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Botulinum Toxin Treatment of Children with Cerebral Palsy - a Short Review of Different Injection Techniques

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The intramuscular application of botulinum toxin type A (BoNT/A) has emerged to be an established treatment option to reduce muscular hyperactivity due to spasticity in children with cerebral palsy. Accurate injection is a prerequisite for efficient and safe treatment with BoNT/A. So far, treatment procedures have not been standardized. This paper is a short review of different injection techniques, *i.e.*, manual needle placement as well as guidance by electromyography, electrical stimulation, and ultrasound. Advantages and disadvantages of the different injection techniques are discussed with a focus on needle positioning within the targeted muscle, injection close to the neuromuscular junction and diffusion of BoNT/A within the target muscles and through fascia. The additional information gained by each injection technique is weighed in terms of the clinical impact for children with cerebral palsy.

Keywords: Botulinum toxin; Cerebral palsy; Ultrasound; Electrical stimulation; EMG; Neuromuscular junction; Diffusion; Dilution

Abbreviations

BoNT/A, botulinum toxin type A; **CP**, cerebral palsy; **EMG**, electromyography; **GMFCS**, Gross motor function classification system; **MEP**, motor evoked potential; **NMJ**, neuromuscular junctions; **U**, unit (mouse units of botulinum toxin type A)

INTRODUCTION

The use of botulinum toxin type A (BoNT/A) for muscle spasticity in children with cerebral palsy (CP) was initially described more than a decade ago (Koman *et al.*, 1993; Cosgrove *et al.*, 1994). In 2000, a group of 15 experienced clinicians and scientists from a variety of disciplines arrived at a consensus and produced detailed recommendations as to appropriate patient selection and assessment, dosage, injection technique, and outcome measurement (Graham *et al.*, 2000). Up to 2004, 22 publications on the use of BoNT/A in patients younger than 19 years with nearly complete information on dosing and injection technique were cited in MEDLINE and PubMed (Kinnett, 2004). The analysis of those publications which used BoNT/A (preparation Botox®) showed a variety of total doses used both in terms of units of activity and volumes injected. Anatomic localization of target muscles using palpation was the most common technique in the reviewed publications (Kinnett, 2004).

Studies looking at the effect of changes in volumes, dilutions, and localization techniques on the response to BoNT/A in children are scarce. In a prospective, 3 month, randomized, double-blind clinical study involving 114 children with CP and dynamic equinus foot deformity, patients in the BoNT/A group (preparation Botox®) demonstrated improved gait function and a 20% reduction in motor evoked potential (MEP) of the gastrocnemius muscle (Koman *et al.*, 2000). The authors rated the predictability of improved gait function as low (Koman *et al.*, 2000). In contrast, mean MEP reduction of the sternocleidomastoid muscle in 34 patients treated with BoNT/A for cervical dystonia was 70 91% depending on dose and BoNT/A brand administered (Dressler *et al.*, 2000).

In another prospective, randomized, double-blind, placebo-controlled clinical study in 40 children with "spastic diplegia" or "hemiplegia", 48% of the 22 children who received BoNT/A (preparation Dysport®)

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showed clinical improvement in the video gait analysis compared to 17% of placebo treated children (Ubhi *et al.*, 2000).

Although the aforementioned clinical studies provided adequate scientific evidence for the use of BoNT/A in the treatment of children with CP, the following four topics are worth to be reviewed in more detail, as there may be room for further improvement in the response to BoNT/A:

1) Muscle localization techniques.
2) Diffusion of BoNT/A within the muscle and through muscle fascia.
3) Injection of BoNT/A close to neuromuscular junctions (NMJ).
4) Additional factors which might influence the focal therapeutic response to BoNT/A.

Diffusion of BoNT/A as well as the potential need for injections close to NMJ is interrelated with volumes, dilutions, and number of injection sites selected. Topics two, three, and four will be discussed regarding the additional knowledge that is gained by technical assisted injection as described in the first topic.

