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MOHAMMED V UNIVERSITY OF RABAT
FACULTY OF MEDECINE
AND PHARMACY
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BOTULINUM TOXIN TYPE (A) IN THE MANAGEMENT OF SPASTIC CEREBRAL PALSY

THESIS

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BY

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Abbreviations

Abreviations

Ach : Acetylcholine

AEs : Adverse effects

AROM : Active range of motion

BTXA : Botulinum toxin type A

BTXB : Botulinum toxin type B

CHQ : Child health quality

CHQe : Child Health Questionnaire

CP : Cerebral palsy

CT : Computed tomography

ED : Emergency department

EDL : Extensor digitorum longus

EHL : Extensor hallucis longus

EMG : Electromyography

ES : Electrical stimulation

ESWT : Extracorporeal shock wave therapy

F : Fibula

FA : Femoral artery

FDS : Flexor digitorum superficialis

FES : Functional electrical stimulation

FH : Head of femoral bone

FL : Fibularis longus

FTAT : Frontalis test

GMFCS : Gross motor function classification system

ITB : Intrathecal baclofen

MACS : Manual ability classification system

MD : Medical doctor

MEP : Motor endplate

MG : Medial gastrocnemius

MUAP : Motor unit action potentials

NMJs : Neuromuscular junctions

OS : Orthopedic surgery

OT : Orthoses

PIP : Proximal interphalangeal

PMR : Physical medecine and rehabilitation

PROM : Passive range of motion

PT : Physical therapy

QOL : Quality of life

RCT : Randomized controlled study

r ESWT : Radial extracorporeal shock wave therapy

ROM : Range of motion

SDR : Selective dorsal rhizotomy

SNAP25 : Synaptosomal- associated protein of 25kDa

SNARE : Soluble N-ethylmaleimide-sensitive fusion protein receptor

TD : Typically developing

UMNS : Upper motor neuron syndrome

URTI : Upper respiratory tract infection

US : Ultrasound

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Summary

Introduction

Cerebral palsy (CP) is the most common cause of physical disability in childhood, it represents a major health problem. In developed countries, the incidence of CP is about 2 to 2.5 per 1000 live births. (1) For developing countries no population-based birth prevalence data are available but rates are assumed to be higher. According to the most recent definition, CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication and behavior, by epilepsy and by secondary musculoskeletal problems. (2) These components contribute in producing a clinical picture of CP unique to each child. CP is classified according to the type of motor movement disorder and topographical involvement in question and the most common movement disorder. One of the most disabling aspects of CP is the development of spastic hypertonia, the incidence of spastic CP varies between 76-89 % in children who suffer from CP. (3) Neuromuscular deficits found in cases of CP include: loss of selective motor control, abnormal muscle tone leading to an imbalance between agonist and antagonist muscles, impaired coordination, sensory deficits and weakness. The ability to maintain posture and balance is automatic in healthy subjects; it is often a challenging goal for children with cerebral palsy. (4)

The increased muscle tone in CP not only produces dynamic deformities with a risk of subsequent fixation, but also leads to relative failure of longitudinal muscle growth. In the long term, this may result in increased disability. An example of this is the equinus foot position secondary to spasticity in young children. Eighty per cent of these children have problems with walking as a result of lower limb spasticity, which can lead to severe contractures and

limb deformities. (5) Calf muscle spasticity is one major factor that can interfere with normal walking by preventing heel strike.

A common goal of the treatment of children with CP is to increase the functional capacity, sustain health and improve quality of life of children and their caregivers. The management of spasticity involves a multidisciplinary approach that includes oral medications, Botulinum toxin type A (BTXA) injections, orthoses, surgical treatment and other physical treatments such as physiotherapy (PT),electrical stimulation (ES), extracorporeal shock wave therapy (ESWT) and others.

BTXA is produced by the anaerobic spore-forming bacterium Clostridium botulinum and is one of the eight immunologically distinct serotypes. It acts by blocking the release of the neurotransmitter Acetylcholine at cholinergic nerve endings. A selective and temporary chemical denervation ensues, causing muscle paralysis that is reversible in time. (6)

BTXA was used for the first time by Dr Alan Scott, an American ophtalmologist, to treat adult patients with strabismus. (7) It has been rapidly adopted into the pediatric armament available for the treatment of focal spasticity or dystonia of different etiology. As the neuromuscular junctions (NMJs) in the muscles are the sites of BTXA action, targeting the correct muscle and the vicinity of NMJs are interrelated with doses, dilutions, number of injection sites and the accuracy of the localization technique. Performance of BTXA injections may be facile, requiring only surface marking or clinical-localization techniques but may be more technically demanding, necessitating the use of equipment, such as electromyography (EMG) or ultrasonography (US). Less often, endoscopic, fluoroscopic or computed tomography (CT) guidance may be required.

The aim of this thesis is to present a review of the literature about the effectiveness of botulinum toxin injections in the management of spasticity in children with cerebral palsy, and study the recent literature publications concerning the optimal doses, number of injection sites and the accuracy of the injection techniques described in the literature.

We gathered the available informations and assembled a sonographic guide for BTXA injections as well as a simplified surveillance handbook, that should be used by practitioners to enhance the quality of the injections and to provide a source of data that can be used in further studies.

First chapter: Cerebral palsy

1. Definition

The concept “cerebral palsy” (CP) stems from “cerebral paralysis” or “cerebral paresis” and refers to a neurodevelopmental condition beginning in infancy or early childhood and persisting through the lifespan.

Over the years many definitions have been proposed for CP. Probably the most frequently cited definition is that by Bax (8), stating that CP is “a disorder of movement and posture due to a defect or lesion of the immature brain. For practical purposes it is usual to exclude from cerebral palsy those disorders of posture and movement which are of short duration, due to progressive disease, or due solely to mental deficiency.” Mutch and associates (9) modified the definition as follows: “an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development.” Both definitions focused on the motor impairment which is the hallmark for this condition.

In 2006, a new definition was proposed by The International Workshop on Definition and Classification of Cerebral Palsy: “Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour; by epilepsy; and by secondary musculoskeletal problems.” The committee sought to promote the idea that “a comprehensive approach to CP needs to be multidimensional and that management of patients with CP almost always requires a multidisciplinary setting.” (2)

2. Prevalence and etiology of cerebral palsy

The overall prevalence of CP has remained around 2-2.5 per 1000 live births in the developed countries. For developing countries, no population-based birth prevalence data are available but rates are assumed to be higher. Even though most children with CP are born at term, the risk of the disorder among very preterm births (defined as births before 32 completed weeks of gestation) may be up to 100 times that associated with term births. (1).

CP is a condition with multiple etiologies and it is often impossible to determine any single causative factor in an individual patient. Prenatal factors may include genetic and chromosomal disorders, congenital infections, cerebral or neural tube malformations/maldevelopments, and periventricular leukomalacia; perinatal factors include brain edema, neonatal shock, intracerebral hemorrhage, sepsis or central nervous system infection, metabolic maladjustment, and hypoxic-ischemic encephalopathy; postnatal factors include central nervous system infection, sepsis, vascular inflammation, infarctation or hemorrhage, and accidental or non-accidental brain injury (10-11).

3. Classification of CP

CP is not an etiologic diagnosis but a clinical one based on the symptoms. The phenotype and severity of motor involvement depend on the location and extent of the central nervous system lesion: spasticity is associated with damage to the corticospinal tracts, usually white matter or focal cortical/subcortical damage (see chapter pathophysiology), and dystonia with damage to basal ganglia and the thalamus (12-13). The accompanying impairments (e.g. epilepsy, communication deficits and mental retardation) tend to be more

pronounced in the most severely affected individuals and they are associated with the extent of white and gray matter lesion and tend to accumulate in the most severely affected individuals (3).

The Surveillance of Cerebral Palsy in Europe (14) adopted and refined a classification by retaining the three types of movement abnormalities but adding one class, “unclassifiable”, for cases not predominantly spastic, ataxic or dyskinetic. The typology classes “unilateral” and “bilateral” were also adopted, abandoning the term “diplegia”. In addition, some authors identify a hypotonic (referring to abnormally low muscle tone and to be distinguished from weakness) and mixed (features of more than one type, usually spastic and dyskinetic) CP group.

4. Spasticity in CP

4.1. Definition

A definition of spasticity was proposed by Lance (15) and it has been widely accepted: *“Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neurone syndrome.”* For the clinician, the difficulty stands in characterizing and quantifying spasticity more than recognizing it. In spasticity the muscle tone (i.e. the resistance felt when a limb is passively rotated about a joint with the subject at rest) is increased (hypertonic) and the resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement (16). Additionally, the resistance to externally imposed movement may rise rapidly above a threshold speed or joint angle felt as “a catch”, which may represent the

threshold for onset of the stretch reflex (16). Spasticity often coexists with other motor symptoms such as dystonia or athetosis.

Spasticity is but one of the many different features of the upper motor neurone syndrome (UMNS). Reducing spasticity will not automatically improve function and addressing the possibly more disabling negative UMNS features needs attention. They may, however, be more difficult to manage than spasticity (17).

It is important to know that spasticity vary depending on a child´s activity, posture and state of alertness (e.g. it may increase with anxiety, emotional stress, pain, surface contact or other sensory input) and is independent from any particular task addressed (16)

4.2. Pathophysiology

Spasticity and other (both positive and negative) features of the UMNS are caused by disruption of the descending corticospinal pathways (pyramidal and adjacent tracts) involved in motor control (18). The pyramidal fibers arise from both pre-central (primary motor cortex and pre-motor cortex) and post-central (primary somatosensory cortex and parietal cortex) cortical areas, the latter contributing by modulating sensory function with motor function (18). The impulse to an intended movement (supplementary motor area) is relayed to the premotor cortex (involved in the preparation for movement) and thence to the primary motor cortex, where an order is given to initiate the appropriate muscular contraction to achieve the desired goal (19). The basal ganglia, cerebellum and brainstem motor nuclei contribute to motor programming and the command is delivered via the corticospinal tracts to the spinal cord, lower motor neurone, peripheral nerve and, finally, the muscle (19).

From the brainstem two balanced systems arise which control the spinal reflexes: one inhibitory (the dorsal reticulospinal tract) and the other excitatory (the medial reticulospinal and lateral vestibulospinal tracts) (18). A lesion to these tracts above the nuclei (i.e. a lesion at cortex, internal capsule or periventricular white matter) produces spasticity. Injury at lower brainstem or spinal level to the reticulospinal and vestibulospinal tracts (i.e. below the reticular and vestibular nuclei) causes intense spinal spasticity, with a tendency to flexor spasms and a flexed posture. Isolated damage to the corticospinal tract produces loss of fine motor control in distal limb muscles, without spasticity. However, an isolated lesion to the corticospinal tract is rare; usually other adjacent motor tracts are injured as well (18, 19).

The spinal reflexes contributing to motor control may be divided into proprioceptive (detecting phasic and tonic muscle stretch, joint-movement position, change in the body´s mass center) and cutaneous/nociceptive (Babinski sign, flexor and extensor reflexes, detecting noxious stimulus, pressure) reflexes and, together with the spinal interneurons, form a complex network mediating diverse afferent input to the spinal cord (18). The monosynaptic reflex arc, the stretch reflex, maintains muscles at a given length. Stretch is detected by muscle spindles within the skeletal muscle and an excitatory impulse is given via the afferent posterior nerve root to the motor neurone to contract the muscle back to the appropriate length. Likewise, muscle spindle and tendon afferents connect polysynaptically with motor neurones which innervate agonist and antagonist muscles: reciprocal inhibition occurs when the afferents inhibit the neurones activating an antagonist muscle, and reciprocal excitation occurs when the afferents bring about a contraction in the agonist muscle. These stretch reflexes

are under the inhibitory influence of the upper motor neurones and muscle tone is maintained as a balance between the excitatory stretch reflex and descending inhibitory supraspinal control (i.e. presynaptic inhibition). As the inhibitory control of the upper motor neurone fails, the spinal reflexes become hyperexcitable and the positive features of the UMNS are manifested (18,20).

Irrespective of whether the basic alteration in spinal reflex transmission responsible for the increased stretch reflex is increased gain or decreased threshold, the common finding has been that spasticity is due to hyperactive tonic stretch reflexes which are velocity-sensitive. The monosynaptic Ia hyperexcitation is the major contributor in the development of spasticity, but many other spinal reflex pathways may increase or reduce the effect of this monosynaptic excitation: excitation/inhibition from muscle spindle group II afferents, inhibition from Golgi tendon organs via Ib afferents, recurrent inhibition via motor axon collaterals and Renshaw cells, presynaptic inhibition of Ia afferent terminals and reciprocal inhibition from muscle spindle Ia afferents of the antagonist muscles (20) . Thus, spasticity is probably not caused by a single mechanism, but rather by a chain of alterations in different interdependent spinal networks (21). What kind of role each component plays remains uncertain.

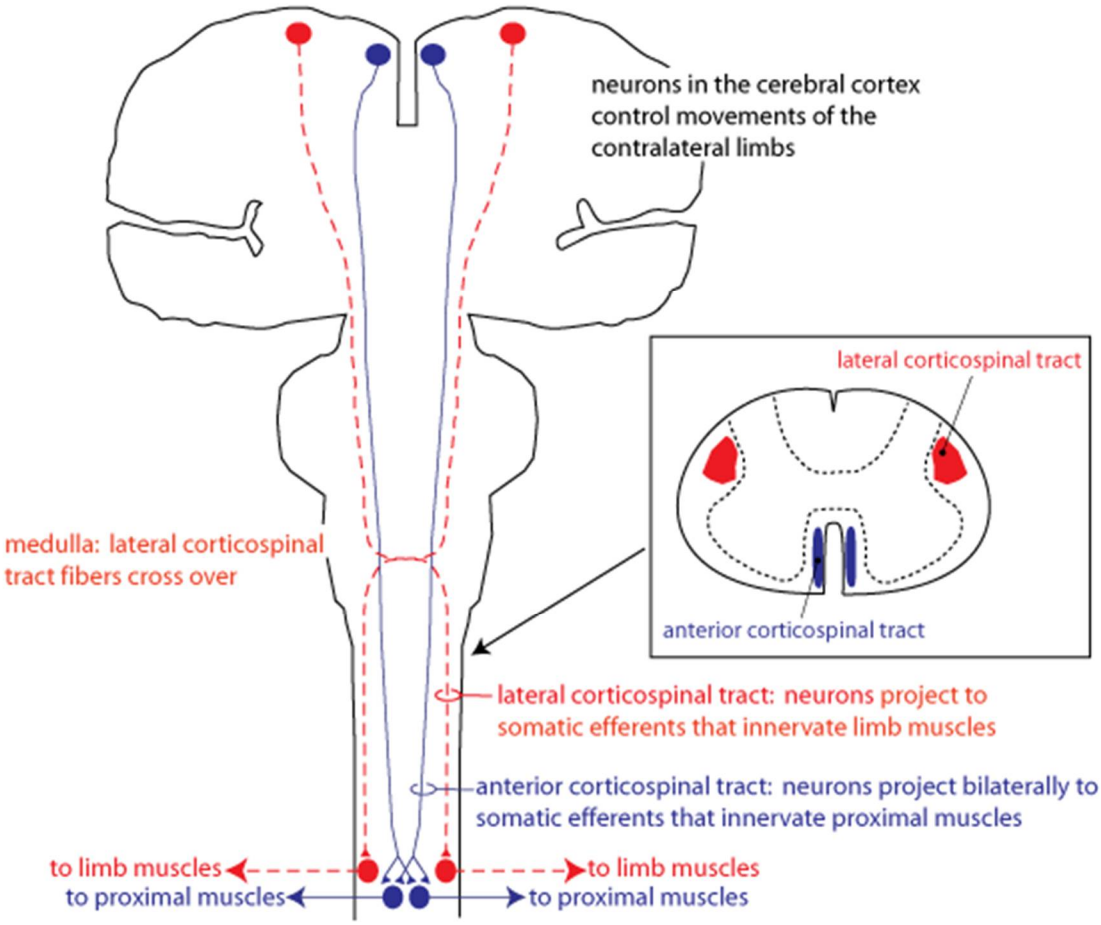

Figure 1 : scheme of motor pathways (21)

4.3. Spastic muscle in CP

While skeletal muscle tissue adapts to altered neural and mechanical input, spastic muscles prefer to remain in shortened state (contracture) and need stretching. At first, they can be stretched more easily as the contracture is dynamic, but eventually, as the muscle tissue transformation continues, they become stiffer (less compliant) and a fixed contracture ensues (22). This is felt as an increased resistance to stretch without reaching the reflex velocity threshold (no catch) and as a reduced range of movement of the joint.

