



## Role of motor end plate-targeted Botulinum toxin type A injections in children with cerebral palsy

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**Botulinum toxin type A (BTX) injections are frequently used in children with cerebral palsy (CP) to control spasticity. Injection variables still lead to variable outcomes of this treatment. Using instrumented spasticity assessment and muscle volume assessment the most effective location of the injection was demonstrated for gracilis and psoas muscles in children with CP. It was found that this treatment is most effective when injected in the motor endplate zones of the selected muscles. This review article presents all available research on the role of motor endplate-targeting of BTX injections in children with CP.**

**Keywords:** Botulinum toxin ; cerebral palsy ; motor end plate.

### INTRODUCTION

Cerebral palsy (CP) is the most common cause of physical disability in children. It is defined as a disorder of the development of movement and posture that is attributed to a non-progressive disturbance of the developing brain (12). In many CP patients this brain lesion causes spasticity and this increased tone leads to contractures and bony malformations (8). An optimal use of spasticity reduction with Botulinum toxin type A (BTX) injections, started at a young age, can prevent these complications to some extent (11). While many clinical studies reported overall good results of this treatment, they also demonstrated considerable variation in outcome.

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This is partly due to injection variables (10). BTX blocks neurotransmission by inhibiting the release of acetylcholine at the motor end plate (MEP) (6). Animal studies already have shown that injecting the toxin near the MEP zone increases its paralytic effect (5,14). This was, so far, only confirmed in one human study on the biceps brachii muscle of adults with spastic hemiplegia after acquired brain lesion (Gracies et al, 2009) (9). Besides the lack of strong clinical evidence of the importance of MEP targeted injections in children with CP, the clinician was confronted with the very limited information on the localization of the MEP-zones in the lower limb muscles.

In order to improve the effectiveness of lower limb treatment with intramuscular BTX injections in children with CP, a research project was implemented to find the most effective injection location.

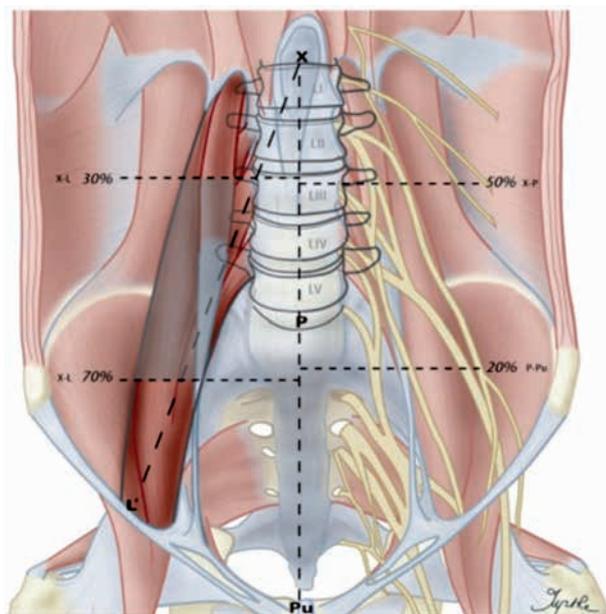
## REVIEW OF STUDIES

A thorough literature search -collecting all relevant histological and anatomical data- provided information on the exact localization of the MEP zone or the zone of terminal nerve ramifications of most of the frequently injected lower limb muscles. As no information was found on the innervation of the psoas muscle, a cadaver dissection study was performed on 24 adult psoas muscles (15). With stereoscopic microscopic dissection as far as the terminal nerve ramifications, the region of intramuscular nerve endings, corresponding with the MEP zone, was identified, as presented in figure 1. In a review article these MEP zones in relation to external anatomical landmarks for all the frequently injected lower limb muscles were presented as a guide for optimal injections (16). After comparing these with clinical practice, it became clear that for many muscles its location was somewhat different than the currently injected areas. For the medial hamstrings (semitendinosus, semimembranosus and gracilis muscle) as well as for the psoas muscle, there was enough evidence to conclude that current popular injection techniques were not injecting the toxin at a site close to the MEP zone. To explore the clinical importance of injecting these MEP zones in children with CP, 'current' versus 'MEP targeted' in-

jection were compared for both muscle groups through the application of innovative assessments.

