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EXPERT REVIEWS

Ultrasound-guided botulinum toxin injections in neurology: technique, indications and future perspectives

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Botulinum toxin (BT) therapy is used in neurology to treat muscle hyperactivity disorders including dystonia, spasticity, cerebral palsy, hemifacial spasms and re-innervation synkinesias as well as exocrine gland hyperactivity disorders. To increase its therapeutic effect and to decrease adverse effects in adjacent tissues, exact BT placement is important. Ultrasonography (US) allows non-invasive, real-time imaging of muscular and glandular tissues and their surrounding structures. It can visualize, guide, and standardize the entire procedure of BT application. Small randomized studies suggest that US-guidance can improve therapeutic efficacy and reduce adverse effects of BT therapy when compared to conventional placement. US-guidance should be used in forearm muscles when functionality is important, and in selected leg muscles. It may be used for targeting distinct neck muscles in cervical dystonia. It is helpful for targeting the salivary glands. Here we review the technique, indications and future developments of US-guidance for BT injection in neurological disorders.

Keywords: botulinum toxin • cerebral palsy • dystonia • hypersalivation • needle navigation • placement • spasticity • task-related dystonia • ultrasonography • ultrasound-guidance

Botulinum toxin (BT) selectively blocks the cholinergic transmission, thus producing paresis when injected into striated or smooth muscles, or secretion blockade when injected into exocrine glands. Its use in non-muscular pain disorders is currently being explored. BT starts to act upon the target tissue within a few days, builds up its maximal effect after 1 or 2 weeks and starts to fade away 2–3 months after it had been injected. With these features, BT has been used for many years in numerous medical specialties [1]. Approximately half of the global therapeutic BT production is used for aesthetic purposes. Out of the other half, neurological indications consume the largest proportion of BT. Tables 1 & 2 show the use of BT in neurology and the respective target structures in which BT is injected. In neurology, most of the BT is used to treat muscle hyperactivity syndromes, such as dystonias, spasticity, cerebral palsy, hemifacial spasm, facial synkinesias, tics and tremor. Another application is the therapeutic weakening of normoactive muscles to relieve nerve entrapment (e.g., neurogenic thoracic outlet syndrome, piriformis syndrome) or muscle-action-related deformities caused by anatomic alterations (e.g., omohyoid muscle syndrome) [2–4]. BT may also be applied in conditions caused by overactivity of exocrine glands, such as hyperhidrosis, hypersalivation and crocodile tears. In non-muscular pain syndromes, the treatment of chronic migraine is now a licensed indication [5]. BT has to be injected directly into the target tissue. Therefore, exact placement is crucial to reduce adverse effects on adjacent muscles and to achieve maximal therapeutic effects within the target tissue at the lowest possible dose. This paper describes technique, indications and future perspectives of ultrasonography (US) for guiding BT application in neurological indications.

Conventional methods for BT application

Clinical examination

Usually, BT is placed by clinical examination. For this, the target muscles can be palpated. Often, it is helpful to put tension on the target

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Table 1. Neurological indications for botulinum toxin therapy and their target structures: muscular targets.

Indication	Target muscles
Dystonia	
Cranial dystonia	
Blepharospasm	Orbicularis oculi, procerus, corrugator supercilii
Oromandibular dystonia	Masseter, pterygoidei, temporalis
Perioral dystonia	Orbicularis oris, depressor anguli oris, risorius, mentalis
Cervical dystonia	Sternocleidomastoid, splenius capitis, trapezius descendens/semispinalis capitis, trapezius horizontalis, levator scapulae, scalenii, deep neck muscles
Pharyngeal dystonia	Pharyngeal muscles
Spasmodic dysphonia	Laryngeal muscles
Writers' cramp	Flexor digitorum superficialis et profundus, extensor digitorum, flexor carpi radialis et ulnaris, extensor carpi radialis et ulnaris, thumb muscles, intrinsic hand muscles
Segmental dystonia	Neck muscles (see above), pectoralis, teres major, latissimus dorsi, deltoideus, subscapularis, infraspinatus, biceps brachii, triceps brachii, wrist muscles (see above), finger muscles (see above), thumb muscles, paravertebral muscles, abdominal muscles, lower limb muscles
Axial dystonia	Selected muscles from some of the above
Generalized dystonia	Selected muscles from some of the above
Musician's dystonias	Selected muscles from some of the above
Peripheral dyskinesias	
Hemifacial spasm	Orbicularis oculi, risorius, mentalis
Re-innervation synkinesias	Orbicularis oculi, orbicularis oris, risorius
Spasticity/cerebral palsy	
Bruxism	Masseter, pterygoidei, temporalis
Neck	Neck muscles (see above)
Shoulder	Shoulder muscles (see above)
Arm	Biceps brachii, triceps brachii, brachialis, brachioradialis
Wrist	Flexor carpi radialis et ulnaris, extensor carpi radialis et ulnaris
Fingers/thumb	Flexor digitorum profundus et superficialis, extensor digitorum, intrinsic hand muscles, thumb muscles
Hip	Adductors, iliopsoas, rectus femoris, sartorius, tensor fasciae latae
Knee	Quadriceps femoris, hamstrings, gracilis
Ankle	Gastrocnemius, soleus, tibialis anterior, tibialis posterior, toe flexors
Great toe	Extensor hallucis longus
Toes	Flexor digitorum longus et brevis, extensor digitorum longus
Migraine	Corrugator, procerus, frontalis, temporalis, trapezius, cervical paraspinal
Tardive dyskinesias	Selected muscles from some of the above
Tremor	Selected muscles from some of the above
Tics	Selected muscles from some of the above
Fibromyalgia? Chronic myofascial pain? Chronic paraspinal pain syndrome?	Selected muscles from some of the above

muscle and to follow the muscle tendon. Alternating active or passive joint movements, reference to anatomical landmarks and the patient's report on muscle tenderness may also be helpful. Observation of the movement of an injection needle placed into the target muscle when it is repetitively activated is another useful trick. However, small and deep muscles remain difficult to target. In the forearm, the following muscles are notoriously difficult to localize: flexor carpi radialis, pronator teres, flexor digitorum superficialis 2 and 3 and flexor pollicis longus [6]. In a study on 226 children with cerebral palsy, the accuracy of manual BT application was compared to guidance by electromyography (EMG) with electrical stimulation and found to be low for the forearm and hand muscles (13–35%), medial hamstrings (46%) and tibialis posterior (11%) [7]. In adults for the gastrocnemius muscle, especially the lateral caput, a surprisingly high targeting failure rate of up to 57% has been reported [8,9]. However, in large and easily accessible muscles typically treated in cervical dystonia and adductor spasticity, clinical placement seems sufficient for the majority of patients [10,11].

