Clinical applications of botulinum neurotoxin in the treatment of spasticity

Petr Kaňovský
Department of Neurology
Palacky University Medical School
University Hospital
Olomouc, Czech Republic

Spasticity has firstly been characterised by William John Little (1810 - 1894) in the description of cerebral palsy:

"Pathology has gradually taught that the fetus in utero is the subject to similar diseases to those which affect the economy at later periods of existence. This is especially true if we turn to the study of the special class of abnormal conditions, which are called deformities..."

On the influence of abnormal parturition, difficult labours, premature birth and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities by WJ Little, MD, Senior Physician to the London Hospital, founder of the Royal Orthopaedic Hospital, Visiting Physician to Asylum for Idiots, Earlswood

Transactions of the Obstetrical Society of London 1861, 3: 293

Spasticity is defined as an increase in the muscle tone, which depends on the increase of the tonic stretch reflex and on the velocity of the passive movement. The hyperexcitability of the stretch reflex has been supposed as its origin (Lance 1980, Brown 1994, Sheean 2004)

Spastic muscle contraction is, in fact, a kind of pathological tonic muscle response appearing as the consequence of phasic increase of muscle tone

The muscle response on the phasic increase of its tone can be tested in two ways:

1) Passive movement in different velocities
2) Tapping on the muscle tendon (reflex examination)

Stretch reflex is managed by the very fast Ia afferent fibres originating in the muscle spindles. Stretch reflex depends on the velocity of passive movement and on the length of the muscle

The increased response of stretch reflex is caused by the central hyperexcitability, which is one of the basic characteristics of the "spastic movement disorder"

Current model of the evolution of spastic hypertonus and spastic muscle contraction:

The reduction of inhibitory inputs from the cortex and basal ganglia leads to the disordered modulation of monosynaptic afferentation via primary Ia afferent fibres and polysynaptic afferentation from the exteroceptors. This disorder of modulation causes the hyperexcitability of spinal alpha motor neurons.

Spinal interneurons are the "key player" in this "modulatory" phase, because of their ability of pre-synaptic and reciprocal inhibition (via Ia fibers).

 Ventromedial pontine reticular formation has an additive inhibitory input to the spinal interneurons. Vestibular nuclei (via vestibulospinal tracts) have, on the contrary, an additive inhibitory input to the spinal interneurons.


Spasticity treatment options and methods:

I. Non-surgical
   A. Non-pharmacological
   B. Pharmacological

II. Surgical

III. Chemodenervation with botulinum toxin A
Evidence-based data

Methods of assessment of patient suffering from spasticity:

Clinical:
- Clinical examination
- Particular tests for presence of spastic signs

Goniometry

Scales:
- Disability Assessment Scale (DAS)
- Medical Research Council (MRC) scale on affected upper limb
- Modified Ashworth scale

Neurophysiological:
- EMG pattern
- Polymography
- Motor evoked potentials

Disability Assessment Scale (DAS)

Hygiene: maceration, ulceration, and/or palmar infection, pain and hand cleanliness, ease of cleanliness, ease of nail trimming, and the degree of interference caused by hygiene-related disability in the patient’s daily life.

Dressing: difficulty of easewhich patient can put on clothing (e.g., Shirts, jackets, gloves) and the degree of interference caused by dressing-related disability in the patient’s daily life.

Limb position: abnormal position of the upper limb.

Pain: intensity of pain or discomfort related to upper limb spasticity.

0 – no disability
1 – mild disability (noticeable but does not interfere significantly with normal activities)
2 – moderate disability (normal activities require increased effort and/or assistance)
3 – severe disability (normal activities limited)

Clinical examination

Clinical examination should be done in the specialist centre.
During clinical examination, the specialist should assess the neurological status of patient, and should remark the signs of upper motor neuron syndrome. Apart from that, the functional ability of patient and the possible treatment outcomes and benefits should be also assessed.

It is important to achieve the co-operation of patient, and to properly show the patient the possible treatment goal (i.e. using midazolam i.v. test).

Particular tests for presence of spastic signs

Increased muscle tone
- Typical (usually last): response to passive muscle stretch
- Brisk and increased tendon reflexes
- Any of abnormal spastic skin responses (Babinski, Roch, Gordon, Chaddock, Oppenheim)
- Clonus

Medical Research Council (MRC) scale on affected upper limb

Elbow - Wrist - Thumb – Fingers (second to fifth finger)

<table>
<thead>
<tr>
<th>Flexors</th>
<th>Extensors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No contraction</td>
<td>0</td>
</tr>
<tr>
<td>Flicker or trace of contraction</td>
<td>1</td>
</tr>
<tr>
<td>Active movement, with gravity eliminated</td>
<td>2</td>
</tr>
<tr>
<td>Active movement against gravity</td>
<td>3</td>
</tr>
<tr>
<td>Active movement against gravity and resistance</td>
<td>4</td>
</tr>
<tr>
<td>Normal power</td>
<td>5</td>
</tr>
</tbody>
</table>
Modified Ashworth Scale
(Bohannon and Smith 1986)