MUSCLE LOCALIZATION TECHNIQUES

The comparison of muscle localization techniques to guide BoNT injections is written from the perspective of a neuropaediatrician. Children are very sensitive to pain, are rarely cooperative and don't like any procedures that require them holding still for a length of time. It is important to understand the paediatric background because an experienced neurologist who specializes on adult patients is used to applying electromyography (EMG) and muscle stimulation with usually excellent results, and thus would not feel any need for introducing a new technique.

Palpation

Manual needle placement guided by adequate expertise in anatomy is still the most common localization technique. In a study comparing the accuracy of manual needle placement with needle placement guided by electrical stimulation, 1372 separate injections for upper and lower limb spasticity were evaluated in 226 children (Chin *et al.*, 2005). A 27 gauge insulated Teflon-coated needle was used to stimulate the muscle and deliver BoNT/A. The needle was first inserted manually into the target muscle using a combination of anatomic landmarks, palpation of muscle bellies where possible, and movement of the distal joints to passively stretch target muscles to confirm needle placement. Following manual needle placement, electrical stimulation was performed to check the needle position. If, following stimulation, a visible or palpable contraction of the target muscle was elicited without contraction of neighboring muscles, the needle position was recorded as accurate (Chin *et al.*, 2005). Table I summarizes the accuracy of manual needle placement in per cent of accuracy calculated per injected muscle as: [(total number of injections) minus (inaccurate injections as per electrical stimulation results)] divided by the (total number of injections) times 100 (Chin *et al.*, 2005).

Manual needle placement proved to be particularly difficult for injections into small, slender, and deep seated muscles. In the cited publication, injection procedure was carried out using general anaesthesia which might have reduced the ability to palpate the relaxed targeted muscle prior to electrical stimulation.

EMG

There are two electrophysiological techniques to localize muscles: electromyography (EMG) and electrical stimulation (for review, Wissel and Poewe, 2003).

In a randomized, controlled clinical study, 28 patient with cervical dystonia received EMG-guided BoNT/A injections (preparation Botox®), whereas 26 patients

Table I Accuracy of manual needle placement in per cent of accuracy calculated per injected muscle as: [(total number of injections) minus (inaccurate injections as per electrical stimulation results)] divided by the (total number of injections) times 100 (Chin *et al.*, 2005).

Upper Limb Muscle	Accuracy	Lower Limb Muscle	Accuracy
Biceps brachii	62% (29/47)	Gastroc-soleus	78% (204/261)
Adductor pollicis	32% (12/38)	Hip adductors (adductor longus and brevis)	68% (26/38)
Pronator teres	22% (3/15)	Medial hamstrings (semimembranosus and semitendinosus)	46% (12/26)
Flexor carpi ulnaris	16% (4/28)	Tibialis posterior	12% (2/18)
Flexor carpi radialis	12% (3/31)		

received injections following manual needle placement (Comella *et al.*, 1992). A significantly greater magnitude of improvement was present in patients with EMG-guided injections as well as a significantly greater number of patients with marked improvement (Comella *et al.*, 1992). In particular, patients with retrocollis, head tilt, and shoulder elevation, *i.e.*, patients with relevant involvement of deep cervical muscles, demonstrated additional benefit with EMG-guided injections (Comella *et al.*, 1992). EMG requires active or passive muscle activation to differentiate a particular muscle from neighboring muscles. Patients with spastic motor disorders are often unable to perform specific movements, limiting the feasibility of localizing muscles by EMG in these patients (Jankovic, 2001). Additionally there is no strong correlation between the extent of spasticity and the muscle activity recorded by the EMG as it is seen in patients with dystonic movement disorders. Moreover, needle EMG is associated with pain, which further limits the cooperation of children. On the other hand, sedation may result in a substantial reduction of the EMG signal amplitude. Thus, the EMG signal of the selected muscle may not be distinguished from cross talk of neighboring muscles.