Electromyography

EMG can identify hyperactive muscles. It can also be used for BT application when a special EMG injection needle is used [12]. This special needle combines an injection needle with an EMG needle. For this, an injection needle is isolated except for its tip, which is electrically connected to an EMG machine. However, passive EMG guidance requires selective activation of the target muscle, which is difficult to perform for patients with higher degree paresis. In patients with dystonia and sometimes also in patients with spasticity, the co-activation of adjacent muscles may superimpose the target muscle activity [10]. EMG guidance may be improved by electric stimulation via the injection electrode (active EMG guidance) [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 lack of control of the applied BT. Obviously, EMG cannot be used for BT placement in glandular tissue.

EMG combined with fluoroscopy

For special target muscles such as the piriformis muscle in piriformis syndrome, the anterior and middle scalene muscles in neurogenic thoracic outlet syndrome and the longus colli muscle in patients with antecollis, EMG was combined with fluoroscopy for exact placement of the needle tip prior to BT injection [13–15]. 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.

Computed tomography & MRI

Computed tomography (CT) and MRI allow high-definition visualization of deep muscles such as the longus colli, obliquus capitis inferior and psoas, of glandular tissue and of critical structures [16–18]. Mixtures of BT and contrast medium allow documentation of the BT placement. However, the visualization is not real time, so that the relationship between the injection needle and the target tissue cannot be monitored continuously. Thus, a relatively high complication rate was reported in a recent prospective study of 146 CT-guided BT treatments of the anterior scalene muscle, such as temporary blockade of brachial plexus (3.4% of procedures) and Horner syndrome (0.7%) [19]. Other disadvantages including exposure to radiation, costs and time prevent both methods from being used routinely.

Ultrasonography

Principle

US allows a simple, non-invasive, real-time visualization of the muscular and glandular tissues and their surrounding structures. US can visualize the entire procedure of BT application. US-guided intramuscular BT injections were first described by Japanese neurologists and later propagated by German pediatricians [20,21]. The availability of US varies widely in different countries. In Central European countries, where neurovascular duplex scanning is usually performed by neurologists, US is readily available in neurological clinics and practices. Provided adequate anatomical knowledge, the localization of glands and muscles on US is straightforward. Needle tracking skills can be trained by practicing on cadavers, gel phantoms, turkey breast, etc. [22], and there are also an increasing number of US workshops and US courses now available. Some non-commercial and commercial online US courses and mobile learning applications (app) available in the internet are listed in Box 1.

Table 2. Neurological indications for botulinum toxin therapy and their target structures: glandular targets.

Indication	Target glands
Autonomic disorders	
Hyperhidrosis	Sweat glands in skin: axillary, palmar, plantar, frontal, temporal, nuchal, truncal
Hypersalivation	Salivary glands: parotis, submandibularis
Hyperlacrimation	Lacrimal gland

Technical considerations

US machines used for BT application are identical to those used for vascular US. Prices for full-size machines range from €45,000 to 100,000, and prices of portable ones from €10,000 to 30,000. In principle, all contemporary US machines can be used if equipped with an appropriate linear-array transducer. The applied US frequency determines both the image resolution and the penetration depth. Increasing frequencies increase image resolution but reduce penetration depth and vice versa. Superficial and small target muscles in the arm require optimal resolution and therefore higher US frequencies of about 13.0 (10–18) MHz. Profound and large target muscles in the neck, trunk and leg are best visualized with lower US frequencies of about 7.5 (5–10) MHz [23]. Typical US system settings, referring to the systems used for acquiring the US images presented in this article, are shown in Table 3.

Measurements

For optimal imaging geometrics, a rectangular probe position with only moderate pressure on the underlying tissue is recommended. Angular deviation of the probe position may reduce tissue echogenicity, whereas increased pressure of the probe towards the skin may increase tissue echogenicity. Rectangular probe position in relation to bone surfaces is recognized by the

Box 1. Internet-based online courses and mobile learning applications.

Internet-based online courses:

- www.munichultrasoundcourse.com/
- https://www.theonlinelearningcenter.com/ultrasound/musculoskeletal-ultrasound-cme
- http://theultrasoundsite.co.uk/category/resources/guided-injections/

Mobile learning applications (app):

- www.imedicalapps.com/2013/01/muc-app-msk-ultrasound-guided-intervention-ap/
- http://en.knicket.com/details/pnyt/android/sono-guide
- https://itunes.apple.com/de/app/sonoguide/id470488939?mt=8

Table 3. Ultrasound systems settings referring to the figures shown in this article.

Ultrasound system†	Acuson Antares‡	MyLab Twice§	MyLab 25 Gold¶
Settings for superficial targets (imaging depth up to 3 cm)			
Probe [name]	VF13-5#	LA435††	LA435‡‡
US frequency range [MHz]	5–13	6–18	6–18
US center frequency [MHz]	11.4	14	12
Preset [name]	Upper musculoskeletal	Musculoskeletal	Musculoskeletal
Dynamic range [level]	High (55 dB)	High (choice #12)	High (choice #10)
Enhance/contour [level]	Low (choice #1)	High (choice #6)	High (choice #4)
Density (line density) [level]	High (choice #3)	High (choice #2)	High (choice #1)
Persistence [level]	Medium (choice #2)	Medium (choice #2)	High (choice #5)
Gray map [choice]	Scale E	0	4
Settings for deep targets (imaging depth up to 5 cm)			
Probe [name]	VF10-5§§	LA332¶¶	LA522##
US frequency range [MHz]	5–10	3–11	2–9
US center frequency [MHz]	10	9	7.5
Preset [name]	Upper musculoskeletal	(User defined)	(User defined)
Dynamic range [level]	High (60 dB)	High (choice #14)	High (choice #8)
Enhance/contour [level]	Low (choice #1)	High (choice #6)	High (choice #4)
Density (line density) [level]	High (choice #3)	High (choice #2)	Low (choice #L)
Persistence [level]	Medium (choice #2)	High (choice #4)	Medium (choice #3)
Gray Map [choice]	Scale E	0	2

†Generally the contemporary ultrasound systems of all manufacturers can equally be used if equipped with appropriate probes; the system settings may be chosen similar to those presented in this table.
‡Stationary ultrasound system; manufacturer: Siemens, Erlangen, Germany.
§Stationary ultrasound system, optionally equipped with CT-US and MRI-US fusion imaging and virtual 3D navigation technology (see Figure 10); manufacturer: Esaote S.p.A., Genova, Italy.
¶Portable ultrasound system; manufacturer: Esaote S.p.A., Genova, Italy.
#System and probe used for obtaining images shown in Figures 4B & 4C & 8D.
††System and probe used for obtaining images shown in Figures 1B & 2B &2D.
‡‡System and probe used for obtaining images shown in Figures 4E & 4F, 7B & 7D & 8B.
§§System and probe used for obtaining images shown in Figures 6B & 6D & 9B.
¶¶System and probe used for obtaining images shown in Figures 3B & 3D & 10.
##System and probe used for obtaining images shown in Figure 5B & 5C
CT: Computed tomography; US: Ultrasonography.

very bright appearance of the surface of the referring bone. For improved comparability, it has been recommended by the German Society for Ultrasound in Medicine that the left side of the US screen shows the medial, ulnar, cranial or proximal side of the examined body part and the right side the lateral, radial, caudal and distal side [24]. Alternatively, at axial transection of a body part, the left side of the US image can display the left side of the referring body region as seen from the investigator which may be more intuitive. Irrespective of which approach is favored in a given laboratory, a laboratory-specific standard for each therapeutically relevant body region should be established.