The biarticular muscles are more commonly affected in spastic cerebral palsy patients e.g. rectus femoris, hamstrings and gastrocnemius. Due to the biarticular involvement, they can result in very complex gait abnormalities.

Typical upper limb posturing includes adduction and internal rotation at the shoulder, pronation and flexion at the elbow/forearm, and flexion and ulnar deviation at the wrist with flexed digits and “thumb in palm.”(fig.2)

Typical lower limb posturing is true equinus which is the basis for all clinical patterns. The muscles involved are the gastrocsoleus; sometimes the tibialis posterior if the posturing is equinovarus; the hamstrings; the hip adductors and hip flexors; and occasionally the rectus femoris when there is a stiff knee gait. (fig.3)

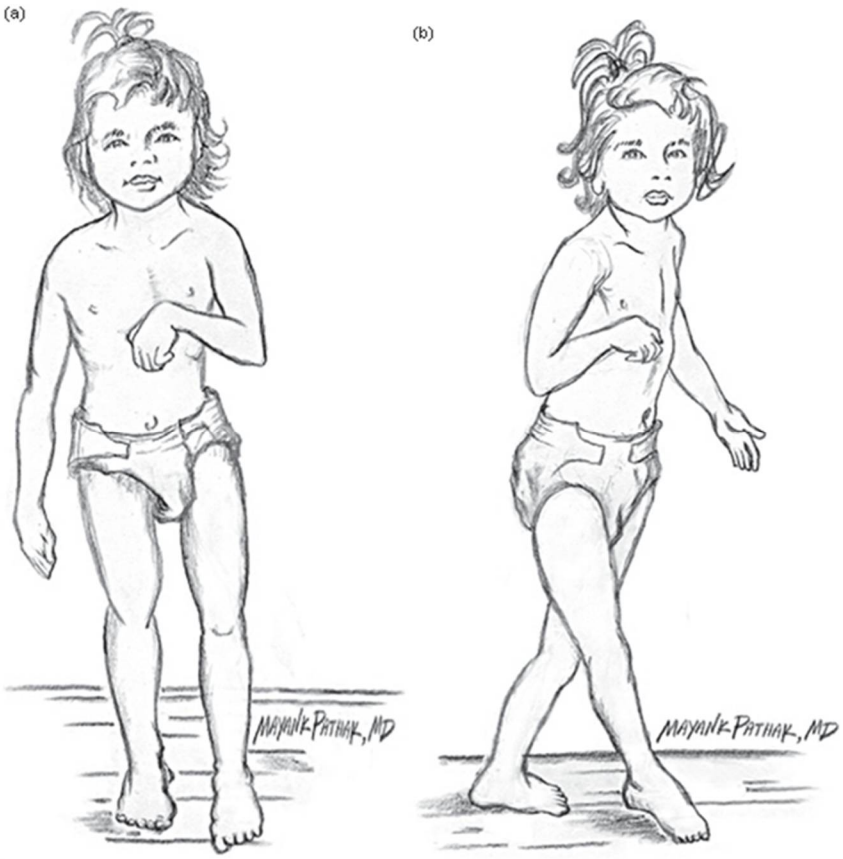

Figure 2 : Spastic hemiplegia, frontal (a) and lateral (b) views. Muscles that are involved in spastic hemiplegia are biceps, brachialis, adductor pollicis, flexor carpi ulnaris, flexor carpi radialis, pronator teres, gastrocnemius, soleus, tibialis posterior.

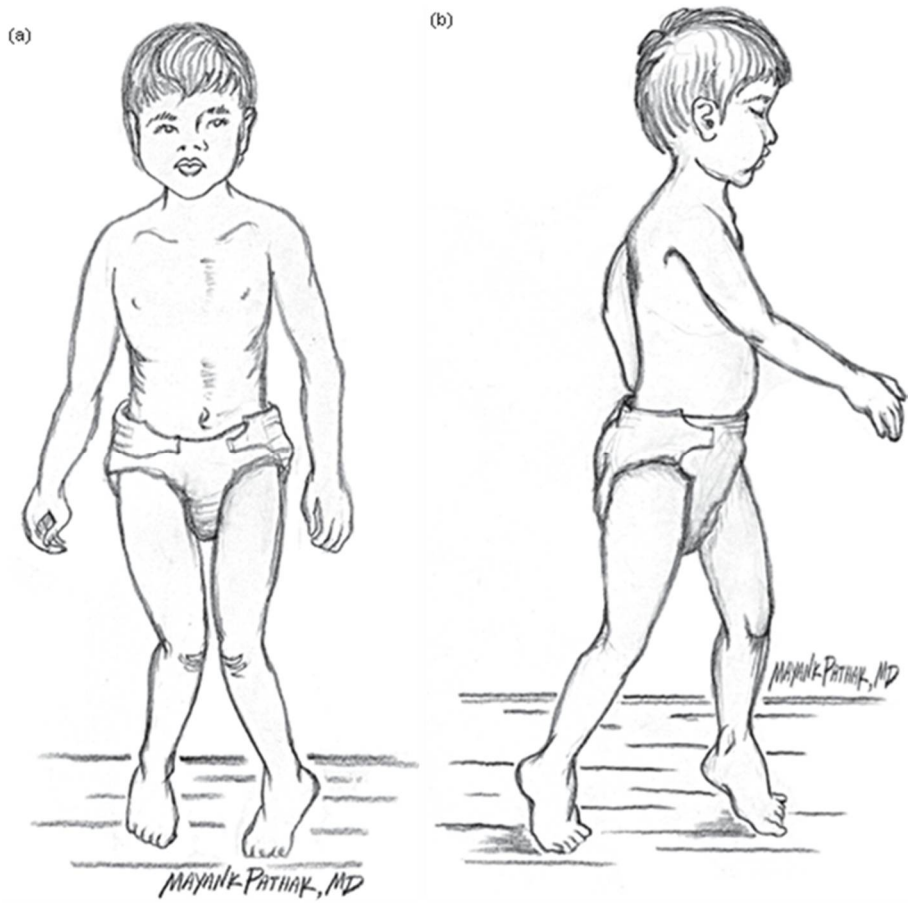

Figure 3 : Spastic diplegia, frontal (a) and lateral (b) views. Muscles that are involved in spastic diplegia are hamstrings, gastrocnemius and soleus.

Recently, Obst and colleagues has used quantitative ultrasound to evaluate muscle composition in children with CP. This study investigated medial gastrocnemius (MG) muscle in children with spastic motor type CP and an age-matched cohort of TD children. The results revealed significant differences between CP and TD children. (23)

There was consistent evidence for reduced muscle size, as compared with a TD cohort, of the more involved limb in children with unilateral and bilateral CP. Compared with TD children, the muscles of the less involved limb in children with CP are smaller in length and possibly volume (23). Compared with those of the less involved limb, muscles of the more involved limb tend to be more stiff and smaller in length, volume, cross-sectional area and thickness, but do not differ in fascicle length and pennation.(23) (figure 4)

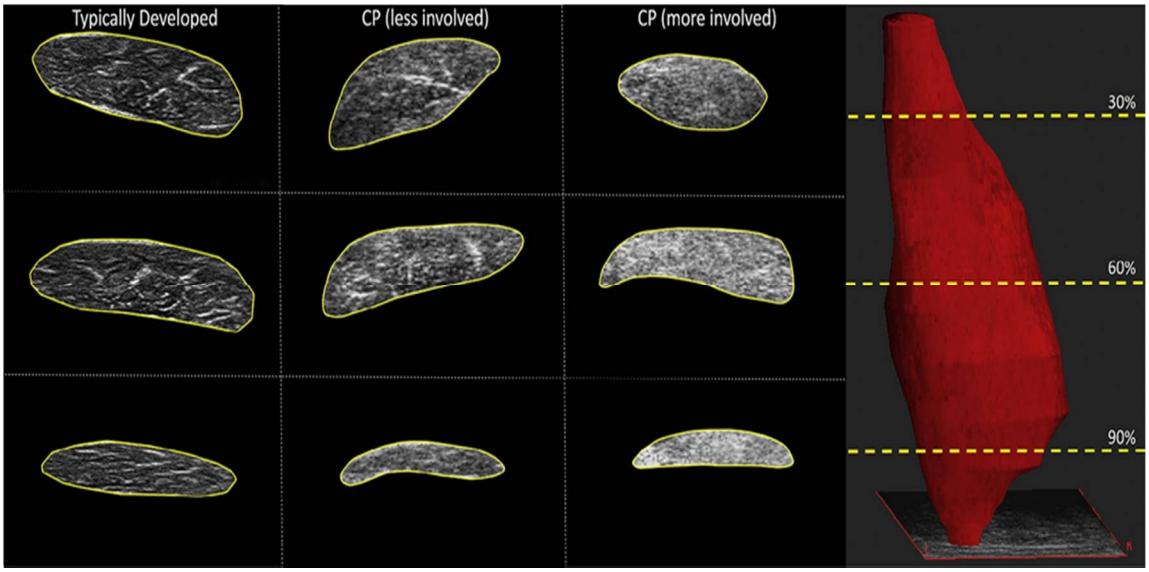

Figure 4 : Representative transverse ultrasound images of the proximal, middle and distal thirds of the medial gastrocnemius (MG) muscle in a typically developing child and the less involved and more involved limb in a child with unilateral spastic cerebral palsy (CP). The area outside the muscle region of interest was masked and excluded from the quantitative ultrasound analysis. Note the small cross-sectional area, high echo intensity and coarse granular appearance of both the less involved and more involved limb in the CP participant. Also note the proximal-distal increase in echo intensity of the CP muscle. (23)

5. Clinical examination of spastic CP

5.1. Medical history

The medical history should include a collection of information regarding birth history, developmental milestones, medical problems, surgical history, current physical therapy treatment, and current medication. Treatment plans depend on parent report of current functional walking level at home, school, and in the community, as well as other functional skills such as stair climbing, jumping, and running.

Birth history and other medical problems are important pieces of information for accurate diagnosis, future prognosis, treatment, and goal setting. Developmental milestones give information regarding the maturity of a skill such as walking and provide insight into the child's future capacity. Complaints of pain, and behavior or learning issues assist the clinician in performing a good evaluation.

5.2. Clinical observation and gait analysis

- Clinical observation

The observation of the child in a spontaneous lying position permits identification of asymmetric attitudes, which are evidence of predominant hypertonia in precise muscular groups. Observation is particularly important for nonambulatory children. They most often exhibit left or right wind-swept attitudes or bilateral flexion-internal rotation-adduction of lower limbs (Fig. 5). (24)

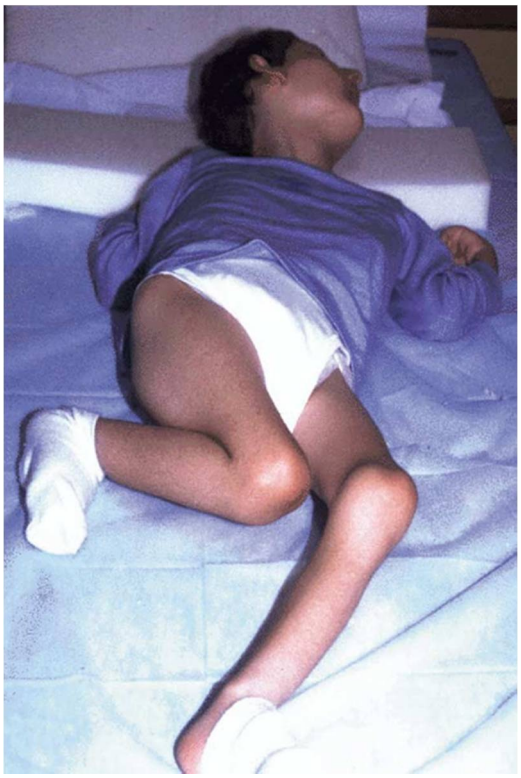

Figure 5 : Observation of spontaneous lying position in a nonambulatory child with cerebral palsy.(24)

- Gait analysis

The most common gait deviation in spastic hemiplegia and diplegia is that known as equinus, which is a result of imbalance between the plantar flexors and the ground reaction force (25). The progression from dynamic to fixed contracture may be rapid in the hemiplegic lower limb compared with the upper limb. The sagittal gait patterns in spastic hemiplegia (Fig.6) have been classified by Winters and colleagues (26), further modified by Rodda and Graham (27). These patterns are easily recognized and provide a useful scheme for management. Equinovarus and equinovalgus deformities are also common and may require tendon transfer and/or bony stabilization.

In spastic diplegia there are gradually evolving deformities at all three levels: flexion/adduction/internal rotation at the hip; flexed/stiff knee at the knee; equinus, usually accompanied by valgus, at the ankle. The principal effect is loaded on the biarticular large muscles such as the hamstrings, the psoas, the rectus femoris and the gastrocnemius. The sagittal gait patterns in diplegia have been classified by Rodda and Graham (27) (Figure 7). In addition, torsional deformities and deformation of joints are common, for example medial femoral or lateral tibial torsion, midfoot breaching with valgus hindfoot and abductus of the forefoot, and hallux valgus or flexion deformities of the other toes. Pelvic obliquity and scoliosis may also occur.

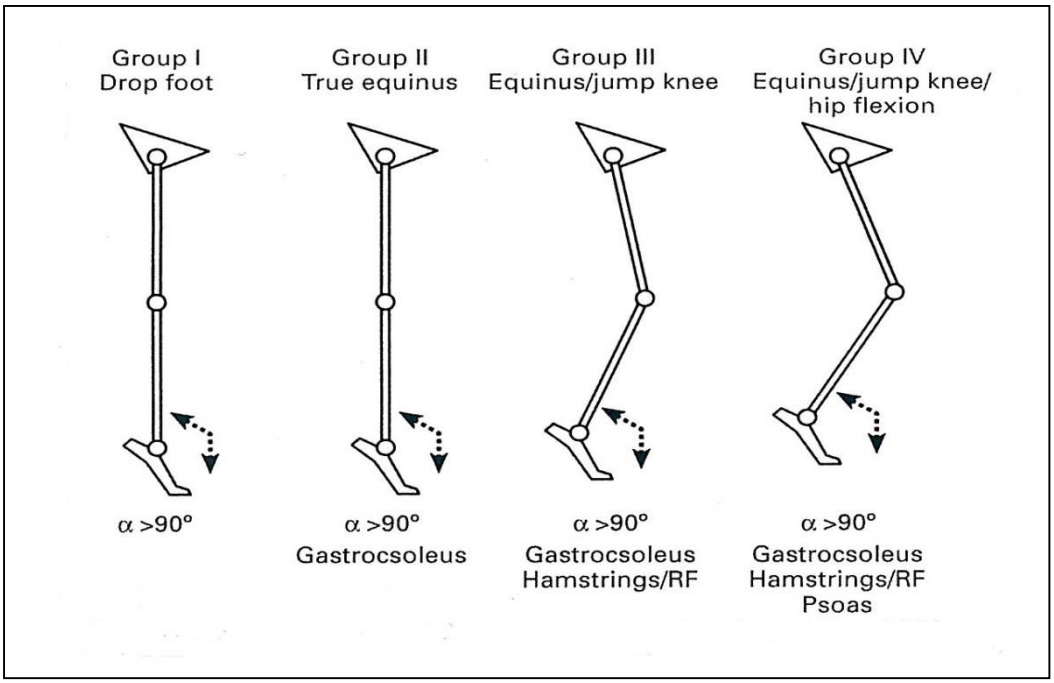

Figure 6 : Sagittal gait patterns in spastic hemiplegia according to Winters et al. (26) and Rodda and Graham (27). Reproduced from Graham and Selber (28) with permission from the British Editorial Society of Bone and Joint Surgery. RF, rectus femoris.