Electrical Stimulation

Electrical stimulation provides reliable information about the position of the needle within the muscle (Barbano, 2001). Nonetheless, electrical stimulation usually requires multiple painful and time-consuming positioning of the needle until its position in the target muscle is accurate. Therefore, the use of electrical stimulation is a viable localization technique in children if adequate analgesia and sedation will be administered. The need for technical equipment is limited although efficient use of electrical stimulation requires experience in electrophysiological techniques as well as familiarity with the relevant anatomical landmarks.

Ultrasound

Ultrasonography is well established as a reliable and reproducible imaging method in muscle anatomy (Fischer *et al.*, 1988). For the injection of BoNT to reduce muscular hyperactivity in spasticity several publications have shown applicability of the procedure offering visually controlled injections as an alternative to electrophysiological techniques (Berweck *et al.*, 2002; Willenborg *et al.*, 2002; Westhoff *et al.*, 2003; Berweck and Heinen, 2004; Berweck *et al.*, 2004).

Between 2000 and 2005, 9863 BoNT/A injections into 31 different muscles of 440 outpatients in 1721 treatment sessions were performed (own data). All patients received combined analgesia and sedation with rectal pethidine plus midazolam prior to their BoNT/A injections. Target muscles included small muscles of the forearm as well as large muscles of the lower extremity. Target muscles were identified based on their characteristic transverse sectional (axial) ultrasound image and, in case of slender muscles, by

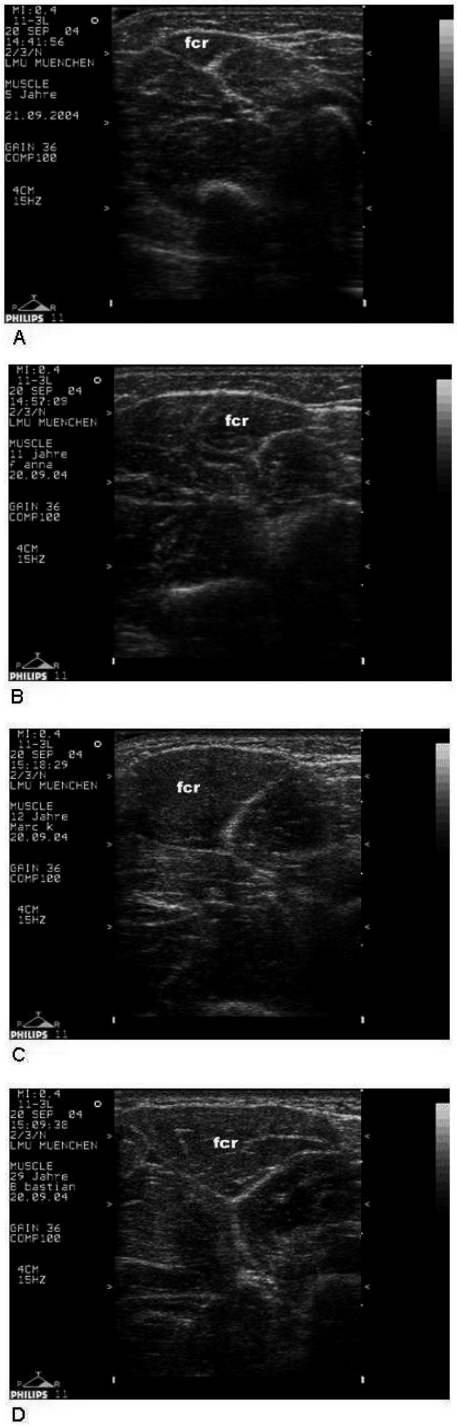


FIGURE 1 Transverse sectional ultrasound images of flexor carpi radialis muscle in healthy children and adults of different ages shown at identical ultrasound settings and probe position. Dependency of muscle size on age. **A**: 5 year old girl; **B**: 11 year old girl; **C**: 12 year old boy; **D**: 29 year old man.

additional passive movement of the concerned limb. Ultrasound in itself is painless. As individual anatomy varies it is properly shown in ultrasound images (see FIG. 1) before placing the needle inside the muscle and the need for multiple needle repositioning becomes highly unlikely. Needle positioning in the center of the muscle belly is possible.