US of muscle tissue

Normal muscles can be identified easily on US by their 'starry night' appearance on transverse view and pennate appearance on longitudinal view, the identification of their origin and insertion and their diameter changes on contraction [22,23]. Muscle tissue has normally a low echogenicity. Its echogenicity is increased in the presence of fibrosis and by the infiltration of fat tissue, which may be caused by a number of neuromuscular disorders [25–27]. Sizes of human limb muscles, paraspinal muscles and even of cranial or facial muscles can be reliably measured with US [28–31]. Individual muscle fibers cannot be distinguished from each other. Muscle fibers are organized in grouped bundles (fascicles) surrounded by fibroadipose septa called perimysium. Hyperechogenic perimysium can be distinguished from muscle fascicles with diameters of more than 2 mm. The highly echogenic epimysium allows distinguishing muscles from each other [23]. Figure 1 shows US images of muscle tissue surrounded by other tissues.

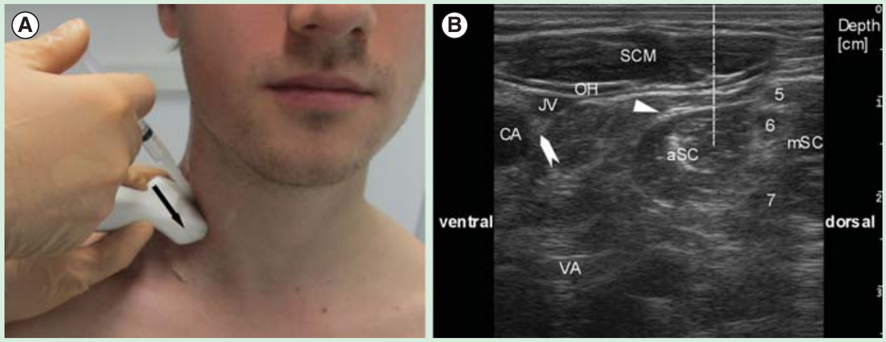

Figure 1. US of the lateral neck region for guiding BT injection into the anterior scalene muscle. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the SCM, OH, aSC and mSC muscles. The triangle indicates the phrenic nerve, and the arrowhead the vagal nerve. Note that the dermis and epidermis are visualized with high echogenicity whereas the subcutaneous fatty tissue has a medium echogenicity. The dashed line indicates the expected path of injection needle.
5: 5th cervical nerve root; 6: 6th cervical nerve root; 7: 7th cervical nerve root; aSC: Anterior scalene; BT: Botulinum toxin; CA: Common carotid artery; JV: Internal jugular vein; mSC: Middle scalene; OH: Omohyoid; SCM: Sternocleidomastoid; US: Ultrasonography; VA: Vertebral artery.

US of salivary glands

US allows easy and high-resolution imaging of salivary glands [32]. Whereas the superficial portion of the parotid gland can easily be localized manually, its retromandibular portion as well as the submandibular gland producing about 70% of the saliva is difficult to localize manually. US displays the parotid and the submandibular gland (Figure 2) as homogenous structures of mild hyperechogenicity.

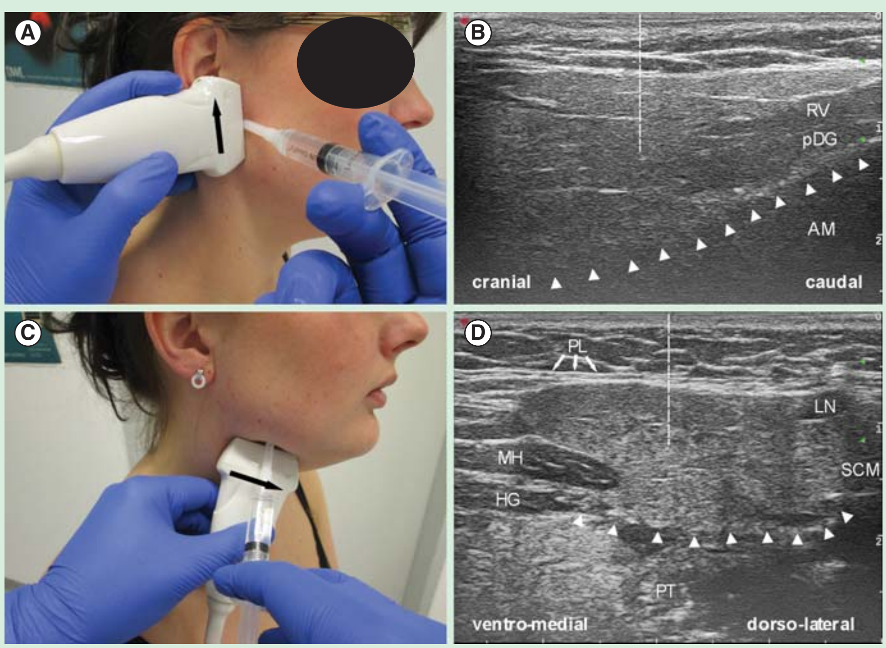

Figure 2. US of the parotid and submandibular glands. **(A)** Position of ultrasound transducer and syringe for injection into the parotid gland (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the parotid gland with neighboring structures. Note that periosteum and bone surface of the AM are highly echogenic, while the inner parts of bone are of low echogenicity due to ultrasound attenuation behind the bone surface. **(C)** Position of ultrasound transducer and syringe for injection into the submandibular gland (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the submandibular gland with neighboring structures. Note that the dermis and epidermis are visualized with high echogenicity, whereas the subcutaneous fatty tissue has a medium echogenicity. The dashed line indicates the expected path of injection needle.
AM: Angulus mandibulae; HG: Hyoglossus muscle; LN: Lymph node; MH: Myohyoid muscle; pDG: Venter posterior of digastric muscle; PL: Platysma; PT: Palatine tonsil; RV: Retromandibular vein; SCM: Sternocleidomastoid muscle; US: Ultrasonography.