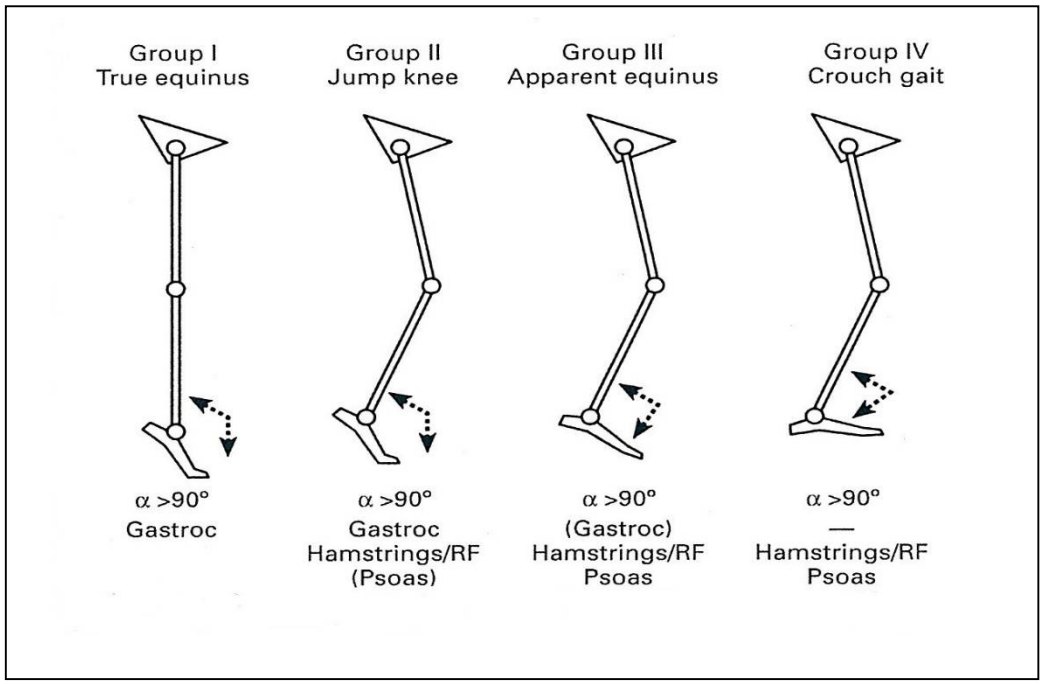

Figure 7 : Sagittal gait patterns in spastic diplegia according to Rodda and Graham (27). Reproduced from Graham and Selber (28) with permission from the British Editorial Society of Bone and Joint Surgery. RF, rectus femoris.

Based on the clinical examination of gait, gait can be classified into five groups: true equinus (Fig.8), jump gait, apparent equinus, crouch gait (Fig.9), and asymmetric gait. Each gait is described with dominant muscle groups identified for the management of spasticity, contracture, or both. Gastrocnemius is the dominant group for the true equinus gait; the gastrocnemius, hamstrings, and psoas for the jump gait; and hamstrings and psoas for the apparent equinus and crouch gait. This first clinical observation provides an idea of which muscular groups are weak and for which it will be dangerous to decrease tonus. It shows which muscular groups present a spasticity disturbing function and will be the target of treatment. This first stage is insufficient.

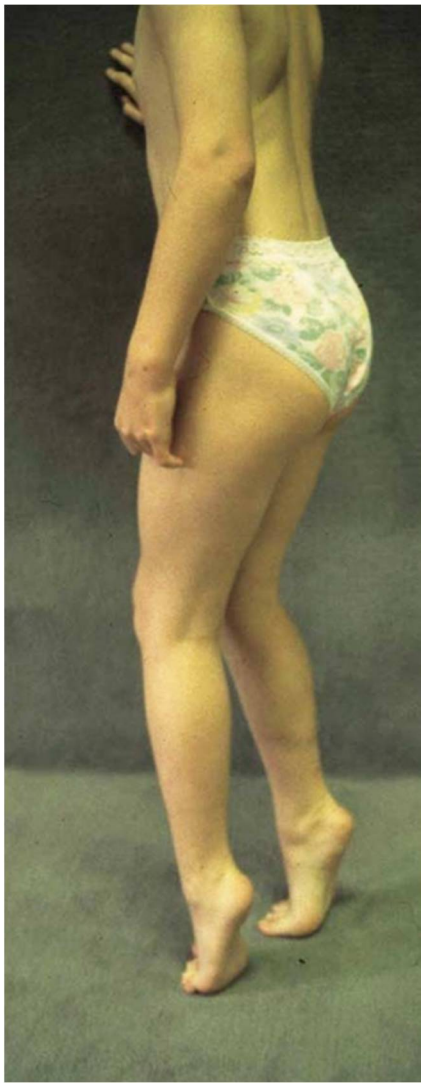

Figure 8 : Observation of a true equinus gait in a child with cerebral palsy.(25)

Figure 9 : Observation of the crouch gait in a child with cerebral palsy.(25)

Visual analysis obviously does not require any equipment, but relies on a skilled observer to assess the child's gait, and to make a record. This limitations of clinical gait analysis explain the use of more accurate gait analysis techniques. In developed countries, most major centers record qualitative video analysis of the patient walking, with and without aids. Using video recordings allows side-by-side analysis of historical footage at various ages, and means that many observers can assess the same segment of gait. Slow motion replay further allows detailed assessment. Additionally, video archives represent a significant resource for research and clinical audit purposes.

Three-dimensional instrumented assessment of a child's gait in a gait laboratory may also be used for gait analysis, as well as utilizing three-dimensional video capture, electromyography and force plate measurements as quantitative measures of gait. The 3-D method is considered the gold standard in objective assessment of gait. It has been shown to be a useful tool both in surgical planning and in assessing outcomes. (25)

5.3. Assessment of Range Of Motion

When strength and tonus of some muscular groups induce the articulations into an asymmetric attitude, the range of motion of articulations decreases and musculoskeletal contractures appear. It can be too late to treat spasticity in first intention. There are some tests performed by the orthopedist that can inform about muscle contractures and they are as follow:

Hip: Thomas' test: Thomas' test assesses fixed hip flexion. The patient lies supine with one leg held to the abdomen, thereby flattening the lumbar lordosis. The fixed flexion of the contra-lateral hip is recorded as the angle from the examination couch to the thigh. In heavier patients, like adults, it may be necessary to feel for loss of lumbar lordosis with one hand (Figure 10).

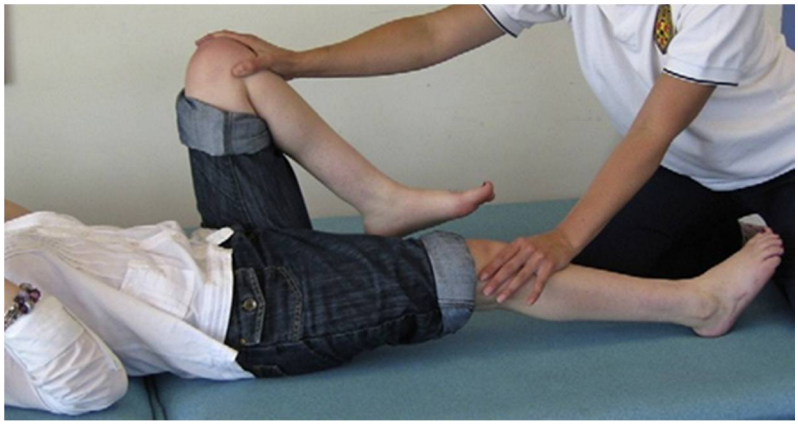

Figure 10 : Thomas' test

Duncan-Ely test (prone rectus stretch test): this is used to assess the contribution made by the medial hamstrings and rectus femoris in causing a stiff-knee gait as co-contraction of these muscles results in reduced knee extension in stance and terminal swing (medial hamstrings) and reduced knee flexion in early swing phase (due to excessive activity of rectus femoris).

The patient lies prone on the examination couch and the knee is rapidly flexed. As rectus femoris acts across two joints with its origin above the hip and insertion below the knee, it is deemed a bi-articular muscle. Thus spasticity will result in the ipsi-lateral hip flexing, causing the buttock to lift from the examination couch (Figure 11).

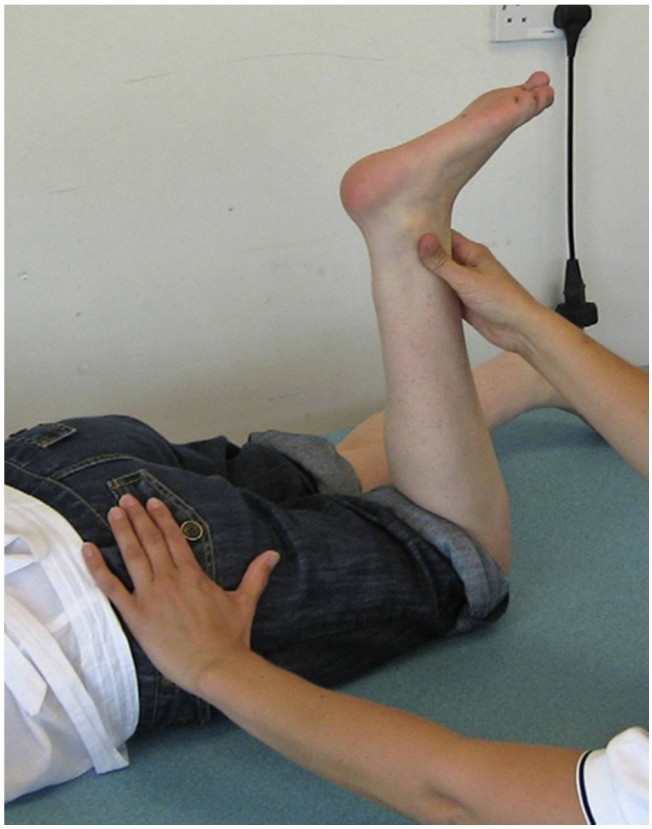

Figure 11 : Duncan-Ely test

Knee (popliteal-femoral angle): the popliteal angle is measured with the hip flexed to 90○ and the knee maximally extended. The angle between thigh and leg is recorded; an angle of less than 20○ is normal.

Knee flexion contractures (KFC) in diplegic cerebral palsy with crouch gait can be secondary to hamstring contracture as well as excessive anterior pelvic tilt (due to tight hip flexors) with normal length hamstrings. Capsular and gastrocnemius contractures are also contributory factors. By assessing the popliteal angles individually with the contra-lateral hip extended and then with both hips flexed (thus relaxing the hamstrings) the relative involvement can be assessed (Figure 12).

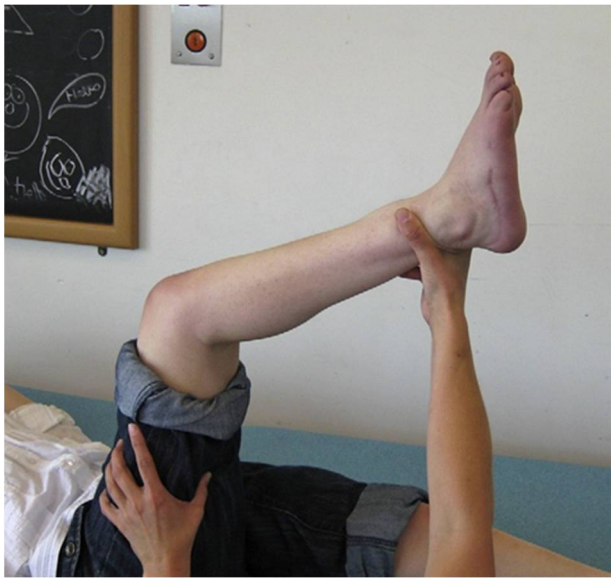

Figure 12 : popliteal-femoral angle

Ankle Silverskiold test: toe walking is commonly seen in spastic cerebral palsy. It is typically due to either dynamic muscle hypertonicity or contractures of the gastrocnemius and soleus. Gastrocnemius is a bi-articular muscle, arising above the knee above the femoral condyles and is likely to be the source of contractures. With the heel in a neutral position and knee flexed, the foot is

maximally dorsiflexed by holding the heel and avoiding pressure on the plantar surface of the foot to preclude a reflex extensor response. If superadded knee extension causes an increase in ankle plantar-flexion then the gastrocnemius contracture can be deemed to be more significant than the soleus contracture (Figure 13).

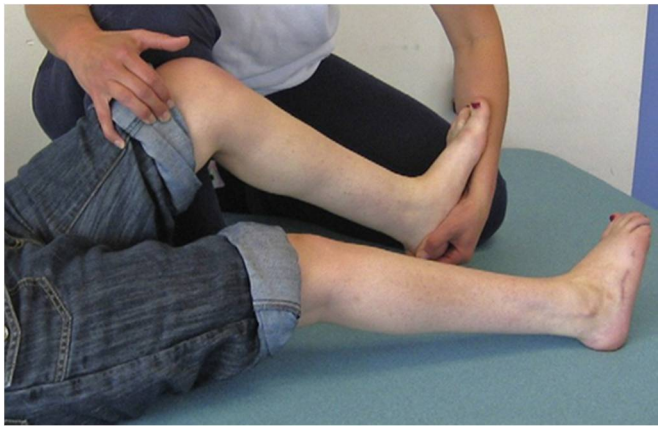

Figure 13: Ankle Silverskiold test

Rotational assessment (torsional profile): In CP the abnormal loading and growth of bones as well as the muscle imbalance often results in torsional deformities. Thus as part of the routine examination one should aim to assess prone internal and external rotation at the hip, femoral anteversion, tibial torsion, thigh-foot angle and the heel bisector line.

5.4. Assessment of spasticity

Two scales are available for the evaluation of children with cerebral palsy: the Ashworth scale (Table I) and the Tardieu scale (Table II). (29-30) The evaluation is performed while the patient is lying, rapidly moving the segments of the limbs: flexion extension of the knees, abduction of the hips, ankle dorsiflexion with knee extension, and knee flexion.

Tableau I: Ashworth Scale (29)

Grade	Patient status
0	No increase in tone
1	Slight increase in tone with a catch and release or minimal resistance at end of range
1+	Same as 2 but with minimal resistance through range following catch
2	More marked increase in tone but limb easily flexed
3	Considerable increase in tone , through range of motion
4	Affected part rigid

Tableau II: The Tardieu scale (30)

Grade	Feature
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of the passive movement with no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by a release
3	Clonus fatigable (less than 10 seconds, when maintaining pressure); appears at a precise angle
4	Clonus indefatigable (more than 10 seconds, when maintaining pressure); appears at a precise angle

Both scales are useful. For the assessment of spasticity, only one scale is insufficient to respond to all cases observed. The Tardieu scale seems to be appropriate for young children who walk and have no contractures. This scale had been designed for the assessment of triceps spasticity and is very useful in this case. The Ashworth scale is best for the assessment of global spasticity in non ambulatory children who are beginning to develop orthopedic complications.