Summary Muscle Localization Techniques

Manual needle placement proved to be inaccurate - especially in general anaesthesia, whereas electrical stimulation and, from our point of view, ultrasound guidance are reliable localization techniques. The usefulness of EMG in particular in children with CP is limited. EMG and electrical stimulation are time consuming compared to ultrasound where typical patterns of the targeted muscle can be recognized in a short period of time without the need of a painful procedure. Sonography was always therefore very popular in paediatrics, and consequently, it seemed the obvious choice to utilize this technique for muscle identification and injection control. Nevertheless, even for adult patients, sonographic imaging offers a completely different approach (*e.g.*, visual *vs* acoustic control) and it has the potential to evolve into a procedure that may equal the current gold-standard of EMG and electrical stimulation. Well-designed studies comparing ultrasound guidance and electrical stimulation for muscle localization may provide adequate scientific evidence for our preferential use of ultrasound guidance. The characteristics of the different techniques are summarized in table II.

DIFFUSION OF BoNT/A WITHIN THE MUSCLE AND THROUGH MUSCLE FASCIA

Diffusion of BoNT/A within the Muscle

In albino rabbits, a diffusion gradient of BoNT/A was noted over a distance of 30-45 mm from the point of injection into latissimus dorsi muscle. In the contralateral latissimus dorsi muscle diffusion was noted over a distance of 15-25 mm (Borodic *et al.*, 1990). Thus, denervation was demonstrated to occur within a definable area which also crossed anatomic barriers, such as fascia (Borodic *et al.*, 1990). In a following study, acetylcholinesterase staining properties were determined 5 weeks after administration of BoNT/A into albino rabbit longissimus dorsi muscle (Borodic *et al.*, 1994). At lower doses (1 U), diffusion occurred over a 15-30 mm segment of muscle. At higher doses (5-10 U), diffusion of BoNT/A effect occurred throughout the entire muscle with no apparent end point, suggesting that the extent of the denervation gradient is dose dependent (Borodic *et al.*, 1994). The influence of BoNT/A dose

Table II Characteristics of different approaches to guide BoNT/A injections (+: advantageous, o: acceptable, -: unfavor-

	EMG	Muscle stimulation	Ultrasound
Accuracy of needle placement	o	+	+
Time required for muscle identification	-	o	+
Availability of technical equipment (children's hospital)	o	o	+
Pain and distress caused by procedure	-	-	+
Dependency on expert knowledge	-	-	o
Necessary number of stabs	-	-	+
Control of injection depth	o	o	+
Differentiation of neighboring (co-contracting) muscles	o	o	+
Differentiation of muscle tissue from surrounding structures (e.g. vessels, nerve, bone)	-	-	+
Independency on patient cooperation	-	+	+
Possibility to ascertain correct placement after finishing the injection	-	-	+
Possibility to document the injection	-	-	+
Disturbance through combined analgesia and sedation	-	+	+
Control of proximity to neuromuscular junctions	+	+	-
Control of muscular hyperactivity	+	o	-
Control of muscle dimension	o	o	+
Control of muscle fibrosis	o	o	+
Potential for further development and research	o	-	+

and injection volume was studied following BoNT/A injections in the rat tibialis anterior muscle (Shaari *et al.*, 1993). Paralysis was quantified by electrically stimulating the nerve to the tibialis anterior and then staining sections of the muscle for glycogen. Increases in dose increased paralysis, however, some of that increase was simply due to the increased volume of injection (Shaari *et al.*, 1993). But in an earlier mentioned study, doubling the area of denervation required a 100 times increase in injection volume at the same BoNT/A dose (Borodic *et al.*, 1990).