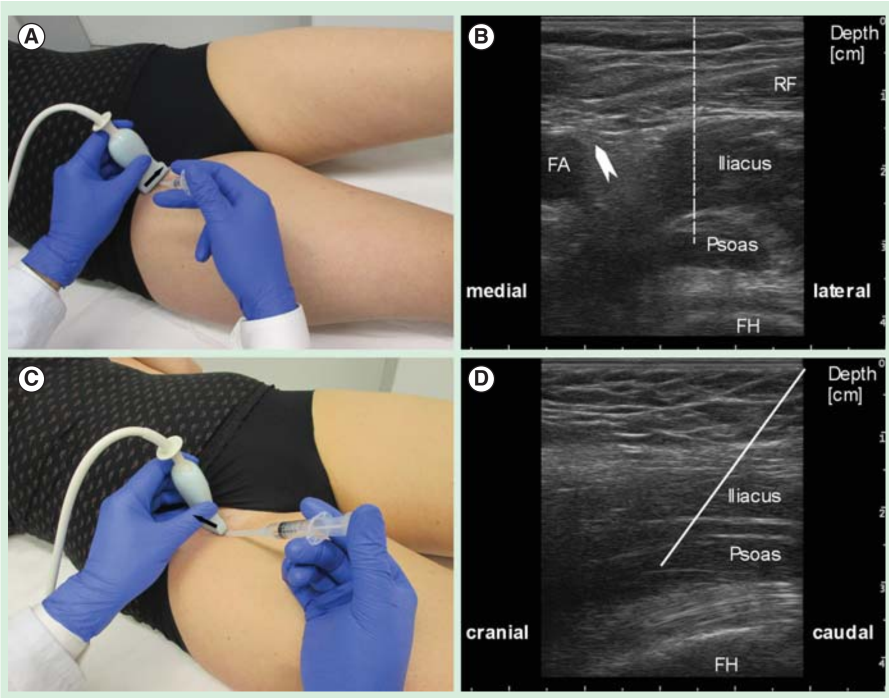

Figure 3. US of the inguinal region for guiding BT injection into the psoas muscle. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the psoas, iliacus and RF muscles and neighboring structures. The arrowhead indicates the femoral nerve. The dashed line indicates the expected path of injection needle. **(C)** Position of ultrasound transducer and syringe (in-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the psoas and iliacus muscles (longitudinal view). The line indicates the path of injection needle which can be visualized completely if using the in-plane injection technique.
BT: Botulinum toxin; FA: Femoral artery; FH: Head of femoral bone; RF: Rectus femoris; US: Ultrasonography.

US of other tissues

The dermis and epidermis are highly echogenic, whereas the subcutaneous fatty tissue has a medium echogenicity (Figures 1 & 2). Thin fatty layers, for example, in sporty individuals, are more echogenic. Periosteum and bone surface are highly echogenic, while the inner parts of bone are of low echogenicity due to ultrasound attenuation behind the bone surface (Figure 2). Tendons are of high echogenicity, which typically decreases when the US transducer is angulated. This decrease of echogenicity can be used to discriminate tendons from nerves. Larger nerves are typically seen with highly echogenic myelin sheaths and less echogenic nerve fibers (Figure 1). Vessel lumina are of low echogenicity, and blood flow inside vessels can optionally be visualized by applying color-Doppler US.

US for BT application

Practical considerations

BT injections are usually performed with 20 mm, 27-gauge (outer diameter: 0.40 mm) needles or 40 mm, 27-gauge needles. For profound muscles, an 80 mm, 23-gauge (0.60 mm) needle or a 120 mm, 25-gauge (0.50 mm) spinal needle may be used. Skin disinfection should be performed with non-alcoholic agents since alcohol may harm the US transducer surface. Then, the injection needle is inserted adjacent to the US transducer. While insertion of the needle through regular ultrasound gel has been proposed to be safe [33], it may be preferable to remove the excess gel with a sterile swap before injection. Bacteriostatic ultrasound gel is available, but does not seem to be necessary. In principle, there are two techniques of US-guided needle insertion with respect to US imaging plane: The in-plane technique and the off-plane technique (Figure 3). Moreover, if an US transducer equipped with a needle guide holder is used together with biopsy software, guide lines in the live US image show the expected course of the needle through the tissue [34]. In our experience, the 'freehand' off-plane technique without external needle guide is sufficient for most applications of US-guided BT injection. For this, the US transducer should be placed in a way that the target structure is displayed in the centre of the US screen. Then the midpoint of the transducer length corresponds to the location of the target structure and can be used as landmark for needle insertion. If necessary, a wooden stick or the needle cap can be pressed toward the skin at the planned insertion site, with pressure movements visible on US (Figure 4), to confirm correct targeting prior to needle insertion. The inserted needle is displayed with high echogenicity, with its intensity depending on the needle size. However, with the off-plane technique, the needle tip itself is sometimes difficult to recognize. In this situation, gentle movements of the needle are helpful to detect the tip. The injected BT solution usually presents as weakly echogenic depot, leading to a local volume increase of the injected muscle or gland, thus allowing documentation of the actual BT placement site and its distribution (Figures 4 & 5). The medical report on US-guided BT placement procedures should include a description of the length and gauge of needle, the type of probe used and an indication of how well the patient tolerated the procedure [35]. It has been recommended to file at least one US image of the needle once it has reached its target [35]. In our opinion, an US image showing the injected BT solution within the target structure may be filed as alternative or in addition.