5.5. Assessment of Gross and fine motor function

Gross motor function*:* The Gross Motor Function Classification System (GMFCS) was developed to provide a standardized classification of motor disability and functional limitations (Table III). The aim was to enhance communication among professionals and families in determining a child's needs and making management decisions, describing the development and prognosis of children with CP and comparing and generalizing the results of evaluations and research (31). The GMFCS is a five-level ordinal grading scale in which the distance between levels is not to be considered equal and children are not expected to be equally distributed between the levels. The assessment of self-initiated movement with emphasis on function during sitting, standing and walking can be graded (separate descriptions are provided for children in several age bands) and the distinctions between the levels are based on functional limitations, the need for walking aids or wheeled mobility, and quality of movement. Children at level I evince the most independent motor function and those at level V the least. The GMFCS has proved a reliable, stable and clinically relevant method for the classification and prediction of motor function in children between the ages of 2 and 12 years (31,32). A classification for adolescents was developped later. (33)

Fine motor function*:* The Manual Ability Classification System (MACS) was developed as a method analogous to the GMFCS to classify the ability to handle objects in daily activities (Table IV). The MACS has been reported to have good validity and reliability (34). Another scale for classifying bimanual function, the Bimanual Fine Motor Function (BFMF) (35), was likewise developed to parallel the GMFCS but it has not gained such wide acceptance as the MACS among professionals.

An assessment with GMFM every 6 or 12 months provides the curve of evolution and permits the motor potential of the child to be judged objectively. The findings can be extrapolated to future motor function, or to observe a patient's progress or degradation. Complete assessment of the child with cerebral palsy is useful before treatment. It permits the choice of the treatment to be weighed against spasticity. After an intervention the achievement of pre-intervention objectives can be established; additional benefits can be observed and complementary treatment considered.

Tableau III: Summary of the gross motor function classification (33)

Level I	Walks without limitations at home, school, outdoors, and in the community.
Level II	Walks in most settings. Environmental factors (such as uneven terrain, inclines, long distances, time demands, weather, and peer acceptability) and personal preference influence mobility choices.
Level III	Walks using a hand-held mobility device (cane, crutches, walker). Outdoors and in the community, youth are transported in a wheelchair or use powered mobility.
Level IV	Youth use wheeled mobility in most settings. Youth require adaptive seating and physical assistance for transfers. Self-mobility can be achieved using power mobility.
Level V	Self-mobility is severely limited even with the use of assistive technology. Physical assistant from one or two persons or a mechanical lift is required for transfers. Youth may achieve self-mobility using powered mobility with extensive adaptations for seating and control access.

Tableau IV: Manual ability classification system (MACS)

Level I	Handles objects easily and successfully
Level II	Handles most objects but with somewhat reduces quality or speed of achievement
Level III	Handles objects with difficulty; needs help to prepare or modify activities
Level IV	Handles a limited selection of easily managed objects in adapted situations
Level V	Does not handle objects and has severly limited ability to perform even simple actions

6. Treatment options for CP

Management of spasticity in CP involves multidisciplinary intervention intended to increase functionality, sustain health, and improve quality of life for children and their caregivers. This may include: oral medications, intrathecal medications, physiotherapy, occupational therapy, orthoses, surgical interventions, and pharmacological agents such as botulinum toxin. (36,37)

The different treatment options for spasticity in children with CP are set out in Table V. Each treatment modality may be used alone or in various combinations depending on the goals and the severity of dysfunction.

Oral medications

If the whole body is affected (generalized spasticity), oral muscle relaxants may relax stiff, contracted muscles. These drugs include diazepam, dantrolene and baclofen. There is some risk of dependency with diazepam, so it’s not recommended for long-term use. Its side effects include drowsiness, weakness and drooling. Side effects of dantrolene include sleepiness, nausea and or diarrhea. Side effects of baclofen include sleepiness, confusion and nausea. Baclofen may also be pumped directly into the spinal cord with a tube. The pump is surgically implanted under the skin of the abdomen.

Botulinum toxin (BTXA) injections

Injections of botulinum toxin A(BTXA) are recommended for isolated (focal) spasticity. BTXA is a serotype of botulinum toxin, produced by the Gram-positive bacterium Clostridium botulinum. This potent neurotoxin selectively inhibits the release of acetylcholine from peripheral nerve terminals by binding to synaptic vesicles. Interruption of neuromuscular conduction by

BTA induces a temporary weakness, which reduces focal spasticity. Early treatment of spasticity with BTXA prevents contractures and deformities, in order to delay or avoid surgical treatment.

The effects of BTXA last for approximately three months as the muscle will recover via proximal axonal sprouting, the formation of new neuromuscular junctions, and the regeneration of the original neuromuscular junctions. The efficacy of BTXA in the management of individuals with CP has been widely reported in the literature (38,39).

Surgical treatment

- **Baclofen pump - intrathecal baclofen (ITB)**

ITB Therapy uses a surgically implanted programmable pump and catheter that delivers medication which helps relieve severe spasticity. This medication is a liquid form of baclofen (baclofen injection) that goes directly into the intrathecal space where fluid flows around the spinal cord.

Because baclofen is delivered directly to where it is needed most in the spinal fluid, it relieves spasticity with smaller amounts of medication than when baclofen is taken orally. This method of delivery may help minimize side effects that can result from oral baclofen.

This form of therapy is most appropriate for children with severe hypertonia and uncontrolled movement disorders throughout the body. The baclofen pump must be filled with medicine every one to six months, depending on child’s dose. The pump lasts about five years. Afterward, it must be removed and replaced during another surgery. However, baclofen infusion is not effective permanently; when it is stopped, spasticity recurs. Also, the baclofen infusion carries risks of overdose, meningitis, and other complications (40).

- **Orthopedic surgery**

Orthopedic surgery (OS) is used to lessen muscle tightness or correct bone abnormalities caused by spasticity. Orthopedic operations include soft tissue procedures (muscle release, tendon and muscle lengthening, tendon transfers) and osteotomies (cutting a bone to change its alignment). Orthopedic surgery can correct severe contractures or deformities, lessen pain, improve mobility. These procedures may also make it easier to use a walker, braces or crutches (41).

Orthopedic surgery is often recommended when spasticity and stiffness are severe enough to make walking and moving difficult or painful. Commonly, surgery involves lengthening muscles and tendons that are proportionately too short. Orthopedists generally time surgeries to coincide with a specific stage of the child's physical development.

Spasticity in the upper leg muscles, which causes a "scissor pattern" walk, is a major obstacle to normal gait. The optimal age to correct this spasticity is 2 to 4 years of age with adduction release surgery. On the other hand, the best time to perform surgery to lengthen the hamstrings or Achilles tendon is 7 to 8 years of age. If adduction release surgery is delayed so that it can be performed at the same time as hamstring lengthening, the child will have learned to compensate for spasticity in the adductors. By the time the hamstring surgery is performed, the child's abnormal gait pattern could be so ingrained that it might not be easily corrected.

- **Selective dorsal rhizotomy (SDR)**

Selective dorsal rhizotomy is a surgery done on the lower spinal cord to reduce spasticity or high muscle tone in the legs. Certain nerve fibers that lead to high muscle tone are cut. The goal of a selective dorsal rhizotomy is to relax the muscles by identifying and cutting those nerve fibers that are causing the abnormal tone. This provides a long-term improvement in muscle tone, because the nerves do not grow back together. SDR is a surgical procedure recommended only for cases of severe spasticity when all of the more conservative treatments have proven ineffective (40).

Functional therapy

- **Physiotherapy**

Physiotherapy for spasticity refers to a range of physical treatments. It is the most common form of treatment for spasticity in children. The treatment should be designed to meet child's specific needs and should reduce muscle tone, maintain or improve range of motion and mobility, increase strength and coordination, and improve care and comfort.

- **Electrical stimulation**

Functional electrical stimulation system (FES), a neuroprosthesis device, is a well known intervention utilized for many years to support muscle groups during walking. It delivers electrical stimulations to a motor nerve which stimulates a muscle group to overcome functional obstacle during gait - for example a stimulation to the common peroneal nerve during swing phase of gait, causes the ankle to dorsiflex and thus preventing foot drop. It enables improvement in walking ability and corrects gait deviations by recruiting the

proper muscle groups at the appropriate timing in the gait cycle. One of the potential benefits of the FES device over braces is its small size, easy use and high-tech that might be more appealing to the patients. FES endeavors to improve walking appearance, ability and correct gait deviations, thus the intensity setting of the stimulation is determined by achieving the required motor action. Surface FES is the preferable type used due to its feasibility and comfortability.

In general, FES attempts to increase muscle strength, reduce muscle spasticity and improve movement control/movement pattern. The efficacy can be demonstrated by the improvement in temporal parameters, however limited data is available to support the efficacy of FES in improving muscle strength and reducing spasticity. It may also serve as an orthotic device used while performing routine daily activities including walking. At present, FES is widely used to control dorsi flexors muscles and prevent drop foot during the swing phase.

- **Hydrotherapy**

Aquatic exercise programme may be useful for improving gross motor functioning, for reducing spasticity and for increasing cardiorespiratory endurance in children with spastic CP (44).

Orthoses

Also known as casts, braces, or splints, orthoses include any device that is used to support, align, prevent, or correct deformities, or improve the function of movable parts of the body. When used to treat spasticity, orthoses may reduce muscle tone and increase or maintain motion.

Tableau V: Treatment options for spasticity in CP children

A.	General care Nutrition and feeding Posture, seating Sleep pattern (melatonin) Pain management (gastro-esophageal reflux, fractures, joint pain, dental abcesses, pressure sores, hip dislocation etc.) Psychological contentment (frustration)
B.	Physiotherapy
C.	Orthotics, casting, positioning
D.	Electrical stimulation
E.	Oral medication Benzodiazepins (diazepam, nitrazepam) Baclofen Dantrolene Tizanidine
F.	Local injections Botulinum toxin Alcohol or phenol Lidocaine
G.	Intrathecal baclofen
H.	Surgery Dorsal rhizotomy Tendon lengthening, release and transfer Osteotomy and derotation Arthrodesis

Second chapter: Botulinum toxin type A injections in children with spastic CP

1. History of botulinum toxin

Intramuscular botulinum toxin injections were initially utilized for managing strabismus by Alan Scott (7). Early clinical trials demonstrated the tolerability of intramuscular toxin injections for the treatment of eye disorders and dystonia (45). In 1988, Koman et al (46) first utilized botulinum toxin A (Oculinum®) to balance joint forces in patients with dynamic extremity deformities secondary to spasticity from CP. Various studies published since 1993 have described the tolerability and efficacy of intramuscular injections of botulinum A toxin for the management of spasticity in patients with CP. (47,48) Commercially produced botulinum A toxin (BOTOX®) became available in 1989. Since its introduction, BOTOX® has been labeled for use in both adults and children with CP in 49 countries, based upon its documented efficacy in the management of equinus foot deformity (49).

2. Mechanism of action

Botulinum A toxin is a parenteral agent that produces dose-related chemodenervation of agonist (target) muscles following intramuscular injection, without producing clinical effects on antagonist muscles. Following intramuscular injection of botulinum toxin, muscles are temporarily paralyzed, and therefore, muscle spasticity is decreased (50).

Botulinum A toxin is one of eight antigenic toxin subtypes (A, B, C1, C2, D, E, F, and G) produced by the spore-forming obligate anaerobic bacteria Clostridium botulinum (50). Botulinum type A is a 150kDa complex composed of a 100kDa ‘heavy’ chain and a 50kDa ‘light’ chain. The light chain is active, cleaves synaptosomal- associated protein of 25kDa (SNAP 25), a soluble N-ethylmaleimide-sensitive fusion protein receptor (SNARE) protein, and prevents

the assembly of the fusion complex necessary for the release of acetylcholine (ACh) at the neuromuscular junction (NMJ), the critical step that is required to initiate a muscle response (fig.14). The blockade of the release of ACh at the NMJ results in flaccid muscle paralysis. Following exposure to botulinum A toxin, functional NMJ activity ceases (50,51). Nerve terminals exposed to botulinum A toxin have been noted to produce sprouts capable of neurotransmitter exocytosis that form a functional synapse (52). In the ensuing 3–12 months, the original NMJ is reconstituted, the sprouts regress, and normal synaptic transmission via ACh resumes within the NMJ. The extent of muscle paralysis is determined by the diffusion of toxin within the muscle, the binding affinity of toxin to SNAP 25, and the percentage of involved NMJs.(50)

Intramuscularly injected BTXA has an approximate 2–4cm diffusion radius, thus increasing the probability that the toxin is delivered to a large number of NMJs (53). In contrast, alcohol (ethanol) and phenol exhibit limited diffusion. Other factors which affect the probability of delivery of toxin to the NMJs include the number of active toxin complexes injected, the volume in which those complexes are diluted, the location of the injecting needle in relationship to the NMJs, and the binding affinity of the toxin to specific NMJs. Theoretically, NMJs may vary in binding affinity based upon the muscle type. NMJs demonstrate different distribution patterns in specific muscles, become ineffective with age, vary in number per gram of muscle tissue in association with skeletal growth or atrophy, and remain relatively constant in absolute numbers in each muscle throughout life. (53)

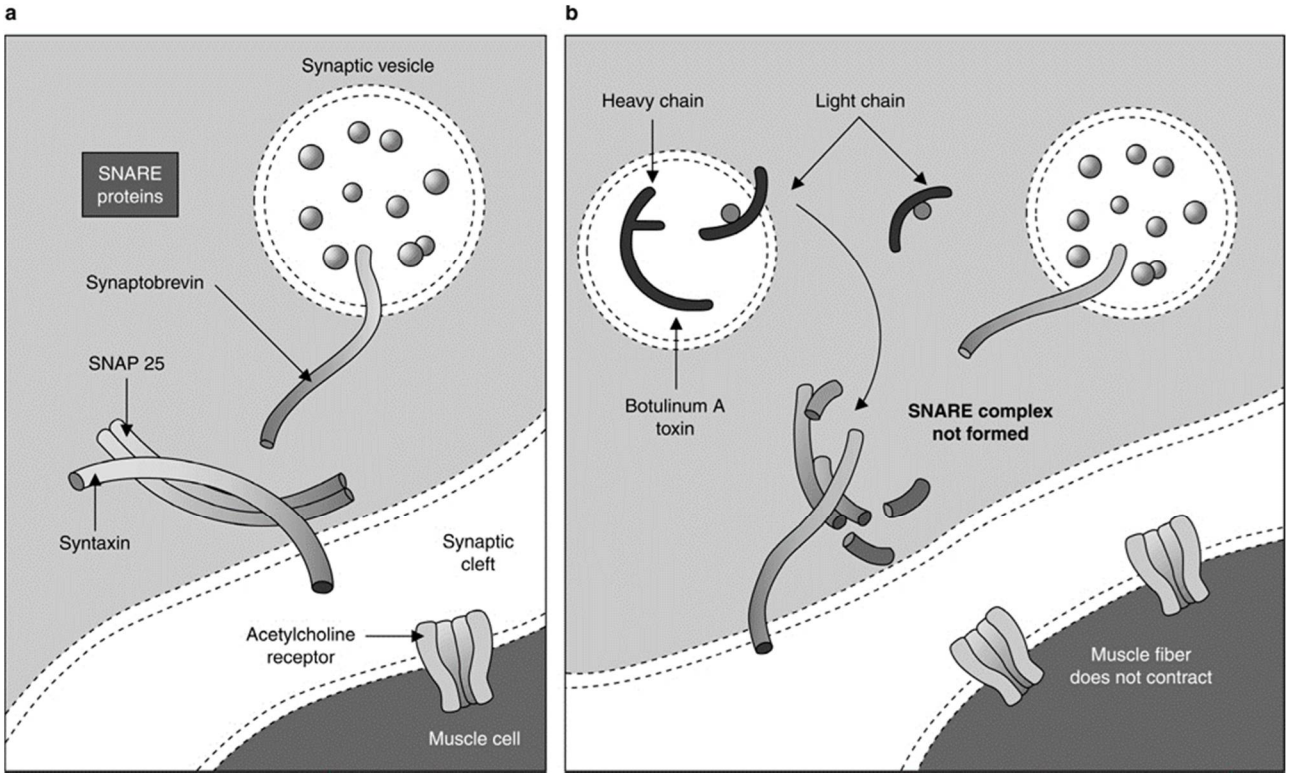

Figure 14: Mechanism of action of botulinum A toxin. (a) In order for the muscle to contract, axonal control must be transmitted via the neuromuscular junction. Normally, a nerve impulse causes presynaptic vesicles to adhere to the cell membrane and acetylcholine is released. For this process to occur, SNARE proteins must be formed to facilitate vesicle contact with the cell membrane. (b) Botulinum A toxin blocks SNAP 25, one of three SNARE proteins, prevents fusion of the vesicle, blocks release of acetylcholine, and produces flaccid paralysis of the muscle. SNAP 25 = synaptosomal-associated protein of 25kDa; SNARE = soluble N-ethylmaleimide-sensitive fusion protein receptor).(54)

3. Adverse effects and safety considerations

Concerns about the safety of BTXA has been raised especially after 2005, when an analysis of the US Food and Drug administration related 28 deaths to BTXA treatment (55). The most frequently reported AEs in children with cerebral palsy were dysphagia (including aspiration), followed by asthenia/fatigue and muscular weakness. Death was reported in 19 cases, mainly due to pneumonia and botulism. The main mechanisms identified were: the spread of BTXA beyond the injection site, coincident treatment with sedative drugs and a severe underlying disease. In 2006, the European consensus was published and have set the recommendations for the optimal use of botulinum toxin to avoid any adverse events. The consensus has been modified later in 2009.