There is no published evidence available on whether the results of these animal experiments can be transferred to the use of BoNT/A in man.

In a preliminary randomized, controlled study, 13 adult patients who had modified Ashworth scale scores of 3 for both wrist and finger flexors received high- (1.2ml) and low- (0.6ml) volume injections of a 60 U dose of BoNT/A (preparation Botox®) in flexor carpi radialis, flexor carpi ulnaris, profound flexor digitorum and superficial flexor digitorum muscle each (Francisco *et al.*, 2002). Blinded modified Ashworth scale ratings of wrist and finger flexor spasticity revealed a significant decrease in both treatment groups. A slight trend toward a better outcome in the high-volume group was seen. However, the two groups did not differ significantly in spasticity reduction (Francisco *et al.*, 2002). It was concluded that a follow up trial should focus on the questions of dilution and proximity of injections to the motor end plate.

Diffusion of BoNT/A Through Fascia

Denervation following BoNT/A injection was demonstrated to cross anatomic barriers, such as fascia, in rabbits (Borodic *et al.*, 1990). In a small study from Shaari and colleagues BoNT/A (0.2 10 U) was placed onto the fascia of rat tibialis anterior muscles (n=6) and also on dose-matched muscles which had their fascia surgically removed (n=6) (Shaari *et al.*, 1991). The tibial nerve was electrically stimulated 24 hours later to deplete the muscle fibers of glycogen. BoNT/A easily passed through muscle fascia even at subclinical doses with fascia reducing the spread by 23% (Shaari *et al.*, 1991). In men, limiting the BoNT/A dose administered to the sternocleidomastoid muscle to 100 U (preparation Botox®) in cervical dystonia reduced the incidence of associated dysphagia significantly (Borodic *et al.*, 1990), suggesting a clinically significant dose-dependency for diffusion through fascia.

Summary Diffusion of BoNT/A within the Muscle and Through Muscle Fascia

It is still unknown whether features of the injection technique such as needle size, rate of injecting BoNT/A, active or passive movement of the injected muscle following injection, have an impact on BoNT/A diffusion. This may be due to the substantial difficulties to directly document the diffusion of BoNT/A using marker techniques. Based on the published scientific literature and clinical experience, intramuscular BoNT/A diffusion is likely to occur up to approximately 5 cm, depending on the volume and the administered dosage. Further studies have to confirm these data in human subjects.

Muscle fascia can easily be passed by BoNT/A. Thus it may be assumed that injecting BoNT/A in the center of the muscle belly should be achieved to optimize the distribution within the muscle and