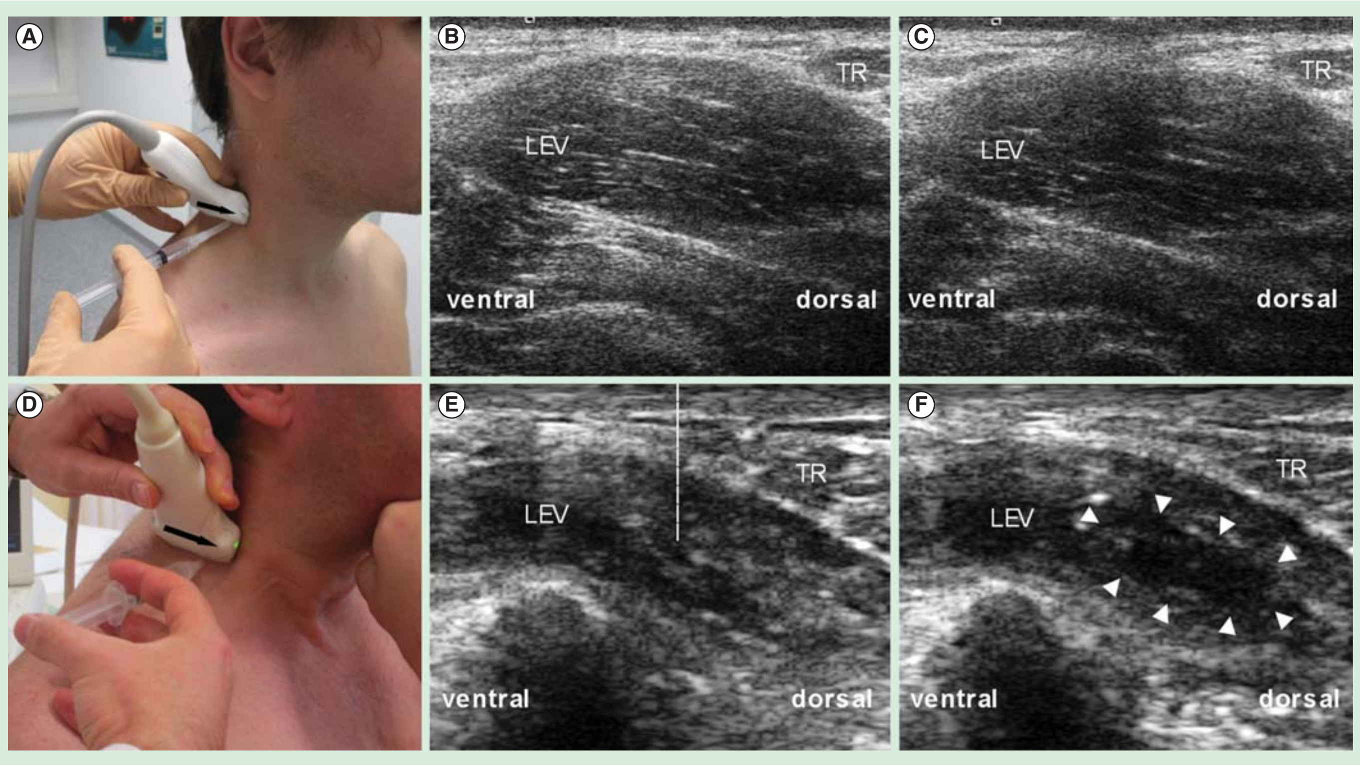

Figure 4. US of the lateral neck region for guiding BT injection into the levator scapulae muscle. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique) covered by the needle cup for the pressing maneuver to confirm the planned injection site. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)** and **(C)**). **(B)** US image showing the LEV (TR) without pressing of the covered syringe. **(C)** US image showing the LEV (TR) with hypoechoic appearance of the central parts caused by pressing of the covered syringe. **(D)** Position of ultrasound transducer and syringe for injection of the levator scapulae muscle (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(E)** and **(F)**). **(E)** US image showing the LEV (TR). The dashed line indicates the path of injection needle. **(F)** US image corresponding to the plane shown in **(E)** showing the hypoechoic depot of the BT solution immediately after injection.

BT: Botulinum toxin; LEV: Levator scapulae muscle; TR: Trapezius muscle; US: Ultrasonography.

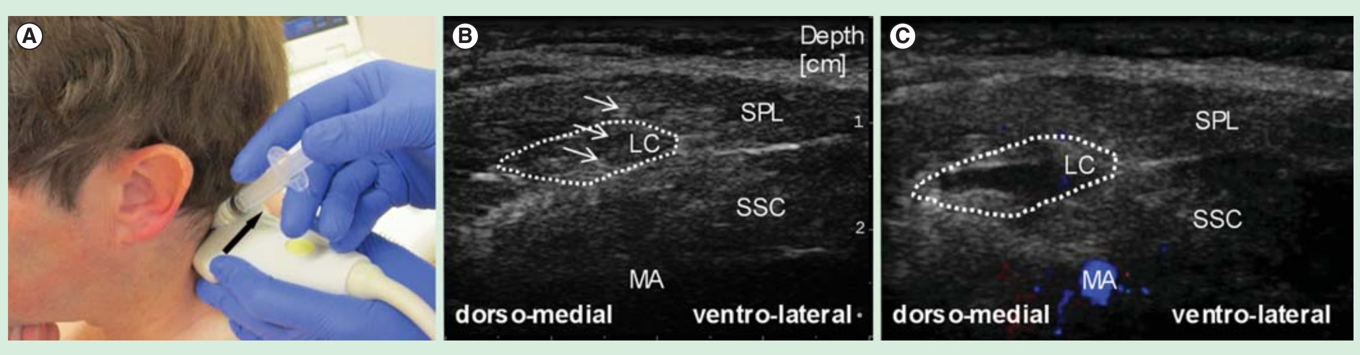

Figure 5. US of the lateral neck region for guiding BT injection into the longissimus capitis muscle. **(A)** Position of ultrasound transducer and syringe for injection of the longissimus capitis muscle (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)** and **(C)**). **(B)** US image showing the longissimus capitis (LC, encircled by dotted line), SPL, and SSC muscles (MA). The arrows indicate echosignals caused by the inserted injection needle. **(C)** US image corresponding to the plane shown in (B) showing the hypoechoic depot of the BT solution inside the LC muscle immediately after injection.

BT: Botulinum toxin; MA: Muscular artery; SPL: Splenius capitis; SSC: Semispinalis capitis; US: Ultrasonography.

Table 4. Feasibility and necessity of ultrasonography-guidance in various muscular and glandular target structures.

Feasibility of US guidance	Necessity for US guidance	Target tissues
Rather low	Low†	Facial mimic muscles‡ Supra- and infrahyoid muscles‡ Pharyngeal muscles§ Glandula lacrimalis‡ Sweat glands‡
	High	Longus colli muscle§, ¶ Longus capitis muscle§, ¶ Laryngeal muscles‡ Psoas muscle (spinal portion)§
Rather high	Low†	Temporalis muscle Masseter muscle Sternocleidomastoid muscle Trapezius muscle Shoulder muscles Proximal arm muscles Intrinsic hand muscles Superficial paravertebral muscles Abdominal muscles Gluteal muscles Leg adductor muscles Tibialis anterior muscle Glandula sublingualis
	Intermediate	Splenius capitis muscle Semispinalis capitis muscle Levator scapulae muscle Ischiocrural muscles Gastrocnemius muscle Glandula parotis
	High#	Obliquus capitis inferior muscle†† Scalenus anterior muscle†† Scalenus intermedius muscle†† Omohyoid muscle‡‡ Longissimus capitis muscle Longissimus cervicis muscle Single forearm muscles Single finger flexors Single finger extensors Psoas muscle (inguinal portion)†† Gracilis muscle Soleus muscle Tibialis posterior muscle†† Extensor hallucis longus muscle Glandula submandibularis

†Low necessity because of easy visual/manual targeting, or low frequency of cases.
‡Difficult because of smallness of target structure.
§Difficult because of depth of target structure.
¶Difficult because of neighboring sensitive structures.
#High necessity in dystonia, mild spasticity, infantile cerebral palsy.
††Attention should be paid to correct injection technique.
‡‡Especially in omohyoid muscle syndrome.
US: Ultrasonography.