To measure the effect of BTX, most intervention studies use clinical spasticity grading scales and/or more invasive assessments of spasticity reduction. These clinical spasticity scales, such as the Modified Ashworth Scale or Modified Tardieu Scale have been found to be not objective, sensitive or valid enough (1). The perceived resistance to the performed passive movement during these tests may be a result of reflex muscle activity, but also of non-neural mechanical properties such as changes in visco-elastic properties of joint structures and soft tissues. Clinical scales fail to decompose both components in order to measure spasticity (7). More objective and qualitative measures can be categorized as biomechanical and/or electrophysiological. Biomechanical methods measure the behavior of muscles by capturing joint position, angular velocity and torque during well-defined motions. In some studies isokinetic devices are used, but these are often bulky and difficult to apply in children. Neurophysiological methods measure the muscle's activity in reaction to specific motions, active or passive. Surface electromyography has been used to identify different spasticity patterns, but to be able to provide information about reactive-resistance a combination with some biomechanical approach is mandatory. So far, hardly any measurement that fully integrates multidimensional signals is clinically feasible and few have been assessed for reliability (4).

Therefore, a project was set up in the laboratory of clinical movement analysis of the University Hospital Leuven, in collaboration with the engineering department KULeuven. The goal was to create an instrumented clinical spasticity measurement and to determine a set of quantitative spasticity-sensitive parameters based on integrated biomechanical and electrophysiological signals. A portable, non-invasive tone assessment device was developed to measure three groups of signals during standardised passive isolated movements in different lower limb joints, which were (1) stretch characteristics (joint angle parameters), (2) reactive resistance and (3) muscle activity (electromyography, EMG). Details of the procedure (data collection and



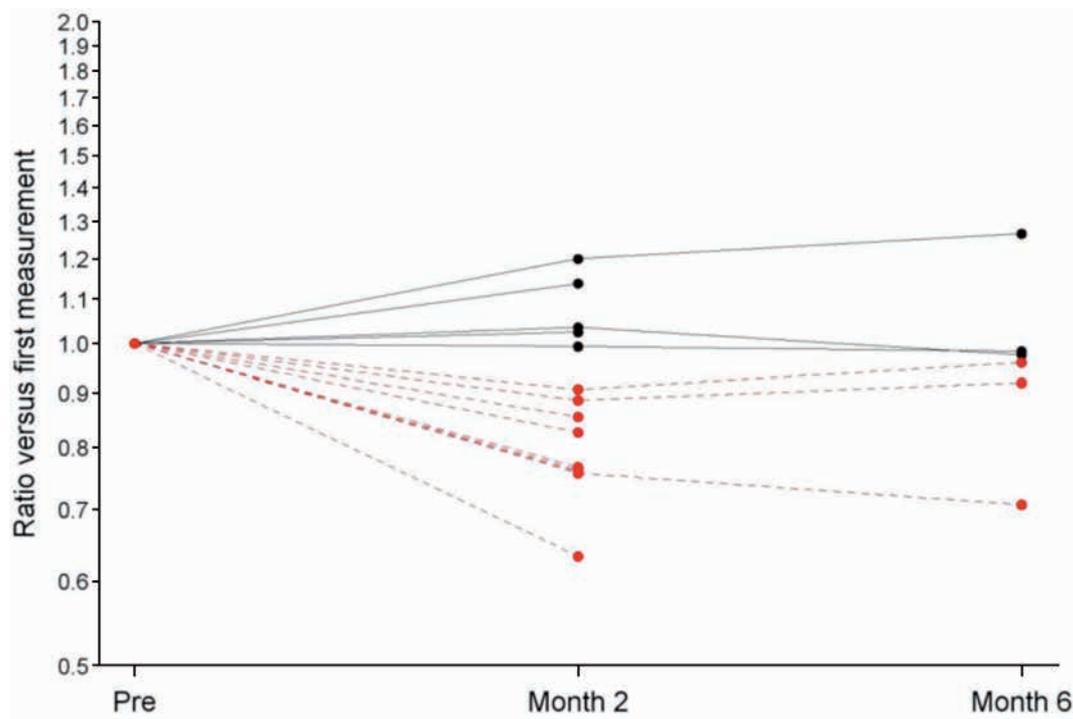
**Fig. 1.** — Innervation of the psoas muscle. On the right side : MEP zone in reference to Th12-L distance, on the left side : MEP zone in reference to Th12-P and P-Pu distance. X = thoracic vertebra 12 (Th12) ; P = promontorium ; Pu = pubis ; L = location where psoas muscle passes under inguinal ligament.

data analysis), validity and repeatability of this instrumented spasticity assessment have been published (2).