During the 2014-2017 period, several controlled clinical trials investigated the occurrence of AEs in CP. Mild or moderate AEs were reported such as pyrexia, local muscular weakness, fatigue, pain, sleepiness and gait abnormalities. No severe AEs, resulting in death or requiring hospitalization, were noticed.

A recent study was published of the adverse events associated with the use of BTXA covering a 15-year period, varying doses of BTXA, and across the entire CP spectrum, from level I to level V of the Gross Motor Function Classification System (GMFCS). The authors found higher BTXA doses to be associated with increased odds of systemic and respiratory complications, independently of GMFCS level. Specifically, higher doses were strongly associated with increased odds of bladder or bowel incontinence and unplanned hospital admission for respiratory complications, and more weakly associated with increased odds of emergency department consultation. Little evidence was found for an association between BTXA and two other respiratory complications examined mainly antibiotic prescription and upper respiratory tract infection (URTI). (56)

In this study and in other studies in the literature, systemic adverse events occur in 1 to 2% of children with CP after injections of BTXA. Incontinence causes a major degree of parental anxiety but resolves quickly and fully in all children. Serious respiratory events may be the result of procedural factors as well as injection of BTXA. In this regard, the risk is related to the child's GMFCS level and pre-existing medical comorbidities, including impairment of bulbar function and history of respiratory disease. Clinicians should be aware of these risks and take appropriate actions to protect children from potentially fatal adverse events. (57) This is particularly relevant when many current injection protocols and doses remain off label.

BTXA should not be used for: (i) individuals with known hypersensitivity to any component of the formulation; (ii) in patients with generalized muscle activity disorders (e.g. myasthenia gravis); (iii) concurrently with aminoglycoside antibacterials or spectinomycin; or (iv) in female patients during pregnancy and lactation. (58)

Botulinum A toxin is well tolerated when used in doses <15 units/kg bodyweight (57). Multilevel lower extremity injections of the iliopsoas, adductors, gastrocnemius, and hamstrings are reported using doses of 29 units/kg bodyweight (58). There are significant safety concerns when toxin dosages exceeding 12 units/kg bodyweight are injected in a single site or single motor group.

4. Antibodies and clinical resistance

Resistance is characterized by absence of any beneficial effect and by lack of muscle atrophy following the injection. Antibodies against the toxin are presumed to be responsible for most cases of resistance. Clinical investigators

(59) have shown that small numbers of patients do develop antibodies with repeated BTXA treatment. Although antibodies appear to cause no harm, they can render the patient unresponsive to further treatments. Patients with resistance to one serotype may benefit from injection with other serotypes.

Immunoresistance to BTXA may be tested with the FTAT (frontalis type A antibody test) when clinical resistance is suspected. Fifteen to 20 Units BOTOX are divided into 2 sites of one side of the corrugator muscle. If the muscle does not move within 2 weeks, and the patient cannot furrow that side of their brow, then they are “not resistant;” if the corrugator moves properly, then they are “resistant.” In the case of no resistance, the patient may be injected on the opposite side to maintain expression symmetry. (60)

The authors have shown that the risk of immunoresistance is related to the amount of protein exposure. Current BOTOX® has a higher specific activity than the original batch that was initiated in 1979 (Allergan, Dear Customer letter, November 1997). Current BOTOX® has approximately 4–5 ng neurotoxin complex per 100 Units (table 9) while the original batch has 25ng neurotoxin complex per 100 Units. After performing an analysis examining the influence of age and cumulative dose, they concluded that the risk of antibody formation following current BOTOX® treatment is lower than the risk with the original batch because of the lower protein exposure.

The authors (59) set recommendations to minimize immunoresistance: (1) use the smallest possible effective dose, (2) extend the interval between treatments as long as reasonable, at least 3 months between treatments, and (3) avoid using booster injections.

5. Toxin preparations and administration

5.1. Commercial preparations

It is important to refer to the most known botulinum A toxin preparations (BOTOX® and Dysport®) by their tradenames because the potency of units for the two different preparations differs (61). The calculation of the 'units' of the two preparations is different, and not interchangeable. Both preparations require reconstitution of the lyophilized, frozen toxin with physiologic saline. In addition, both drugs have a limited shelf life, must be administered shortly after reconstitution, and are injected intramuscularly. Both toxin preparations have documented utility when used in the appropriate dosage. BOTOX® is injected intramuscularly in dilutions of 25–100 units/mL, while DYSPORT® is injected at a recommended dilution of 500 units/mL.(62)

Currently, four toxin brands exist, two other brands were developed in addition to the previous ones, one containing BTXB (NeuroBloc/MyoBloc) and one being another type of BTXA without complexing proteins (Xeomin). BTXA products proved to be effective in a range of extraocular conditions, such as dystonia syndromes (blepharospasm, hemifacial spasm, cervical dystonia, Meige syndrome, oromandibular dystonia, and writer's cramp), spasticity and others. Currently, in most western countries the following botulinum toxin products are branded: three BTXA (onabotulinumtoxinA or Botox®, abobotulinumtoxinA or Dysport®, incobotulinumtoxinA or Xeomin®) and one BTXB (rimabotulinumtoxinB or Neuroboc®/Myobloc®) (62). Additional trade names are also used for these toxins and other toxin brands are produced in Korea, China, and USA with a variety of names (Table VI)

Tableau VI: Marketed BT products.(63)

Botulinum toxin A	Botulinum toxin type B
Botox (onabotulinum toxin A), Allergan, USA	Myobloc /Neurobloc (rimabotulinum toxin B) Solstice, USA
Dysport (abobotulinum toxin A), Ipsen, UK	
BTXA (LIBP), China	
Puretox (Mentor), USA, Europe, Canada	
Xeomin (incobotulinum toxin)	
Reloxin (Ipsen / Medicis) UK, France	

5.2. Dosage and dose modifiers

The maximum dose of BTXA is calculated based upon bodyweight of the patient. However, ideally the number of units should be based upon the number of NMJs in the muscle to be injected. The maximum dose administered at one injection session reported in the peer reviewed literature is 29 units/kg bodyweight of BOTOX®; this dose of toxin was divided among multiple muscles (64). When only one or two muscles are injected, the recommended maximum single total dose is 10–12 BOTOX® units/kg bodyweight (61). (table VII)

For administering BOTOX® to pediatric patients with CP, the appropriate toxin dose of units is calculated empirically, based on 1–6 units/kg per bodyweight per muscle. This dosage was established arbitrarily by Koman in 1988, with a major variation being the number of units utilized per muscle, and the concentration of the toxin. This dose has been shown to be well tolerated, while also demonstrating clinical efficacy. (65) However, it is extremely likely

that the optimal dose should be based upon the number of NMJs per muscle and the mass of the muscle. When administering BOTOX®, multiple variables should be considered in establishing the optimal dose. These include: muscle mass, number of muscles to be injected, general health of the patient, upon individual patient characteristics, with subsequent refinement of the toxin doses used for spasticity management based upon the outcomes experienced by individual patients. The wide range of doses used by various physicians reflects these considerations. Large total doses of botulinum A toxin (29 units/kg bodyweight) have been injected for the management of spasticity in pediatric patients (64) (fig.13). However, the dilution of the toxin and patient characteristics impact the tolerability of the injected toxin dose and must be taken into account when evaluating the amount of toxin to be injected into each individual patient. Most clinical data report the use of botulinum A toxin injected at a concentration of 100 units/ml.

At this time, significant questions remain regarding the importance of various factors in relationship to the most effective administration regimen. These factors include NMJ distribution within the muscle, the volume of drug injected, and the concentration of toxin used. Furthermore, the relationship between the patient's age and toxin required for clinical efficacy is delineated incompletely. Theoretically, small children should require more toxin per bodyweight than adolescents or adults due to the increased density of NMJs in their muscles; however, no clinical reports in pediatric patients have been published that calculated toxin doses based on the number of NMJs. Currently, the number of units injected per muscle is based upon consensus recommendations (61,66) and the preference of specific authors.

For administering Dysport® to patients with CP, the current recommendation for equinus foot deformity is 15 units/kg body- weight per calf muscle (medial and lateral gastrocnemius).

Tableau VII: Guidelines for dosing of botulinum neurotoxin for children

Onabotulinum toxin A	**Abobotulinum toxin A**
1. Maximum dosing per session: the lesser of 15 U/kg or 400 U; experienced injectors may use more 2. Dose range: • upper extremity, 0.5–2.0 U/kg • lower extremity smaller muscles, 1–3 U/kg and larger muscles 3–6 U/kg • no more than 50 U per injection site 3. Reinjection interval 3 months or greater 4. Dilution 1–2 ml of non-bacteriostatic saline per 100 U vial 5. Spread of the neurotoxin is 4–5 cm in the muscle; therefore muscles may need more than one injection site based on size, fascial planes and dose	1. Maximum dosing per session: the lesser of 10–20 U/kg or 1000 U; experienced injectors may use more 2. Dose range: • upper extremity, 1–10 U/kg • lower extremity smaller muscles, 3–10 U/kg and larger muscles 3–15 U/kg • no more than 250 U per injection site 3. Reinjection interval 3 months or greater 4. Dilution 1–5 ml of non-bacteriostatic saline per 500 U vial 5. Spread of the neurotoxin is 4–5 cm in the muscle; therefore, muscles may need more than one injection site based on size, fascial planes and dose

Additional dose modifiers which have to be considered when planning the injection protocol may be: severity of CP according to GMFCS, accompanying diagnoses (e.g. dysphagia, aspiration, breathing problems), predominance of

movement disorder (spasticity, dystonia), activity of the injected muscle, muscle size, dynamic versus fibrotic muscle, knowledge about the distribution of motor endplates in the injected muscle, and experience from previous BTXA injections. Dilution will depend on body region and muscle size (e.g. forearm versus upper leg). In animal models higher dilutions showed greater dissemination, but clinical evidence to support this information is missing.

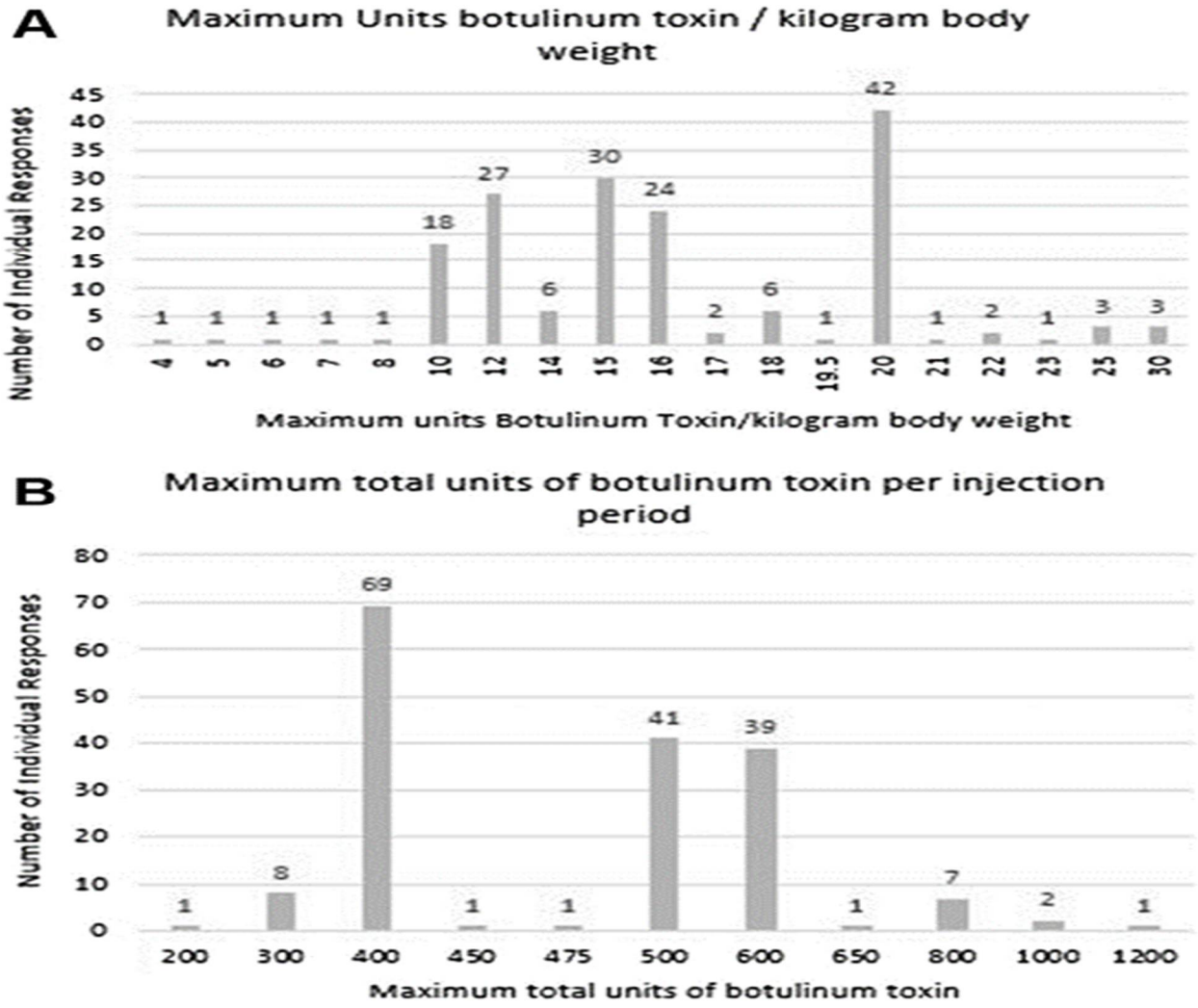

Figure 15: Maximum dose in units/kilogram body weight (A) and maximum total dose (B) of OnabotulinumtoxinA for a single injection event as reported by pediatric physiatrists(67)

5.3. Dilution

Animal studies have demonstrated that increasing injection volume increases muscle paralysis (68). In rabbits, high-dilution preparations (BotoxR 10U/0.5 ml), with or without electrical stimulation and exercise, have resulted in more extended gastrocnemius paralysis and histological changes compared with low-dilution preparations (10 U/0.1 ml) (69).