Intramuscular BT applications

Table 4 shows the feasibility and usefulness of US guidance in muscular and glandular target tissues. In certain cranial and cervical muscle groups, US guidance is not (pterygoid) or only hardly (mimic, pharyngeal, laryngeal) feasible [31,36,37]. However, the usefulness of US guidance is low for mimic and pharyngeal muscles because of their direct accessibility. The laryngeal muscles (vocalis, posterior cricoarytenoid) can be injected transorally using endoscopic guidance, or transdermally. For transdermal injection, EMG guidance is crucial, either alone or, optionally, in combination with US [38,39]. Supra- and infrahyoid muscles can be visualized with US [36,40]. However, guided BT injection is rarely necessary. US guidance is feasible for lateral and dorsal neck muscles, axial muscles, shoulder muscles, proximal and distal arm muscles, intrinsic hand muscles and leg muscles. Out of those, the usefulness of US guidance is low in shoulder muscles, proximal arm muscles and superficial axial muscles, because of their size and accessibility. It is intermediate in superficial nuchal and superficial leg muscles. It is high in deep nuchal muscles, forearm muscles, intrinsic hand muscles and deep leg muscles, unless spasticity is massive and functionality is not an issue. According to a European consensus statement, children with cerebral palsy should generally receive BT injections using EMG guidance or US guidance [41]. Because of better tolerability, US guidance is preferable in children. For some muscles (e.g., longus colli, obliquus capitis inferior, forearm muscles, psoas, leg muscles) US visualization may protect sensitive structures (nerves, large vessels) adjacent to the target muscles (Figures 1, 3, 6–9) [42–46]. Distinct thin, unselectively activated muscles (e.g., omohyoid, longissimus capitis) can only be targeted with US guidance (Figures 1 & 5). Side effects (dysphagia) resulting from BT injection into the sternocleidomastoid muscle can be significantly reduced by switching from EMG guidance to US guidance [47]. However, manual application into the upper third of the sternocleidomastoid muscle is often already sufficient to reduce dysphagia considerably. A recent small prospective randomized study that compared US guidance with active EMG guidance and manual application in forearm muscles (flexor carpi radialis and ulnaris, flexor digitorum superficialis and profundus) in adults with poststroke spasticity demonstrated superiority of both US guidance and active EMG guidance [48]. Another similar study compared US guidance with active EMG guidance and manual application in the lateral and medial head of the gastrocnemius muscle in adults with spastic equinovarus posture after stroke. This study showed superiority of US guidance over both manual application and active EMG guidance, suggesting that US guidance may be helpful at least in the calfs [49]. 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 [50]. In many of our patients with writer's cramp, the BT dose could be reduced when switching from manual application to US guidance.

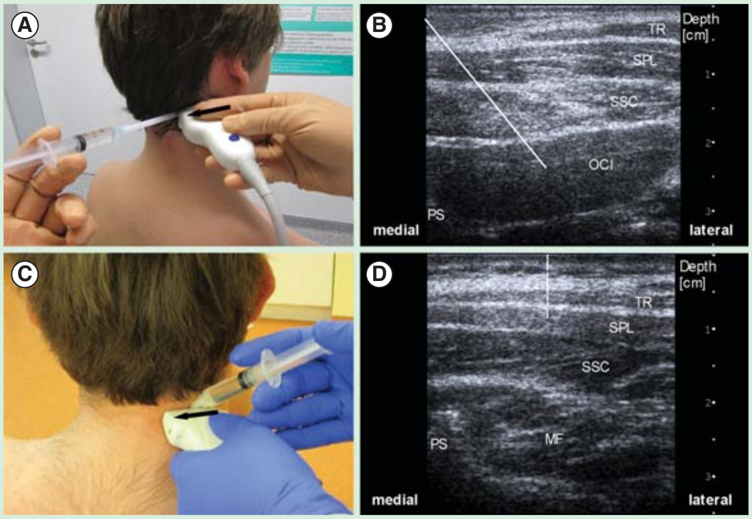

Figure 6. US of the dorsal neck region for guiding BT injection into the obliquus capitis inferior and the splenius capitis muscles. **(A)** Position of ultrasound transducer and syringe (in-plane injection technique) at level of 2nd cervical vertebra. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the TR, SPL, SSC, and OCI muscles (PS). Note that for injection of the OCI, only the in-plane injection technique with the needle guided from medio-dorsal to latero-ventral direction (indicated by the line) should be applied in order to avoid touching the vertebral artery. **(C)** Position of ultrasound transducer and syringe (off-plane injection technique) at level of 5th cervical vertebra. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the TR, SPL, SSC, and MF muscles (PS). The dashed line indicates the expected path of injection needle.

BT: Botulinum toxin; MF: Multifidus; OCI: Obliquus capitis inferior; PS: Processus spinosus; SPL: Splenius capitis; SSC: Semispinalis capitis; TR: Trapezius; US: Ultrasonography.

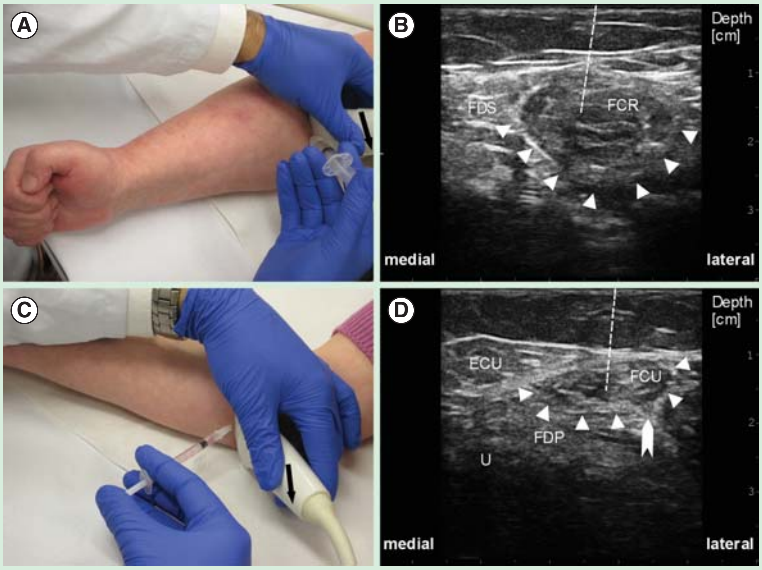

Figure 7. US of the proximal forearm region for guiding BT injection. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BT injection into the flexor carpi radialis muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the flexor carpi radialis (FCR, indicated by triangles) and FDS muscles. The dashed line indicates the off-plane path of injection needle. **(C)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BoNT injection into the flexor carpi ulnaris muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the FCU (indicated by triangles; arrow: ulnar nerve), ECU and FDP muscles. The dashed line indicates the off-plane path of injection needle.