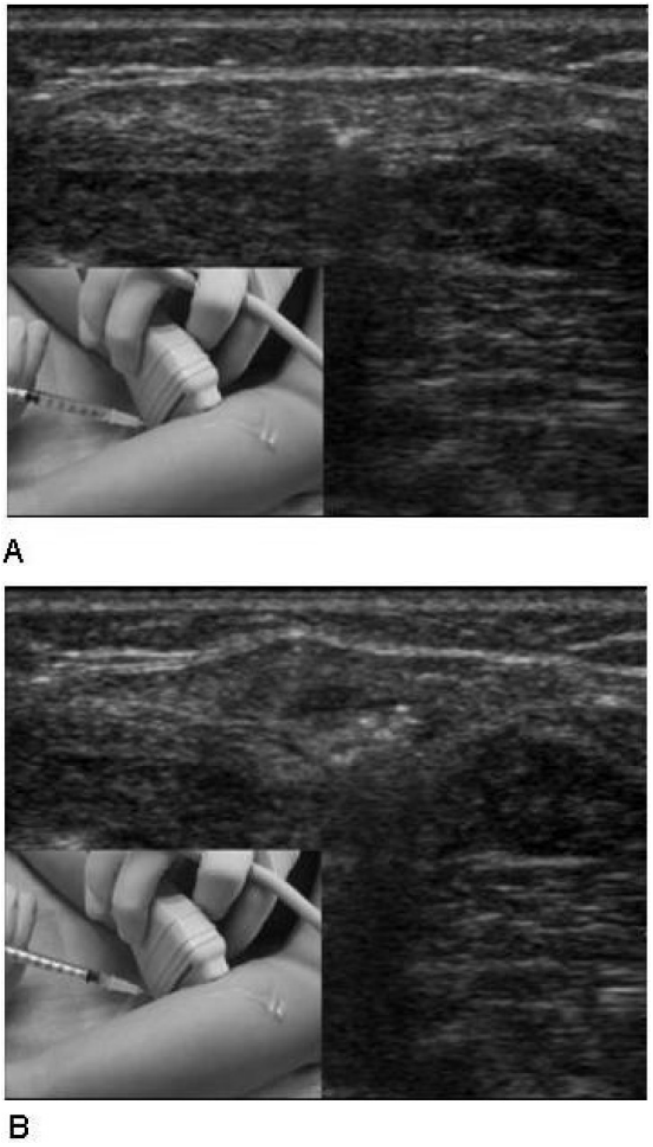
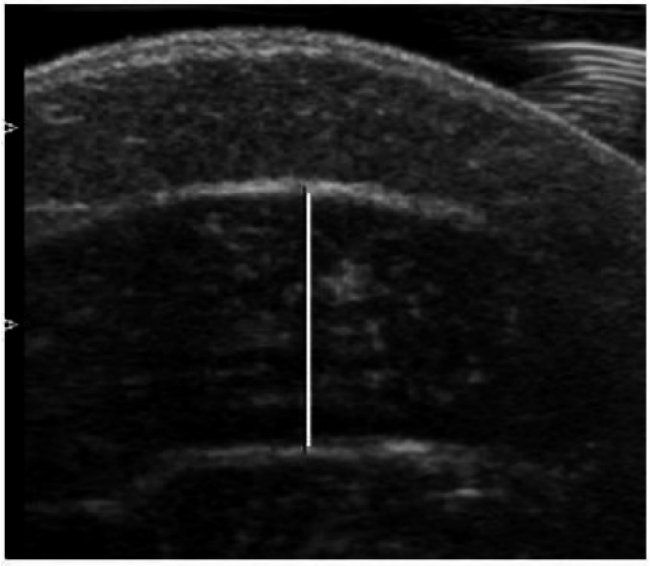
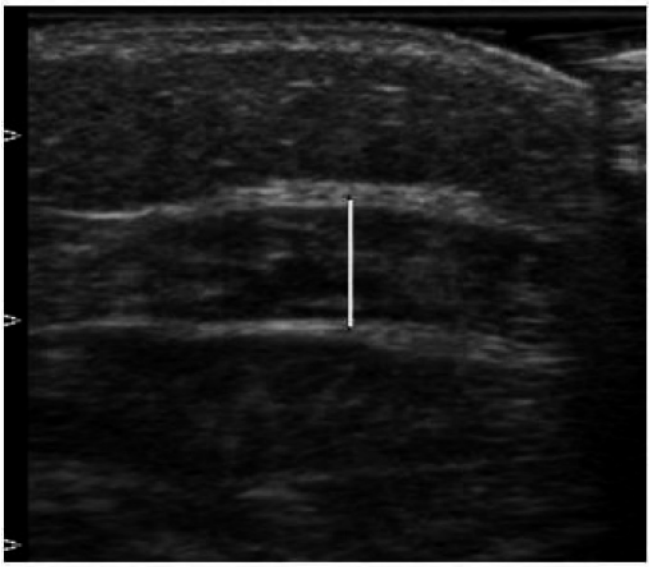


FIGURE 2 Ultrasound images of gastrocnemius medialis muscle before (**A**) and immediately after BoNT/A injection (**B**) of a 0.5 ml volume (4 year old boy with spastic bilateral spastic CP, GMFCS Level III)