Francisco and associates (70) found no statistically significant difference between the groups with dilutions 100u/1ml and 200u/2ml was detected in muscle tone (Modified Ashworth Scale), though there was a trend toward greater improvement in the more diluted preparation group. The dilution difference between the two preparations might not have been large enough to exert the desired effect. Lee (71) investigated children whose calf muscle spasticity score on the Modified Ashworth Scale was 2-3. The right gastrocnemius was injected with a high-volume (100 U/4 ml) and the left gastrocnemius with a low- volume (100 U/1 ml) preparation of BotoxR. No significant differences between the groups were noted in spasticity (measured on the Modified Ashworth Scale and as dynamic muscle length), passive ROM, and amplitude and area of compound muscle action potential or pain at injection site. The authors explained the results by the fact that the muscles of children may be smaller, the BTXA dose may reach the endplates despite the volume used.

The most common concentrations used in pediatric studies have been 100 U/ml or 50 U/ml for BotoxR and 200 U/ml for DysportR.

5.4. Pain on injection

Botulinum A toxin, when injected through a 25–27G needle, produces a sensation described as both ‘cool’ and ‘warm’ during injection. This sensation does not persist beyond the injection, and normally no post-injection inflammatory reaction occurs.

There are no published studies that evaluate the pain associated with intramuscular toxin injections of botulinum A toxin. Practitioners perform injections using methods ranging from no intervention to general anesthesia. Options to diminish pain associated with the injection include: (i) nothing; (ii) topical anesthetics; (iii) topical thermal techniques; (iv) oral narcoleptics (conscious sedation); and (v) general anesthesia. All these procedures are efficacious and well tolerated;(66,72) however, some options (iv and v) are significantly more expensive, and are associated with morbidity.

The Wake Forest University experience, with over 7000 toxin injections, supports the use of minimal analgesia. For over 95% of their injections, patients received either no analgesia or topical cooling spray [e.g. dichlorodifluoromethane 15% plus trichloro-monofluoromethane 85% spray]. In a recent study of children with CP, pain assessments provided by family members and/or patients indicated that pain was ‘minimal’ 10 minutes after injection in 98% of the patients. However, other practitioners have voiced concern over the emotional impact of the injections on the children and their parents. These practitioners prefer the use of sedation with narcoleptics or general anesthesia when administering toxin. EMG-guided injections require sedation or anesthesia except for cooperative patients which is rare in children. General anesthesia is appropriate for most children undergoing iliopsoas injections. (73)

Lidocaine (lignocaine)/prilocaine (2.5%/2.5%) cream (EMLA® cream) is reported to provide effective analgesia for the skin at the injection site; however, penetration of the analgesic beneath the skin is limited and is unlikely to prevent muscle discomfort during the injection. According to the package insert, the cream is applied to the area to be injected and is covered with an occlusive dressing. The dressing must be maintained in place over the injection site for 1 hour before the start of a routine procedure, or 2 hours before the start of a painful procedure, in order to provide optimal analgesia.

Oral midazolam, a short-acting benzodiazepine, may be utilized; however this drug requires the implementation of conscious sedation guidelines when doses superior to 0.5 mg/kg bodyweight are used.

6. Injection technique

6.1. Site of injection

To act effectively, the toxin should be injected into the motor endplate area (MEP). The importance of using MEP-targeted BTXA injections has been demonstrated in animal models (74) and in a clinical human study in the biceps brachii. (75)

Several practical guides on BTXA injection technique describe where to inject the toxin for most of the upper and lower limb muscles. (76-77). In these guides, usually no references about the localization of MEP zones are given. The presumed localization of the endplate zone in the middle of a muscle belly is – where possible – taken into account; however, until recently, for many frequently injected muscles the exact anatomy of innervation and localization of the MEP zone was unknown.

Current knowledge on the localization of the MEP zone is based on a few older histological studies, and for some of the more frequently injected muscles also on more recent anatomical dissection studies.

Several studies (78-80) evaluated the distribution of MEPs in adult muscles. In all these studies, MEP zone is located with dissection of the muscle or more precisely the muscle belly itself, this studies didn't use measurements in relation to anatomical land-marks. Therefore, the practical use of this guidelines when injecting BTXA is limited. Another limitation for this studies is that not all skeletal muscles were examined; there are no histological data on some muscles that are very frequently injected.

The more recent anatomical descriptions were done by macroscopic, and in some studies by stereoscopic microscopic, dissection of the nerves supplying the muscles. In some studies the intramuscular branches and terminal arborizations were traced until it was no longer possible to follow them; others only describe the motor points or the point where the motor branch enters the muscle belly. This allows us to determine the proximal and distal limits of the territories where most nerve endings were observed in relation to external anatomical landmarks.

In 2015, Van Campenhout et al (81) published an excellent work mapping the end plate zones in a total of 30 muscles in upper and lower limbs. They examined the muscle fiber orientation in adult cadavers, determined the relationship of the muscle with surface landmarks and developed figures showing the approximated end plate zones (Fig.14.15.16.17.18). Their work enables the clinician working with children to extrapolate the maps to patients of varying sizes. (80)

Figure 16:Gastrocnemius muscle (muscle belly; proximal, up; distal, down; no markings were made by Christensen about left–right or medial–lateral) after cholinesterase staining. Dots represent MEPs, according to Christensen

Figure 17: Optimal injection area for gastrocnemius muscle. Left leg, posterior (81)

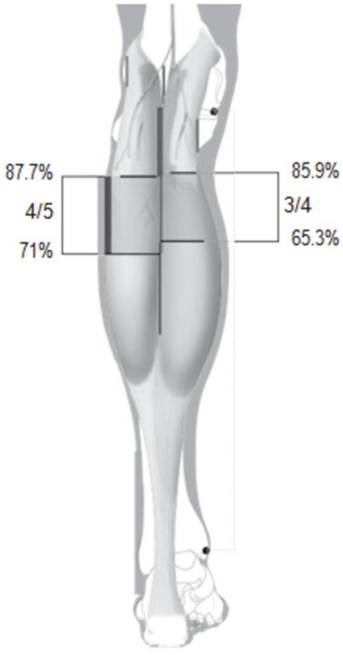

Figure 18: Gastrocnemius on a left leg, posterior view. MEP area according to Parratte et al.

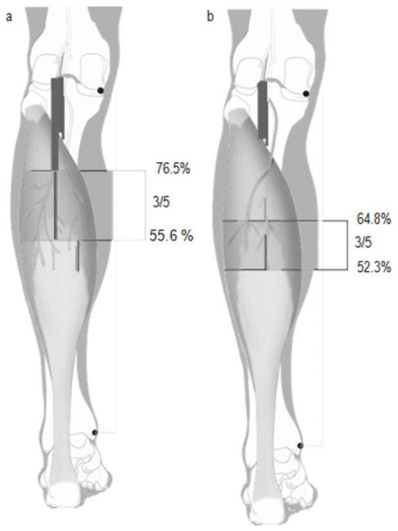

Figure 19: Soleus muscle on a left leg, posterior view.(a) Area innervated by the posterior branch from the tibialis nerve. (b) Area innervated by the anterior branch

Figure 20: Semitendinosus muscle (muscle belly; proximal, up; distal, down) after cholinesterase staining. Dots represent MEPs, according to Christensen.

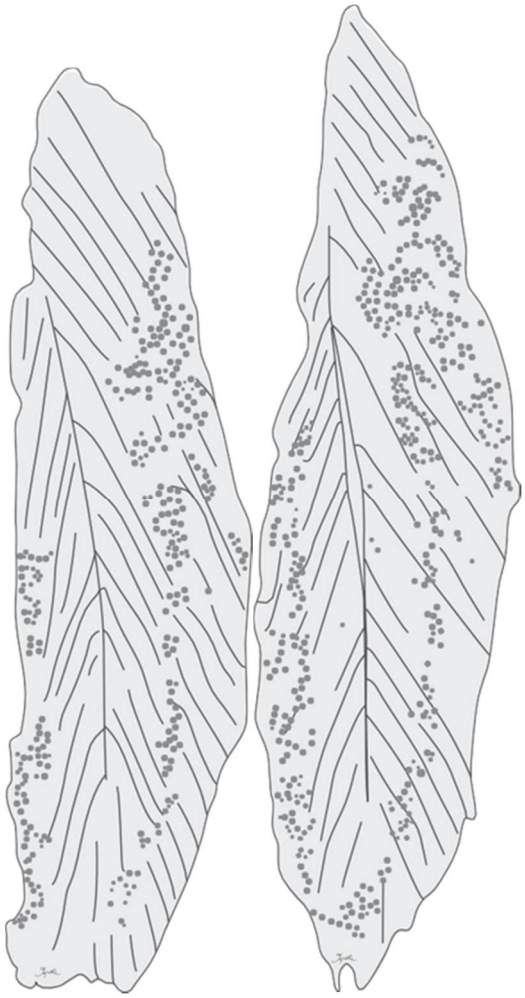

Figure 21: Rectus femoris muscle 2 (two different muscle bellies; proximal, up; distal, down) after cholinesterase staining. Dots represent MEPs, according to Christensen.

6.2. Involved muscles, doses and number of injection sites

6.2.1. Involved muscles

In the lower limb, multilevel injections typically are directed to the spastic gastrocsoleus; sometimes the tibialis posterior if the posturing is equinovarus; the hamstrings; the hip adductors and hip flexors; and occasionally the rectus femoris when there is a stiff knee gait.

In the upper limb, muscles that are frequently involved are biceps, brachialis, adductor pollicis, flexor carpi ulnaris, flexor carpi radialis, pronator teres.focal treatment with BTXA alone is rarely indicated and it should usually be combined with a program of splinting and occupational therapy or upper limb training.

The muscles typically involved in each clinical pattern are indicated in Tables VIII and IX, along with guidelines for injection of BTXA as onabotulinumtoxinA (Botox, Allergan, Irvine, CA, USA).

6.2.2. Doses

Since the first report of Koman and colleagues (46) on BTXA treatment in children, using a total dosage of 1-2 U/kg, the amounts used at a single session have increased, doses over 16 U/kg now being frequently administered. There has been a corresponding increase in the amounts used in single muscles. This elevation is, however, less pronounced than in the total dose, which may reflect injection of more muscles per session. Guidelines for treating children have been published by groups under Russman (82) and Graham (83) based on the experience of experts in combination with research known at that time. Recently, the European Consensus Table (84) has been developed, the

maximum total amount being set at 400-600 U or 25 U/kg for BotoxR and 900 U or 15-25 U/kg for DysportR. Adult dosing recommendations are to be substituted for children heavier than 60 kg (84).

Lower limb: Russman and associates (82) proposed for the gastrocnemius (medial or lateral part) a dose of 3-6 U/kg (BotoxR). Likewise, Graham and colleagues (83) supported a dosage of 3-6 U/kg (BotoxR) for the lower limb, but the muscles in question are not specified. To this day, studies focusing on the effects of different doses in children are few.

Upper limb: Doses of 0.5-1 U/kg for the adductor pollicis, 1-2 U/kg for the forearm muscles and 2-3 U/kg for the arm muscles have been recommended (82, 83). Kawamura and colleagues (85) proposed dosage as follows: biceps 1 U/kg, brachioradialis/pronator teres 0.75 U/kg, finger/wrist flexors 1.5 U/kg, adductor/opponens pollicis 0.3 U/kg (max. 10U).

- **Number of injection sites: single or multiple site injection**

The number of injection sites per muscle may be determined by the morphology (and hence to the end plate zone configuration) of a given muscle. Borodic and associates (86) conducted a study to evaluate the single versus the multiple site injection of BTXA in adults with blepharospasm. The authors found significant better results with the multiple site technique. In another study, the multiple site injection strategy has proved its superiority to the single site injection strategy when treating adult spasmodic torticollis, (86) in terms of pain reduction, improvement in posture and range of motion, and improvement in activity endurance, but not in hypertrophy reduction or involuntary movements.

The number of injection sites may also vary according to the size of the muscle. In a small muscle (e.g. in the upper limb), the toxin presumably diffuses

well through the whole muscle and the risk of spread into adjacent muscles is increased with larger doses. In larger muscles (e.g. in lower limb or biceps brachii in the upper limb), larger doses may have to be used and dividing the dose along the assumed end plate zone might increase the effect.

In children, one or two injection sites in the adductors, the lateral hamstrings, soleus and each head of the gastrocnemius, and two to four sites in the medial hamstrings has been recommended (82,83). It has been shown that at a certain dose saturation of the NMJs occurs and a plateau is reached (84), which may allow spread of the toxin overflow into neighboring structures and the systemic circulation (82). It is recommended to split the volume into multiple sites in a given muscle in order to reduce unwanted spreading and adverse effects (82). Hence for children the recommendations suggest a maximum dose of 50 U of BotoxR, or a maximum volume of 0.5 ml (82,83) per injection site. In practice, the number of injection sites used may also depend on other factors such as the total number of muscles needing treatment and the availability of general anesthesia or sedation (83). However, no studies have been published specifically evaluating the single or multiple site injection technique and the related incidence of side-effects in children.

Tableau VIII: involved muscles of the upper limb and dosing guidelines.(87)

Clinical pattern	Potential muscles	Onabotulinum toxin A		Abobotulinum toxin A	
		Dosing U/Kg bodyweight	Number of injection sites	Dosing U/Kg bodyweight	Number of injection sites
Internally rotated shoulder	Pectoralis complex	2	2-3	5-10	2-3
	Latissimus dorsi	2	2	5-10	2
	Teres major	2	1-2	5-10	1-2
	Subscapularis	1-2	1-2	5	1-2
Flexed elbow	Brachioradialis	1	1	5-10	1
	Biceps	2	2	5-10	2
	Brachialis	2	1-2	5-10	1-2
Pronation	Pronator quadrates	0.5-1	1	5	1
	Pronator teres	1	1	5-10	1
Wrist flexion	Flexor carpi ulnaris	1-2	1	5-10	1
	Flexor carpi radialis	1-2	1	5-10	1
Thumb in palm	Flexor pollicis longus	0.5-1	1	5	1
	Flexor pollicis brevis				
	Adductor pollicis	0.5-1	1	5	1
		0.5-1	1	5	1
Clenched fist	Flexor digitorum superficialis	1-2	1-2	5-10	1-2
	Flexor digitorum profundus	1-2	1-2	5-10	1-2
Intrinsic hand muscles	Lumbricals/interossei	0.5-1	1	5	1

Tableau IX: Involved muscles of lower limb and dosing guidelines (87)

Clinical pattern	Potential muscles	Onabotulinum toxin A		Abobotulinum toxin A	
		Dosing U/Kg bodyweight	Number of injection sites	Dosing U/Kg bodyweight	Number of injection sites
Hip flexion	Iliacus Rectus femoris Psoas	1–2 1–2 2–3	1 2 2	3-15/muscle group 3–15/muscle group 3–15/muscle group	1 1 2
Knee flexion	Medial hamstrings Lateral hamstrings Gastrocnemius	3–6 2–3 3–6	3–4 2–3 3–6	3–15/muscle group 3–15/muscle group 3–15/muscle group	3–4 2–3 3–6
Scissoring adduction	Adductor group	3–6	1–2	3–15/muscle group	1–2
Extended knee	Quadriceps	3–6	3–4	0.03–15/muscle group	3–4
Equinovarus foot	Gastrocnemius medial/ lateral Soleus Tibialis posterior Flexor digitorum longus/ brevis Flexor hallucis longus	3–6 2–3 1–2 1–2 1–2	2–4 1–2 1 1 1	3–15/muscle group 3–15/muscle group 3–15/muscle group 3/muscle group 3/muscle group	2–4 1–2 1 1
Striatal foot	Extensor hallucis longus	1-2	1	1-3	1

7. Techniques of localizing muscles and motor enplate zones

Since the NMJs in the muscles are the sites of BTXA action, targeting the right muscle and close to the motor end plates is considered essential. Localization techniques have evolved over time, but each technique has its own limitation in locating the motor end plates. Injection methods may also be determined by a number of other factors such as the patient's age and diagnosis, the anatomic site (accessibility) of the target muscle, and the training and preferences of the treating clinician.