BT: Botulinum toxin; ECU: Extensor carpi ulnaris; FCU: Flexor carpi ulnaris; FDP: Flexor digitorum profundus; FDS: Flexor digitorum superficialis; U: Ulna; US: Ultrasonography.

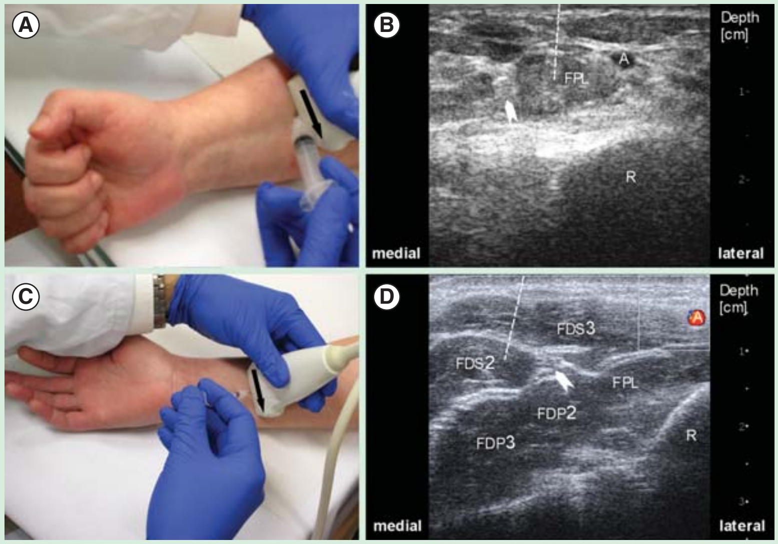

Figure 8. US of the distal forearm region for guiding BT injection. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BT injection into the flexor pollicis longus muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the FPL muscle, the radial artery **(A)**, the median nerve (arrowhead) and the radius (R). The dashed line indicates the off-plane path of injection needle. **(C)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BT injection into the 2nd flexor digitorum superficialis muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the FDS, FDP, and FPL muscles, the radial artery **(A)**, the median nerve (arrowhead) and the radius (R). Note that the 2nd and 3rd FDS (but not the FDP) muscles are paradoxically 'exchanged' in anatomic order, which may cause needle displacement if using other techniques than US guidance for needle placement. The dashed line indicates the off-plane path of injection needle.
BT: Botulinum toxin; FDP: Flexor digitorum profundus; FDS: Flexor digitorum superficialis; FPL: Flexor pollicis longus; US: Ultrasonography.

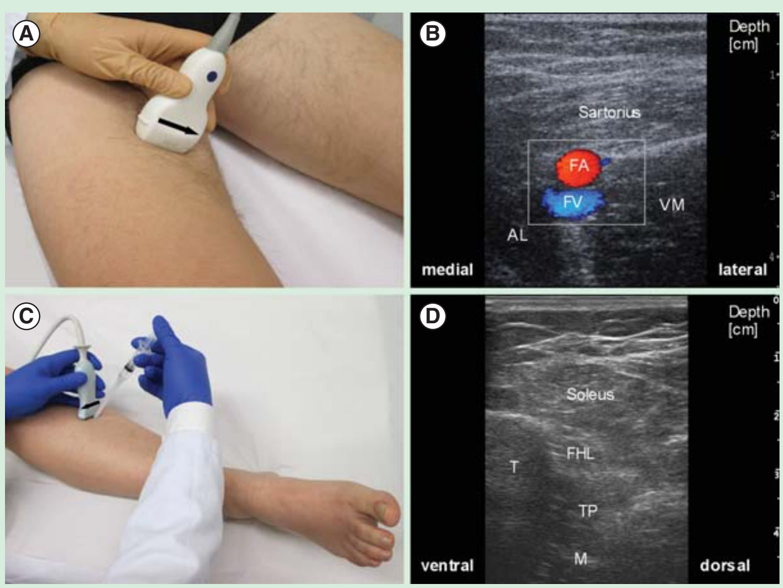

Figure 9. US of leg muscles for guiding BT injection. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BT injection into the sartorius muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** US image showing the sartorius, VM, and AL muscles, the FA and FV. **(C)** Position of ultrasound transducer and syringe (off-plane injection technique) for guiding BT injection into the tibialis posterior muscle. The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(D)**). **(D)** US image showing the soleus, FHL, and TP muscles, the T and the M.
BT: Botulinum toxin; AL: Adductor longus; FA: Femoral artery; FHL: Flexor halluscis longus; FV: Femoral vein; M: Membrana interossea; T: Tibia; TP: Tibialis posterior; VM: Vastus medialis; US: Ultrasonography.

Intraglandular BT applications

The helpfulness of US guidance for the parotid gland injections is intermediate, whereas it is high for the submandibular gland. Small studies suggest superiority of US guidance versus manual application for parotid BT injections in sialorrhoea in Parkinson's disease patients [51]. Effective treatment of sialorrhoea by US-guided BT injection to the submandibular and parotid glands has been reported in children and adults with various neurologic disorders [52–56]. The sublingual and lacrimal glands can also be visualized by US [32,57]. However, the helpfulness of guidance for these glands is low.

