along the middle of the IZ through its longer axis perpendicular to the muscle fibers' alignment which is medio-lateral for the biceps brachii muscle. The needle should reach to the other border of the muscle and then, while removing the needle backward, the toxin should continuously be injected. As such, the BoTX molecules can homogeneously be distributed through the IZ, before they reach the other parts of the muscle which contain fewer or no NMJ. Of course, the length of the syringe needle should be selected depending on the size of the muscle to be injected (Figure 2).

Orientation of the IZ is determined by the arrangement of muscle fibers.[8] While it is almost on the transverse plane in biceps brachii, the IZ of gastrocnemius muscle is almost on the coronal plane. Therefore, orientations of the IZ should be taken into account during the application of this technique. Video 1 shows intramuscular BoTX injection into the spastic gastrocnemius muscle using the "seeding" technique. Herein, there are two important issues which should also be kept in mind. First, some skeletal muscles may have more than one IZ and second, the neuromuscular compartments are under selective motor control of the central nervous system.[1] Hence, IZ-targeted and ultrasound-guided intramuscular BoTX injections using the "seeding" technique as well as considering the neuromuscular compartmentalization would probably help to achieve better/optimal therapeutic goal with lower doses and fewer side effects. Clinical studies are needed to compare the clinical effectiveness of our proposed BoTX injection technique and that of the currently applied approach.

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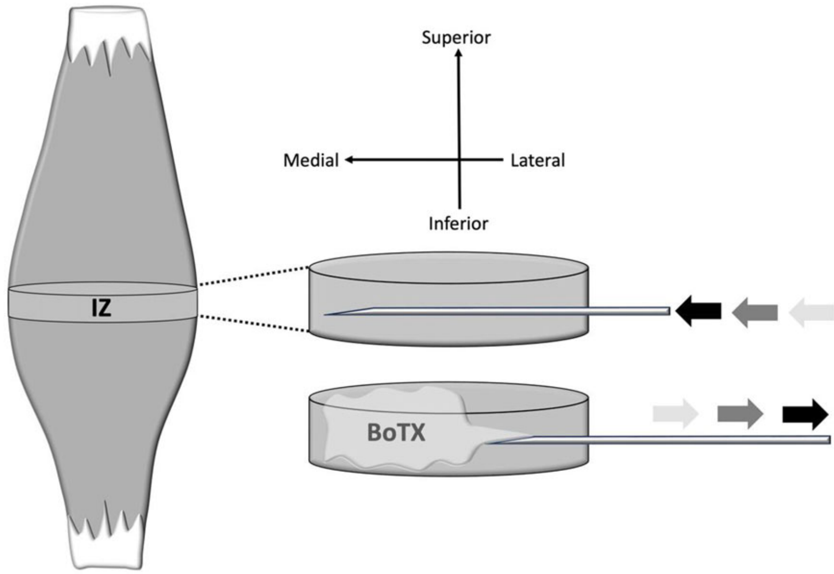

Figure 1. Seeding technique for botulinum toxin injections. Combining needle movements (arrows) through the long axis perpendicular to muscle fiber alignment (medio-lateral) in the target muscle's innervation zone, and the slow release of the botulinum toxin (BoTX), three-dimensional distribution at the IZ can be optimized.

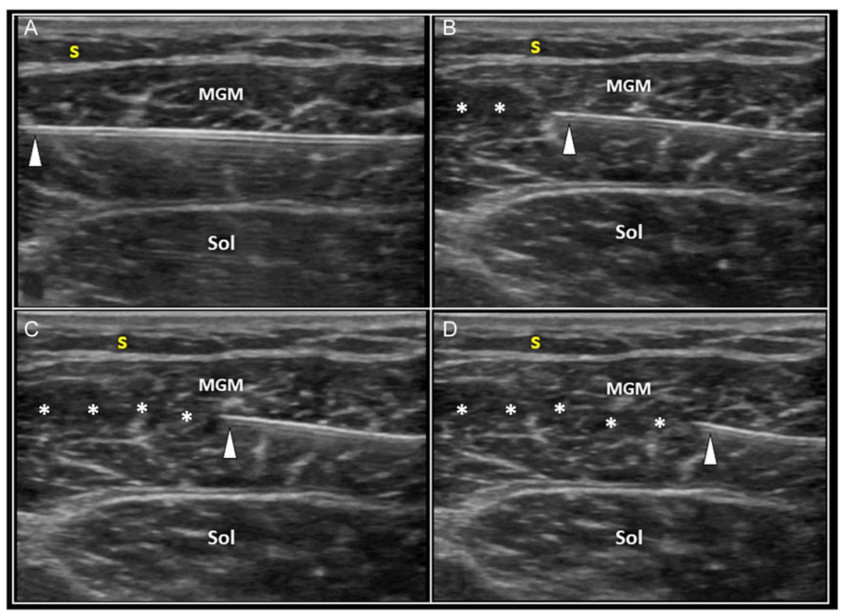

Figure 2. Ultrasound-guided, innervation zone-targeted botulinum toxin injection using the direct in-plane technique. Sequential axial images (A–D) show the distribution of toxin diluted with saline (asterisks) within the gastrocnemius medialis muscle (MGM) while removing the needle (arrowheads) backward. s = subcutaneous tissue; Sol = soleus muscle.

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