This instrumented spasticity assessment was used to evaluate the effect of BTX injections in the medial hamstrings. Biomechanical (position and torque) and electrophysiological signals were measured when applying passive stretches to the medial hamstrings at different velocities. The biomechanical and electrophysiological parameters proved to be adequately sensitive to assess the response to treatment with BTX (3). Further, it was demonstrated that the instrumented spasticity assessment showed higher responsiveness than the clinical scales (18). A prospective randomized trial was set up, including 34 gracilis muscles which were injected with BTX in 27 children with CP ( $8.5 \pm 2.5$  y). Seventeen muscles were treated by a popular proximal injection (at 25% of the length of the upper leg)

and 17 muscles by MEP targeted injections (half the dosage at 30% and half at 60% of the upper leg). Clinical and instrumented spasticity assessments were performed before and after the injections. The MEP targeted injections showed a significantly better decline in pathological EMG signal compared to the conventional proximal injections, demonstrated by a higher reduction of a normalized EMG parameter. This difference could not be demonstrated using the clinical scales. It was concluded that BTX injection in the gracilis muscle at the sites with a high concentration of MEPs resulted in improved spasticity reduction in children with CP. Further, we demonstrated that different injection protocols could be compared sensitively and objectively using the instrumented spasticity assessment that integrates biomechanical and electrophysiological measures.

An objective evaluation of the spasticity of the psoas muscle remained a challenge. For the instrumented spasticity assessment, a surface EMG is needed and this is not possible for the psoas muscle. Using fine wire EMG for this muscle is not an option in children and due to its direct retroperitoneal position even dangerous in adults. Therefore, an alternative tool to measure the effect of different injection protocols was selected for the psoas muscle. As BTX selectively blocks neurotransmission, it will cause a temporary chemical denervation and muscle atrophy (13). Measurement of the muscle volume will therefore give us an insight on the effectiveness of the injection protocol. As the psoas muscle is a multipennate muscle and we want to compare injections at different locations, we need a 3D reconstruction of the complete muscle volume to be able to compare the different injection protocols. Therefore, to evaluate injection techniques for the psoas muscle, a quantitative evaluation using muscle volume assessment by digital magnetic resonance imagination (MRI) segmentation was done (17). MRI sensitively identifies the changes in muscle volume as was confirmed by a good intraclass correlation (0.988) and within-subject coefficient of variation of 3.506%. In seven spastic diplegic children, the MEP targeting versus a widely used more distal injection technique were compared. Five patients received two different injection



*Fig. 2.* — Ratio of the post-injection volume of the psoas muscle in relation to the pre-injection volume at 2 months and 6 months after injection. Dashed lines : MEP oriented injection technique ; solid lines : distal injection technique.

techniques randomly applied to both psoas muscles and in two patients a bilateral MEP targeting technique was used. MRI images of the psoas were taken before, two months and – in three patients – six months after the injections. The injection volumes two months after the injection (in relation to pre-injection volume) is presented in figure 2 with an average injection volume for the nine MEP targeted muscles of 79,5% versus 107,8% for the five distal injected psoas muscles. This difference was statistically significant. In all five asymmetric injected patients, the MEP targeted psoas had an average of 27% (range 9-37%) larger volume reduction than the more distal injected psoas muscle. This atrophy remained even six months after the treatment. This demonstrates that injections in the MEP zone of the muscle, which is the more proximal part of the psoas muscle, caused muscle atrophy – as a demonstration of the effect of the toxin –, in contrary to more distal injections where this atrophy was not observed.

## DISCUSSION

Both newly developed assessment tools – the instrumented spasticity assessment and the digital MRI segmentation muscle volume assessment – proved to be reliable and valid to compare different BTX injection protocols. The results from the gracilis and psoas study have shown that BTX injections at the sites with high MEP concentrations, have an improved efficacy compared to injections more distant from these MEPs. It is therefore reasonable to state that all BTX injections preferably should be given close to the MEP zone(s) of the injected skeletal muscles. Future studies comparing different dosage and dilution protocols injected at these MEP zones, documented by the sensitive instrumented spasticity assessment and muscle volume measurement, can further improve the treatment efficacy. This can eventually lead to the use of lower dosages thus decreasing economic costs and the risk of side effects of BTX injections.

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