There are several localization techniques available to physicians that allow for identification of the selected muscles. These methods include anatomic localization in isolation or in conjunction with EMG guidance, electrical stimulation (ES) guidance, or ultrasound guidance. There are also other less frequently used localization techniques including fluoroscopy, CT, and endoscopic guidance.

It is important to note that the overall outcome following treatment relies heavily on the experience of the physician in muscle selection. Recognizing patterns of spasticity and a thorough understanding of the function and action of each of the involved muscles increases the likelihood of appropriate muscle selection by the experienced physician. It is important to consider that the patient may be utilizing some spasticity for functional activities, such as assisting with standing or transfers. Identifying appropriate muscles requires clear treatment goals and a comprehensive physical examination, including passive and active range of motion, motor testing, evaluation of degree of muscle tone using the Ashworth or Modified Ashworth scales, and observation of antagonist muscle co-contraction.

-Anatomic Localization

Of all of the available localization techniques, anatomic localization is the simplest and does not require equipment. When using anatomic localization, the physician identifies bony landmarks and uses palpation to identify the target muscles. The anatomic landmarks provide the general location for the injection, however it is crucial that the physician have a good understanding of the three dimensional anatomical positioning of the target muscle and surrounding muscles, as the potential exists to inadvertently inject an adjacent muscle. The likelihood of this error may be decreased by using other maneuvers and indirect signs to assist with verifying location. Prior to injection the physician may palpate hypertrophied spastic muscles, and in patients who are unable to voluntarily activate the target muscle, the physician may perform a passive movement that will initiate a stretch on the target muscle that will be palpated by the physician as movement in the target muscle belly. Once the needle is inserted into the target muscle, the passive motion may be repeated and the physician may feel a tug on the needle or see movement in the needle during passive range of motion of the affected joint/limb.(88) For patients who have the ability to voluntarily contract their muscles, the same effect can be accomplished by asking the patient to perform the movement that will result in contraction of the target muscle prior to and after needle insertion.

There are several advantages surrounding the use of anatomic localization. The most obvious advantage is that no equipment is required. The physician will also be able to use a small gauge needle to complete the injection rather than the larger gauge insulated needles required with EMG or ES; the use of the smaller needle may cause less discomfort. Finally, this is a relatively quick method and involves less emotional stress, which may be preferable in children or those who fear needles.

Several disadvantages exist when using anatomic localization in isolation, rather than in conjunction with other injection techniques. Although large, superficial muscles may be easily identifiable using anatomic localization alone, other small, deeper muscles may not be as easily identified. In addition, the muscle hypertrophy and/or atrophy that can occur in patients with spasticity can potentially alter the anatomic location of the motor endplate and the muscle itself, making targeting challenging. Achieving ideal limb positioning for injections can be difficult in individuals with spasticity, and many patients cannot be positioned as demonstrated in the standard texts. If inappropriate muscles are inadvertently injected due to suboptimal localization, patients may experience unexpected weakness and inadequate relief of spasticity in the muscles that were being targeted.

-Electromyography Guidance

EMG guidance is often used to more precisely identify spastic muscles. This technique requires use of an EMG auditory signal amplifier or an EMG machine, and a hollow insulated monopolar needle electrode. When identifying target muscles, the physician will initially use anatomic localization and then use EMG guidance. Once the EMG needle electrode is advanced into spastic muscle the physician will hear the involuntary motor unit action potentials (MUAPs) which may initially have a dull muffled sound, but will become sharper as the needle is advanced closer to the end plate. For physicians who use an EMG machine rather than an EMG amplifier, the MUAPs can be visualized in addition to the auditory feedback provided by the amplifier unit. The physician may then utilize various secondary techniques to ensure that the needle is indeed within the target muscle. If the patient has voluntary control over the muscle

being targeted, the physician can ask the patient to activate that muscle and listen for increased firing of MUAPs. Alternatively, if the patient is unable to voluntarily contract the muscle, then the physician may perform passive range of motion to initiate a stretch on the target muscle, which will result in depolarization bursts due to reflex spastic motor unit recruitment. (89,90) For example, if the physician is targeting the Flexor Digitorum Superficialis (FDS) the fingers may be passively extended with a resultant burst of increased MUAP activity.

Several advantages exist with the use of EMG guidance. This is a technique that is widely available and familiar to many physicians who use BTXA for treatment of spasticity. An auditory EMG device is inexpensive, and provides a mechanism for more precisely localizing appropriate target muscles. For example, if a patient present elbow flexor spasticity and the physician is trying to determine which of the elbow flexors is most involved, the physician may choose to evaluate each of the muscles responsible for elbow flexion using EMG guidance, and then choose to target the muscles for injection that demonstrate the most activity on EMG evaluation. In addition to assisting the physician with choosing target muscles, the EMG guidance will also allow the physician to target the delivery of the BTXA near the motor endplate of the muscle or in the area of a high concentration of active MUAPs, both of which may increase the uptake of BTXA into the nerve terminal. (91, 92)

There are potential disadvantages associated with the use of EMG guidance. Although EMG guidance will allow the physician to identify spastic muscle by locating areas with increased frequency and intensity of MUAPs, this technique does not guarantee that the needle is in the target muscle. If the needle

is not in the target muscle the physician may inadvertently inject into a muscle that while spastic, may not be appropriate for injection. Secondary techniques, such as voluntary activation and passive range of motion as described above, are utilized to decrease this risk; however for deeper or overlapping muscles there may be a higher probability for misplacement of the needle. In addition, localizing the motor endplate may take extra time compared to using anatomic guidance in isolation, and this is often painful once located. Because of these reasons this technique may not be ideal in some patient populations who have a low threshold for pain, including young children. Other potential disadvantages of this technique are the cost of the insulated EMG needle, as well as the cost of the EMG amplifier or machine.

- Electrical Stimulation:

ES is another popular option for muscle localization. In this procedure a hollow insulated monopolar needle is connected to a portable ES machine; alternately the stimulation mode on an EMG machine can be used. The approximate location of the target muscle is determined using standard anatomic landmarks as described above. Once the needle electrode is positioned in the target muscle, ES is delivered through the needle electrode to the muscle. Typically, a 5 mAmp stimulus at 1 Hertz intervals produces muscle contraction. For example, if the physician is targeting the FDS he/she will be expecting flexion of the proximal interphalangeal (PIP) joints; if instead the physician observes wrist flexion indicating that the needle electrode is in the flexor carpi radialis, he/she will know that the needle electrode needs to be repositioned until the appropriate muscle activity (flexion at the PIPs in this case) is achieved. Once the appropriate muscle contraction is obtained, the physician will typically

try to maintain a robust contraction while slowly decreasing the intensity of stimulation, and making discreet adjustments to the needle electrode as needed. If the physician is able to maintain muscle contraction at low stimulus intensity, such as a 1 mAmp, the physician can be relatively certain that the tip of the needle electrode is in proximity to the motor endplate. One major advantage of this technique is the accuracy of localization. The visual feedback of appropriate muscle contraction confirms that the needle electrode is likely in the target muscle, especially when muscle contraction is obtained at low intensity stimulation. The more precise targeting, specifically when using lower intensity stimulation with maintenance of appropriate muscle contraction, may allow lower doses of BTXA to be utilized and reduce costs (93,94) Although there are definite benefits to using ES for localizing target muscles, there are negative aspects as well. This technique may be more time consuming and require more training than the above mentioned techniques. In addition, this technique may be more uncomfortable to the patient given the increased amount of time the needle electrode remains within the muscle, as well as the discomfort from the ES that is delivered to the muscle. Contraction of individual muscles may be difficult to assess in patients with severe spasticity and limited range of motion. Finally, as with the use of EMG guidance, the cost of the needle electrode and ES device must be considered.

-Ultrasound Guidance

Ultrasound (US) has been used for many years for various diagnostic and therapeutic applications, however in recent years US has been more frequently used for musculoskeletal procedural guidance. Schiano et al were the first ones that reported use of US to guide BTXA injections for the treatment of achalasia.

(95) Since that time the advantages of US in the use of BTXA injections have been recognized, and the use of this technique is becoming more widespread.

US images are produced using high frequency sound waves emitted by the transducer that penetrate the soft tissues, with a portion of the sound waves being reflected back to the transducer. Transducers are available in high and low frequencies, with higher frequency transducers being used for evaluation of more superficial structures at a high resolution; lower frequency transducers can be used to assess deeper structures, however the resolution is of a lower quality than that seen with the higher frequency transducers. Individuals using US guidance for BTXA injections are able to recognize the various structures (bone, nerves, tendons, and muscles) based upon echogenicity of the structures, and they are able to readily identify the location of the target structures based upon cross-sectional images produced by the machine through experience and pattern recognition.

There are several potential advantages to using US guidance for BTXA injections. This technique allows real-time visualization of needle advancement into target structures. This not only allows the physician to avoid penetrating certain structures, including blood vessels and nerves, but may also allow more precise identification of target muscles. The physician who is experienced with the use of US guidance will recognize the cross sectional anatomy that is displayed on the monitor, and will be able to visualize the needle tip advancing into the appropriate target muscle. The physician may also use secondary techniques to verify correct placement; while the needle is in the target muscle the physician is able to ask the patient to activate that muscle, or if the patient is unable to voluntarily contract the muscle the physician may passively range the

joint to cause movement of the target muscle. This active or passive movement of the target muscle can be directly visualized on the US display. In addition, this technique can provide visualization and identification of specific fascicles of target muscles. For example, if a patient has significant spasticity in the FDS to digits 2 and 3, the physician may choose to target the fascicles of FDS to only those digits, and may use the above measures of active or passive movement to appropriately identify and target these fascicles. (96)

Other potential benefits of US guidance include the ability to correctly target complex or overlapping muscles and more easily identify muscles that have significant degrees of atrophy. This procedure is relatively quick and may result in less pain, as a smaller gauge needle may be used if US guidance is being used in isolation without EMG or ES. (97) Another potential benefit mentioned by physicians who utilize this modality is that the ability to visualize the procedure on the screen may distract the patient from the discomfort of the actual procedure.

In addition to the ease and accuracy of localizing the target muscle, the use of US may help to reduce side effects, such as BTXA spread. With the use of US guidance, the physician has the ability to visualize the volume of the BTXA solution being injected in real time; if it appears that there is too much volume being injected into one area of the muscle the physician can relocate the needle tip to a different area within the target muscle to complete the injection and avoid spread to contiguous muscles. (e.g the psoas muscle injections require obligatory guidance (fig.20)

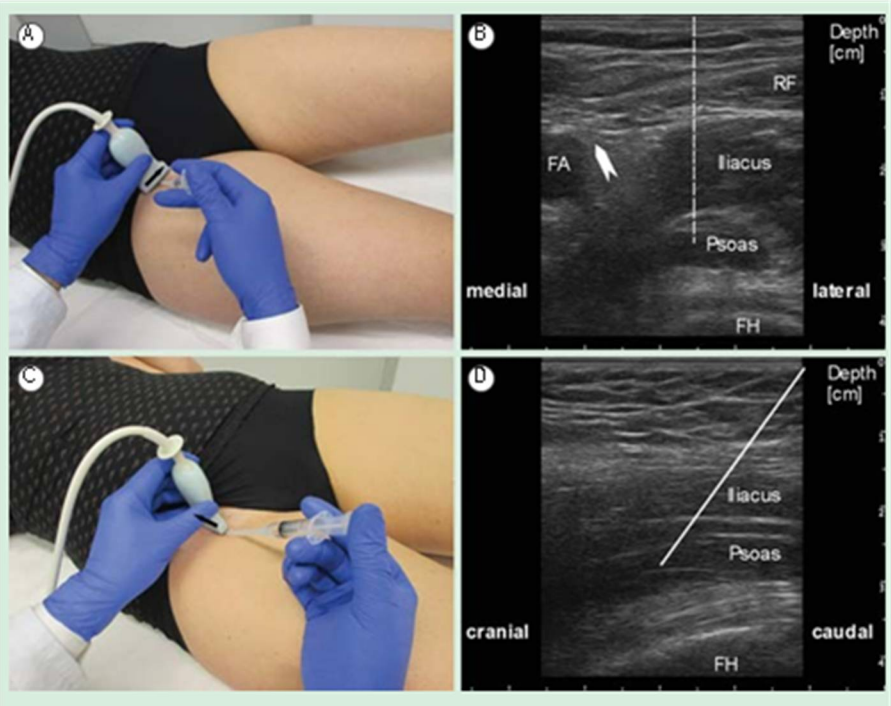

Figure 22: US of the inguinal region for guiding BT injection into the psoas muscle. (A) Position of ultrasound transducer and syringe (off-plane injection technique). The arrow indicates the orientation of the transducer (arrowhead corresponding to the left side of US image shown in (B)). (B) US image 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.(98)

Recently, Kaymak et al studied ultrasound guided botulinum toxin injections, the research included a brief explanation regarding the ultrasound injection technique used with commonly injected muscles of the upper limb, the lower limb and pelvic girdle mainly in spasticity. (figs 21.22.23) (99,100)

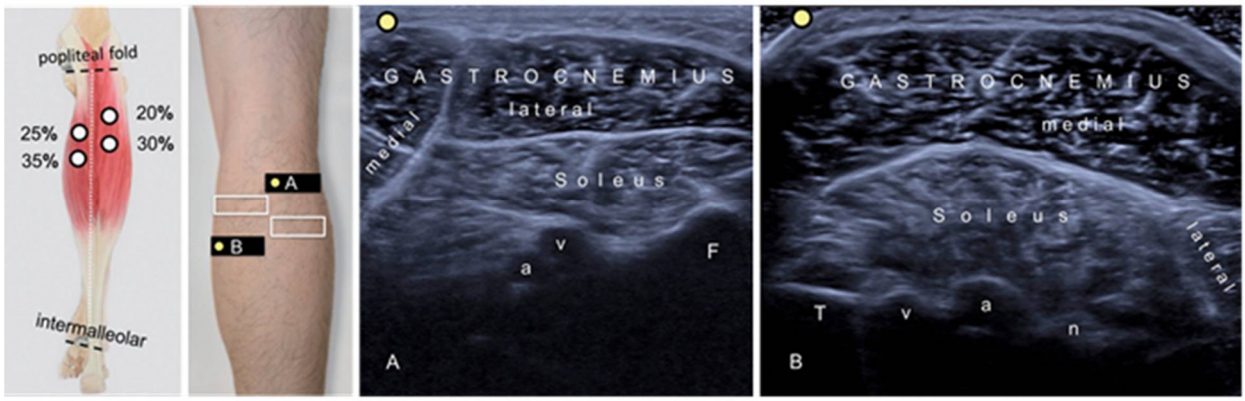

Figure 23: Gastrocnemius muscle. T :tibia F: fibula ; v : vein ; n :tibial nerve

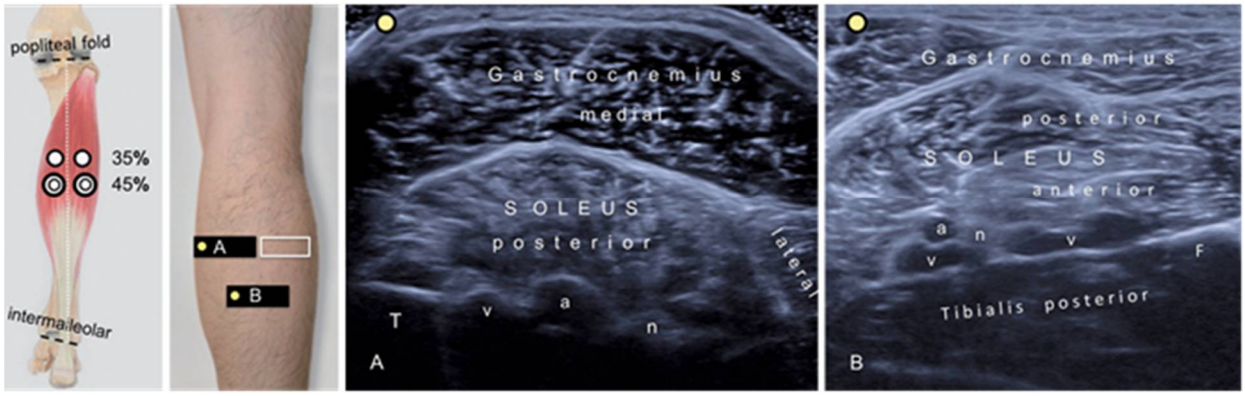

Figure 24: soleus muscle. Circles at 45% level show the injection points for anterior and posterior parts of the soleus muscle. F:fibula; v: vein; a:artery .