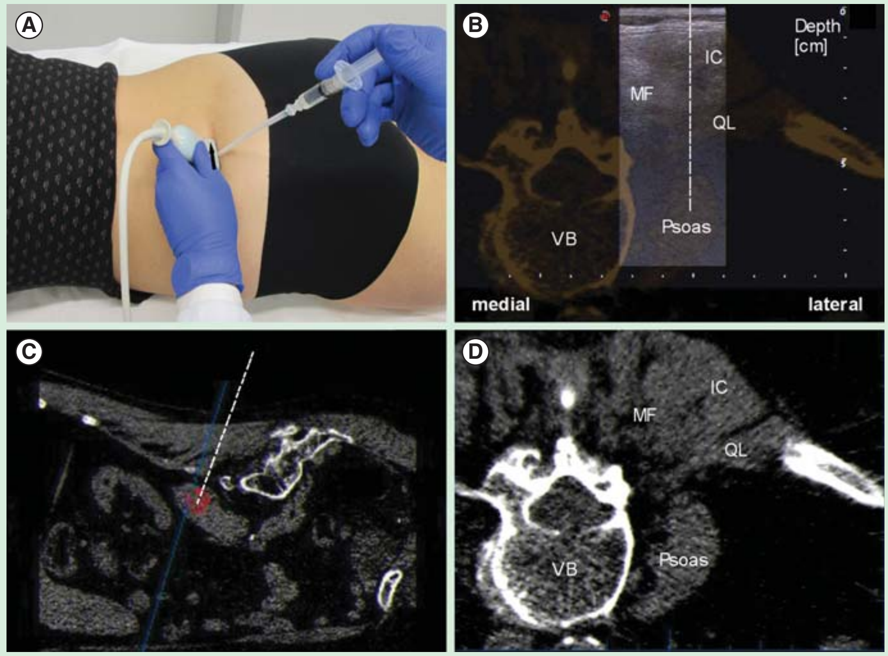

Figure 10. US and CT-US fusion imaging for injection of the dorsal paraspinal muscles. **(A)** Position of ultrasound transducer and syringe (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in **(B)**). **(B)** CT-US fusion image (ultrasound image displayed only in the central rectangular fraction of the fusion image) showing the IC, MF, paraspinal psoas and QL muscles. VB = vertebral body. The superficial IC, MF and QL muscles can be visualized sufficiently with US only, allowing for stand-alone US-guided BT injection. However, the deep paraspinal psoas muscle can only be visualized with US if using fusion imaging. **(C)** Sagittal CT image. **(D)** Axial CT image corresponding to the fusion image shown in **(B)**. The dashed lines in **(B)** and **(C)** indicate the expected path of injection needle. In near future, electromagnetic needle position-tracking devices will become available that allow the freehand needle navigation based on CT-US or MRI-US fusion imaging.

CT: Computed tomography; IC: Iliocostalis; MF: Multifidus; QL: Quadratus lumborum; US: Ultrasonography.

Expert commentary

US allows a simple, non-invasive, real-time visualization of muscular and glandular tissues and their surrounding structures. It can visualize the entire procedure of BT application. With this, it is able to guide and standardize BT application, US guidance of intramuscular BT injection is superior to EMG guidance in that it can visualize neighboring, electrically silent structures, especially solid organs, blood vessels and nerves, in addition to target muscles. We recommend that users, after having trained the US-guidance technique on a phantom, start in patients with treatment of larger, easily visualized muscles to further improve their eye–hand coordination, which is the major challenge in this technique. In principle, US guidance may well be applied in any BT injection if time is not an issue. However, even if conducted by well-trained users, US guidance is more time consuming than the simple manual technique, which is a limiting factor in a busy clinic. Therefore in the present article, we differentiated between high-level and low-level indications with respect to patients' clinical outcomes based on current evidence in the literature and on our personal practice experience.

Considering feasibility and necessity for US guidance, it should be used in forearm muscles especially when functionality is an issue, especially in task-related dystonia and mild spasticity. US guidance is also recommendable for the anterior and middle scalene muscles. Distinct thin, unselectively activated cervical muscles (e.g., omohyoid, longissimus capitis) can be targeted practically only with US, which may be of benefit in special conditions such as omohyoid muscle syndrome or complex, otherwise refractory cervical dystonia. US guidance should also be used for BT application in the submandibular gland. It may be used in leg muscles, especially in children, and in the parotid gland. In other muscles, it may or may not be used. Some clinical studies suggest that US may improve BT placement in even easily accessible muscles. The results of small randomized studies suggest that US-guided injection may improve therapeutic efficacy and reduce adverse effects of BT therapy when compared to manual or EMG-guided injection techniques. Large-scale studies comparing US with other techniques for guidance of BT application are warranted.

Five-year view

So far, US has only been used for BT application. In the coming years, US may also be available for detection of muscle hyperactivity in the process of planning of BT therapy. For this, US simply using conventional B-mode may detect muscle hypertrophy indicating muscle hyperactivity [29]. Advanced US technologies such as sono-elastography, tissue velocity imaging and space-time myosonology promise a more specific detection of dystonic and spastic muscles [58–61]. Studies are underway to elucidate the clinical use of these approaches.

Novel technologies enabling the real-time image fusion of US with MRI, CT or positron emission tomography images that were previously obtained and imported into the US system as Digital Imaging and Communications in Medicine volume dataset [62,63] may provide improved guidance in deep muscles such as the paraspinal psoas and piriformis muscles (Figure 10). The accuracy of fusion imaging has much improved with the recent implementation of motion sensors not only at the ultrasound transducer but also at the patient's target body part [64]. In near future, electromagnetic needle position-tracking devices will become commercially available that allow the freehand needle navigation based on CT-US or MRI-US fusion imaging [65]. These improved techniques should be regarded as a prerequisite for US-guided BT injection into deep muscles neighboring critical internal organs such as the paraspinal psoas muscle. The main advantages of the upcoming fusion imaging technologies are the possibility of continuous (needle) navigation within the image volume and the avoidance of repeated CT images. However, these techniques still require further refinement with respect to validity and reliability before they can be used in clinical practice.

As US is an ideal instrument to standardize the BT application into target muscles, future studies applying US guidance for BT placement may allow a more detailed analysis of therapeutic effects on functional outcome measures such as manual task performance in patients with upper-limb tremor [66], or standing balance in patients with poststroke spasticity [67].

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Key issues

- Ultrasonography (US) allows real-time imaging and guidance of the entire procedure of botulinum toxin (BT) application into target muscles and glands.
- US guidance should be used in forearm muscles when functionality is important, especially in writer's or musician's cramp and mild forearm spasticity.
- US guidance should be used especially in children for targeting selected leg muscles including psoas, lateral gastrocnemius and posterior tibial.
- US guidance is the only way for treating omohyoid muscle syndrome.
- US guidance may be used in patients with cervical dystonia when the anterior or middle scalene, longissimus capitis and the obliquus capitis inferior are target muscles.
- US guidance may also be used for targeting the submandibular and, optionally, the parotid gland.
- Small randomized studies suggest that US guidance can improve therapeutic efficacy and reduce adverse effects of BT therapy when compared to conventional placement.
- Large-scale studies comparing US with other techniques for guidance of BT application are warranted.
- In near future, electromagnetic needle position-tracking devices will become commercially available that allow the freehand needle navigation based on real-time image fusion of US with previously acquired MRI or computed tomography volume data sets.
- Upcoming advanced US technologies may enable even the detection of most hyperactive muscles on US for planning the optimum targets of BT application.

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