A



B

FIGURE 3 Ultrasound images of gastrocnemius medialis muscle in 5 year old twin girls with different severity of CP. (**A**) Muscle diameter in the less affected sibling (GMFCS Level I) compared with (**B**) the more severely affected child (GMFCS Level III). Images were taken at comparable anatomic positions using the same preset for the ultrasound machine.

to avoid any diffusion in neighboring muscle. This aspect of needle placement can be controlled by ultrasound guidance, whereas EMG and electrical stimulation can only identify an accurate position in the target muscle per se. Palpation does not give efficient information on accurate needle position. Due to the studies mentioned above and our own experience using ultrasound guidance, we distribute the total injection volume throughout the muscle via multiple injections. In large muscles volume can be as high as 1 ml per injection site. In small muscles and if spread of BoNT/A to neighboring muscle adversely affects the therapeutic goal, delivering small volumes is deemed advisable. Even volumes as low as 0.5 ml may already "stretch" the muscle as detected by changes in the muscle's ultrasound image (FIG. 2). Higher administered volumes may lead to increased pain during the injection. Therefore proper analgesics and/or sedation should be used in order to reduce discomfort due to the procedure.

INJECTION OF BoNT/A CLOSE TO NEUROMUSCULAR JUNCTIONS

There is evidence from animal models and clinical studies that distance to NMJ influences efficiency of BoNT/A treatment. Injections 5 mm apart from the NMJ resulted in a 50% decrease in paralysis in rabbit longissimus dorsi muscle (Shaari *et al.*, 1993). Thus, delivering BoNT/A in small volumes near the NMJ band of a muscle should produce the most effective paralysis (Shaari *et al.*, 1993). Sixty patients with idiopathic cervical dystonia were treated a total of 240 times with BoNT/A (preparation Dysport®) (Brans *et al.*, 1995). Selected muscles were injected under EMG guidance. The authors concluded that BoNT/A may be effective at lower dosages if injections are delivered closer to the NMJ (Brans *et al.*, 1995). In the human biceps brachii muscle, NMJ are known to be centered in the distal third (Gracies *et al.*, 2002). Injecting a small volume of BoNT/A close to the NMJ was more effective than injecting the same volume distantly to the NMJ. Nevertheless, injecting a larger volume distantly to the NMJ was similarly effective as the small volume close to the NMJ (Gracies *et al.*, 2002).

Summary

Electrophysiological techniques reliably localize NMJ, whereas ultrasound and palpation are unable to provide this kind of information. Unfortunately, the location of NMJ is not well defined for many target muscles in the treatment of spasticity and searching for the maximum muscle response during stimulation requires multiple needle placements. Distributing the total BoNT/A dose within the center of the muscle by multiple injections of small or large volumes (depending on the size of the target muscle) may be equally or even more effective, in particular in muscles with less well-defined NMJ distribution.

ADDITIONAL FACTORS WHICH MIGHT INFLUENCE THE FOCAL THERAPEUTIC RESPONSE OF BoNT/A

Secondary Muscle Pathology in Cerebral Palsy

A recent literature review summarizes the alterations of skeletal muscle tissue itself in spastic conditions (Lieber *et al.*, 2004). It was suggested that a spastic muscle is altered in a unique way which is inconsistent with simple transformation due to chronic stimulation or disuse. Secondary muscle pathology due to spasticity is an active field of research, but still published evidence on muscle alterations in CP is limited.

Using electrophysiological techniques, functional muscle parameters such as muscle strength, neuromuscular activation, firing rate, recruitment, short-term synchronization (Rose *et al.*, 2005), normalized Force-Frequency Relationship and fatigability of muscle contraction (Stackhouse *et al.*, 2005) can be assessed. In conclusion, muscle weakness in CP seems to have a strong central component (Rose *et al.*, 2005) and voluntary contractions for strength training may not produce sufficient forces to induce muscle hypertrophy (Stackhouse *et al.*, 2005). Nevertheless, strength training has shown to effectively improve motor function in children with CP (Damiano *et al.*, 1998).