0= no increase in tone
1= slight increase in tone giving a “catch” when the limb was moved in flexion or extension
1+=slight increase in tone giving a “catch” when the limb was moved in flexion or extension (less than one half of ROM)
2= more marked increase in tone, but limb was easily flexed
3= considerable increase in tone – passive movements difficult
4= limb rigid in flexion or extension

Assessment of adductor tone
(Snow 1990)

0= no increase in tone
1= increase in tone, abduction of hips is possible to 45° with one person
2= abduction of hips is possible to 45° with one person and medium effort
3= abduction of hips is possible to 45° with one person and strong effort
4= two persons are needed for hip abduction to 45°

Spasm frequency scale
(Snow 1990)

How many spasm were present in the region of affected muscle or limb in the last 24 hours?

Spasm frequency
0= no spasm present
1= ≤ 1 spasm
2= 1-5 spasms
3= 5-9 spasms
4= ≥10 spasms

EMG pattern

Polymyography

Motor evoked potentials
Practical Issues

27-30G needles, 1-3 cm length
1-2 ml syringes 0.1 ml scale
EMG hollow needles in indicated cases

Preparation of BTX solution
2-4 ml normal saline/vial of XEOMIN®
resulting in 50/25 U/ml in XEOMIN®

Target muscles of the upper limb

Upper arm girdle
Flexed elbow pattern
Flexed wrist and fingers

Biceps, brachioradialis, brachialis
FCR, FCU (FDS, FDP)
FDS, FDP plus
FPL, AP, 1st DI plus

Common Muscle Patterns and Targets in the Upper Extremity

Flexed elbow: biceps, brachioradialis, brachialis
Flexed wrist: FCR, FCU (FDS, FDP)
Clenched fist: FDS, FDP plus
Thumb-in-palm: FPL, AP, 1st DI plus

Practical Issues

BTX-A should be injected directly into the muscle belly
Muscle belly should be localized by palpation
In indicated cases (upper limb, forearm) it should be localized by EMG using recording and direct muscle stimulation
No need to target injections into the motor points
Usually one point per one muscle belly
Very slow (1ml/30s) injection to prevent muscle fibres rupture and pain
Short pressure on the injection point is useful
Practical Issues
ON/A/INOC/ABO - BTX doses for muscles of upper limb (U):

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>m. deltoideus</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. pectoralis major</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. pectoralis minor</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. biceps brachii, long head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. biceps brachii, short head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. triceps brachii</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. brachioradialis</td>
<td>100/400/400</td>
</tr>
<tr>
<td>m. flexor carpi radialis</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. flexor carpi ulnaris</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. extensor dig. communis</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. flexor dig. superficialis</td>
<td>80/80/300</td>
</tr>
<tr>
<td>m. flexor dig. profundus</td>
<td>80/80/300</td>
</tr>
</tbody>
</table>

Possible Combinations Causing Equinovarus…..

| G-S, TA                      | G-S, FHL, EHL |
| G-S, TP                      | G-S, FHL, TA, TP |
| G-S, TA, TP                  | G-S, FHL, TA, TP, EHL |
| G-S, TA, TP, EHL             | G-S, FHL, FDL, TA |
| G-S, TP, EHL                 | G-S, FHL, FDL, TP |
| G-S, EHL                     | G-S, FHL, FDL, TA, TP |
| G-S, FHL, TA                 | G-S, FHL, FDL, TA, EHL |
| G-S, FHL, TP                 | G-S, FHL, FDL, TA, TP, EHL |

Practical Issues
ON/A/INOC/ABO - BTX doses for muscles of lower limb (U):

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>m. gastrocnemius, medial head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. gastrocnemius, lateral head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. soleus</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. tibialis posterior</td>
<td>150/150/600</td>
</tr>
<tr>
<td>m. tibialis anterior</td>
<td>150/150/600</td>
</tr>
<tr>
<td>m. flexor hallucis longus</td>
<td>50/50/200</td>
</tr>
<tr>
<td>m. biceps femoris, long head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. biceps femoris, short head</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. semitendinosus</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. semimembranosus</td>
<td>100/100/400</td>
</tr>
<tr>
<td>m. adductor femoris (group)</td>
<td>200/200/800</td>
</tr>
<tr>
<td>m. psoas</td>
<td>100/100/400</td>
</tr>
</tbody>
</table>
Conclusions

Botulinum toxin is a safe and effective treatment of spasticity caused by different disorders of the brain structures.

It causes substantial reduction of spastic muscle tone, and in younger cases it also allows the normal growth of treated muscles.

It even can prime the changes of the activation of motor structures, which are involved in the control of movement and muscle tone.

Intensive physiotherapy is needed for the whole time of BTX-A induced effect to achieve the best results in improving motor function.

Brain cortex plasticity in the spastic movement disorder

Brain hemisphere affected by the stroke or MS lesion can improve the motricity of hemiparetic limb and reduce spasticity; both by the mechanism of cortical plasticity.

The botulinum toxin A treatment can relieve focal spasticity (due to stroke or MS) not only by the local effect, but predominantly due to dynamic changes at several levels of central nervous system, including the brain cortex.

The processes primed by the cortical plasticity and changes due to the BoNT-A treatment should be reflected in the patterns of cortical activation during the motor or mental tasks examined by the functional MRI.

Treatment-induced change of cortical activation: fMRI evidence of the central effect of botulinum toxin A in post-stroke spasticity

Brain cortex plasticity in the spastic movement disorder

Patients (3 groups)

9 patients (6 males/3 females) suffering from the distal upper limb spasticity due to stroke, without the direct involvement of the eloquent cortex

14 patients (9 males/5 females) suffering from the upper limb spasticity due to stroke

14 patients (8 males/6 females) suffering from the upper limb spasticity due to stroke, 7 with paretic upper limb, 7 with plegic upper limb

Functional MRI was done in three paradigms:

1) active movement of the fingers of the paretic hand in the Roland’s paradigm (9 stroke patients)
2) active and resting phase, in the active phase patients performed knee flexion and extension; 34 flexions per minute in average (4 MS patients)
3) mental movement simulation, i.e. imagination of the sequential movement in the Roland’s paradigm by the paretic hand (14 stroke patients); block paradigm, 15 s mental movement simulation in turns with 15 sec resting state

Brain cortex plasticity in the spastic movement disorder

fMRI examination has been done 1 week prior to and 4 and 12 weeks following to injection of BoNT-A injections into the spastic muscles detected by the palpation, EMG and electrical stimulation; the injection has always been done with the EMG guidance.

Spasticity itself has been scored using the Modified Ashworth Scale (MAS) and Rankin scale.

fMRI processing and analysis:

1. Side swapping of MRI data of right-lesioned brains
2. MRI data registration into common anatomical space (MNI template)
3. Two-stage statistical analysis using general linear model (FSL software), treatment effect was tested using linear contrasts

Study 1

9 patients (6 males/3 females) suffering from the distal upper limb spasticity due to stroke, without the direct involvement of the eloquent cortex, who performed the sequential finger movement of the paretic hand in the Roland’s paradigm
Study 2

14 patients (9 males/5 females) suffering from the upper limb spasticity due to stroke and performing the mental simulation of the movement with the paretic hand interchanged with the resting state.

Fig. 4
Activation of extensive network of motor areas by the paretic hand movement (green markers’ crossing = ipsilateral M1).

Fig. 5

In the group data, the pre->post-BoNT contrast showed a significant decrease of activation of posterior cingulum / precuneus regions following the BoNT-A treatment.

Study 3

14 patients, suffering from spasticity of upper limb due to stroke:
7 patients with paretic upper limb, performing the sequential finger movements in the Roland’s paradigm
7 patients with plegic upper limb, performing mental movement simulation (MMS) of sequential finger movements in the Roland’s paradigm.
Functional MRI activation during imagery of finger movement in group A (plegic): before BoNT treatment (a), 4 (b) and 11 weeks after BoNT application (c). The Z-statistical images were thresholded using a corrected cluster significance threshold of P<0.05 and overlaid on top of averaged high resolution T1-weighted images.

Functional MRI activation during sequential finger movement in group B (paretic): before BoNT treatment (a), 4 (b) and 11 weeks after BoNT application (c). The Z-statistical images were thresholded using a corrected cluster significance threshold of P<0.05 and overlaid on top of averaged high resolution T1-weighted images.

The reduction of spasticity (either following stroke or due to multiple sclerosis) by the botulinum toxin A treatment is - to the important extent - caused by the change of central modulation of sensorimotor structures. Undoubtedly, there is an important involvement of the structures outside the classical motor system. The areas posterior cingulum/precuneus, frontopolar cortex, DLPFC and mesial occipital cortex were linked with the functions as global attention, complex motor learning, motor memory or visual cognition rather than active movement control. In the condition of existing spasticity following stroke these structures – thanks to the brain cortex plasticity – used for the controlling of the volitional movement.

Senkarova Z et al. J Neuroimaging 2010
Tomasova et al. J Neuroimaging 2011
Veverka et al. J Neurol Sci 2012
Veverka et al. J Neurol Sci 2014

©http://fmri.upol.cz

Department of Neurology, Palacky University Medical School, Olomouc

fMRI laboratory team:
Petr Hlustik, Pavel Hok, Tomas Veverka, Robert Opavsky, Zuzana Senkarova-Tomasova, Jana Klosova

EMG & BoNT-A team:
Pavel Otuba, Martin Nevrlík, Katerina Mensikova, Miro Vastík, Igor Nestrasil