Shortland and colleagues (2002) used ultrasound to look at the structural changes within the muscle by investigating muscle diameter, fascicle length and deep fascicular aponeurosis angle of the medial gastrocnemius in children with CP. They suggest that muscle contracture may be better explained in terms of shortness of the aponeuroses of pennate muscles, than through reduced muscle fiber diameter.

Electrical Stimulation After Injection

BoNT/A-induced paralysis of neuromuscular transmission involves at least 3 steps: an initial binding step, a translocation step, and a subsequent lytic step which ultimately produces blockade of transmission (Simpson, 1980). The lytic step was facilitated by nerve stimulation in animals (Simpson, 1980). In a clinical study, 5 hemiparetic patients received 2000 U BoNT/A (preparation Dysport®) injections into the soleus, tibialis posterior, and both heads of gastrocnemius muscles alone, whereas another 5 patients received BoNT treatment plus additional repetitive alternating electrical stimulation of tibialis anterior and plantar flexors for 30 min 6 times per day during the 3 days following the injection (Hesse *et al.*, 1995). After 4 weeks, the combined treatment proved to be more effective in terms of muscle tone reduction (Ashworth score), gait velocity, stride length, stance- and swing-symmetry (Hesse *et al.*, 1995).

In a second randomized, controlled clinical study looking at this issue, 6 children with dynamic equinus foot deformity received BoNT/A (preparation Botox®) injections in calf muscles followed by adjuvant electrical stimulation and another 6 children received injections only (Detrembleur *et al.*, 2002). The electrical stimulation procedure was carried out as described in the study of Hesse *et al.* (1995). Clinical assessment and instrumented gait analysis were performed before and 1, 3, and 6 months after treatment (Detrembleur *et al.*, 2002). The combined treatment was not superior to BoNT/A alone. For all patients, improvement of the clinical and gait variables occurred at 1 and 3 months after BoNT/A injection (Detrembleur *et al.*, 2002).

The results of the two clinical studies therefore are inconclusive concerning any potential impact of post-injection electrical stimulation of the target muscles. This may be due to the different patients and assessment parameters used [5 adults treated 8 month after their first stroke (Hesse *et al.*, 1995) versus 5 year old children with spastic CP (Detrembleur *et al.*, 2002)]. In the study carried out by Detrembleur *et al.* (2002), the intensive and specific physiotherapeutic treatment after injection may have lead to comparable beneficial results in both treatment groups.

Summary

Electrophysiological techniques and ultrasound provide additional and complementary information on the activity and the architectural structure of spastic muscles. Ultrasound may help to customize BoNT/A treatment in individual patients by looking at the individuals structural changes (see FIG. 3). Using ultrasound, atrophy and fibrosis in a spastic muscle can be specified which both might limit the response to the treatment with BoNT/A. Nevertheless, it is still impossible to attribute changes in ultrasound images of target muscles to either spasticity or inactivity/paresis. The combination with electrophysiology could add this additional information. The combination of ultrasound and electrophysiological characterization may help in the future to define, which muscles are most suitable for BoNT treatment.

Before electrical stimulation is introduced into pediatric standard of care, additional benefit, duration and intensity of the procedure would have to be well defined in further studies.

CONCLUSION

Although BoNT/A treatment of children with CP has become an integral feature of the multimodal treatment

of these patients, very limited published evidence is available on how different injection techniques translate into therapeutic success. In addition to the existing electrophysiological techniques, ultrasound offers a quick, painless, and easy to learn approach to gain relevant information about individual anatomy and morphology. Future research has to evaluate whether ultrasound and maybe electrophysiological techniques have the potency to enhance our knowledge on how to distribute BoNT/A.

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