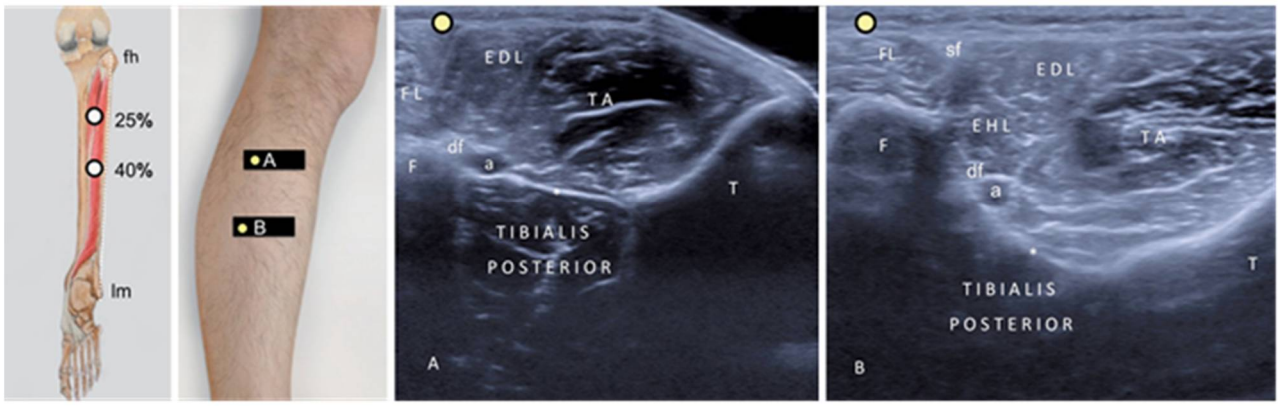

Figure 25: Tibialis posterior muscle . FL : fibularis longus ; EDL : extensor digitorum longus ; EHL : extensor hallucis longus ; T :tibia ; F :fibula, fh :fibular head ; lm :lateral malleolus ; df : deep fibular nerve ; sf :superficial fibular nerve

Although physicians who routinely use US guidance for BTXA injections consider this modality the most accurate for targeting muscles, there are certainly drawbacks to using this technique. First and foremost, this is a technique that is operator dependent and requires a significant amount of practice to become proficient in its use. Simultaneous operation of the US transducer and the syringe may require the presence of an assistant, especially for the beginners. Physicians using US guidance report that it takes repetition before becoming reliable with this technique alone.

-Less Commonly Used Techniques:

There are other techniques that are less frequently used by most physicians, including guidance with fluoroscopy, computerized tomography (CT), cystoscopy, or endoscopy. Fluoroscopy and CT guidance techniques are typically used for deeper, difficult to isolate muscles, such as the iliopsoas or piriformis muscles. Endoscopy and cystoscopy guided BTXA injections are

techniques used by specialists treating disorders such as achalasia, spasmodic dysphonia, and neurogenic bladder.

7.1. Indications for botulinum toxin in children with CP

Botulinum A toxin (BOTOX®) is approved for use in CP in 49 countries. Although BOTOX® is not FDA-approved for use in pediatric patients with CP in the US, it is utilized for the management of dynamic deformity in children and adults with CP, with payment for its use by the majority of insurance carriers. Dysport® is available and approved for the management of equinus gait in CP in the UK, many European countries, and some Commonwealth countries.

The use of botulinum A toxin is approved for the following general indications in selected patients: (i) to improve function in patients with dynamic deformity; (ii) to improve health-related quality of life in children with excessive deformity and/or painful spasticity; and (iii) to potentiate or replace other treatment modalities. The specific use of botulinum A toxin injections has been reported or suggested for equinus gait, crouched gait, knee flexion deformity, scissoring, varus hindfoot, knee extension during swing phase, shoulder deformity, elbow flexion deformity, wrist flexion deformity, finger flexion deformity, thumb-in-palm, excessive pronation, painful spasticity, movement disorders (athetosis and dystonia), enhancement of neuromuscular electrical stimulation, facilitation and/or reduction of specific caregiver functions, decreased postoperative pain, alleviation of painful spasticity, and improvement in self-esteem due to decreasing reflex posturing.(101)

The use of botulinum A toxin in the upper extremity has been approved in many studies. (102-104). This studies have set indications for upper extremity botulinum A toxin injections as follows: (i) thumb-in-palm; (ii) wrist flexion;

(iii) forearm pronation; (iv) elbow flexion; and (v) shoulder internal rotation and/or adduction. Injections reliably decreased muscle power and spasticity, and patients demonstrated selective improvements in appearance, function, and caregiving.

7.2. Post-injection assessment and monitoring

At each follow-up visit, patients should be evaluated using the same physical examination used before the toxin injection. In addition, ambulatory patients may be followed using motion analysis performed before and after the injections. Parents/caregivers also complete health-related quality of life questionnaires in order to monitor the effects of the toxin injections from their perspective. Parents/caregivers are instructed to call immediately if they notice any adverse events following their child's toxin injection. In addition, at each follow-up visit parents are asked to describe any adverse events they may have noted following their child's most recent injection. Although most patients do not report adverse events, the most commonly reported adverse event is soreness of the injected muscle.

7.3. Goals of Botulinum toxin therapy in the management of spasticity

It is vital to define the goals of treatment, in consultation with the patient and the caregiver, in a multidisciplinary environment before treatment with BTXA therapy begins. BTXA treatment goals are discussed with the patients' parents/caregivers before injections are administered. The overall goals for upper and lower extremity injections include reduced pain, improved function, improved self-esteem, improved ease of caregiving, and facilitation of hygiene. Specific goals also are identified (table X).

Tableau X: Common goals for BTXA injections

Improved function	Prevention of musculoskeletal complications
- Mobility - transfers - seating and positioning - balance - wheelchair management and mobility - sexuality - energy demand reduction - Increased ease of care - dressing - feeding - hygiene and bathing - positioning increased comfort - pain reduction - Sleep improvement - orthosis fit improvement	- prevention of contractures - increased efficacy and reduced need for casting - prevention of spasm - prevention of subluxation - pressure sore reduction - improved body image

8. Botulinum toxin type A: part of an integrated approach

An essential component of any BTXA treatment concept is the multimodal treatment approach, which may include physiotherapy or orthoses, among the range of other treatments. When relevant, patient-centered goals have been set and BTXA treatment is potentially indicated based on severity and age, the place

of BTXA within the integrated treatment should be assessed, since the timing of other treatments will influence the timing of BTXA treatment.

The integration of BTXA treatment with other therapies can be illustrated with some of the examples below. Many treatment combinations may be indicated.

8.1. Botulinum toxin injections combined with physiotherapy

Physical therapy program after BTXA still remains central to treatment. It has been suggested that targeted motor training may prolong the effect of botulinum toxin type a most studies recommend physical therapy after botulinum toxin type a. however the most effective physical therapy program is unknown. Intensive physical therapy treatment is currently the standard for management of spasticity after botulinum toxin injections in cerebral palsy children in the hope of providing improved long term benefit.(105)(see appendix)

8.2. Botulinum toxin type A combined with electrical stimulation

We found 2 protocols in the literature among studies but there were inconsistencies about the preferred protocol. The first protocol (106,107) used electrical stimulation in the gastrocnemius muscles after BTX injection in the triceps surae versus BTX alone. Different modalities of stimulation exist in terms of type of current (continuous or rectangular biphasic, high or low frequency), duration (15 to 30 min) and frequency of application (1–6 times/day for 3 days to 6 weeks). The second protocol (108,109) consisted of functional electrical stimulation in antagonist muscles after BTX injection in the wrist and finger flexors (108) and in the triceps surae (109) associated with a physical therapy programme.

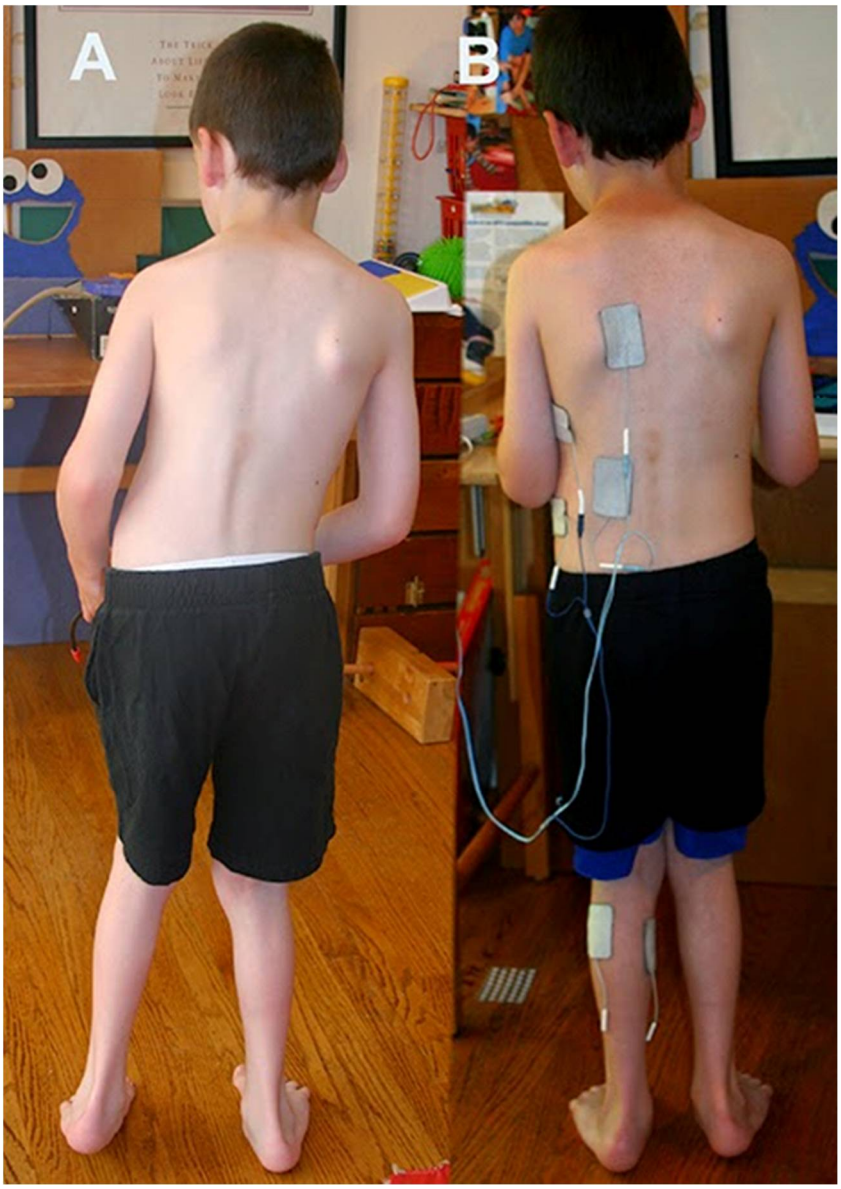

Figure 26: Photo A (below) on the right shows the child's standing posture without ES. Before ES was used he stood with the upper body leading to the right and the hips to the left with more weight on the toes than the heels and the knees closer together than the feet. The hips knees and ankles are not aligned and the right shoulder is lower than the left.

Photo B shows him standing at the end of his PT session as ES continues to stimulate the trunk. The child's hips and upper trunk are better aligned, the feet ar closer tougher, the knees more over the ankles and the weight shifted back more on the whole foot not just the left toes. (110)

8.3. botulinum toxin Type A combined with extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) is a physical therapy that has been proposed to improve the treatment of people with spasticity, it has been found to effectively reduce muscle spasticity in children with CP due to its purported neuromodulatory and rheological effects (111- 115). Recently, ESWT was demonstrated to increase the positive effects of botulinum toxin type A in reducing upper limb spasticity.(111-115)

For children with spastic, it is plausible that combining ESWT and BTXA therapy could be useful to increase their effects on spastic muscles, since the two therapies have different mechanisms of action. To date only one previous study on adults with post-stroke spasticity has investigated the combined effects of BTXA and ESWT. (116)

Figure 27: Application of radial extracorporeal shock waves (rESWs) on the gastrocnemius muscle (lateral head) of a 12-month-old patient suffering from cerebral palsy (note that rESWs were evenly distributed over the gastrocnemius and soleus muscles). The applicator of the handpiece (asterisk) of the rESW device is coupled with ultrasound gel to the skin directly over the spastic muscle (arrow). (117)

8.3.1. Orthoses

There are limited data on the benefits of combining BTXA therapy with orthoses (118), and one study has suggested that orthoses may not be as beneficial as casting when used as part of multimodal treatment involving BTXA therapy (119). Reduced muscle tone may be best treated with stabilising orthoses. A splint is a removable device designed to support weak and

ineffective joints or muscles (120). For managing spasticity, splinting is mainly based on 2 approaches: the biomechanical approach, which aims to prevent deformity by aligning, mobilizing and stabilizing joints, and the neurophysiological approach, which aims to reduce spasticity by sustained stretch and reflex-inhibiting positions (121). Orthoses are orthopedic devices aimed to replace or substitute for the loss of muscle function; to correct, compensate or prevent abnormal postures or deformities; and to aid movements of an injured limb. Orthoses are often used in conjunction with other interventions such as physical therapy and/or BTXA treatment (118). The literature is sparse on the use of splinting and orthoses as adjuvant treatment to BTXA injection in patients with spasticity.

8.3.2. Casting

For managing spasticity, casting should be considered in order to reduce excitatory input of muscle spindles, preventing changes in muscle length and reducing contractures (120). Casting is usually applied to the affected (upper or lower) limb to immobilize it in a predetermined position with molded casts made of plasters or tape materials (122). In addition, serial casting allows for progressively increasing the angle of stretch in order to improve ROM by changing passive mechanical properties of the muscle and increasing the number of sarcomeres (120-122). It has been proposed as adjuvant treatment after BTXA injection in children with cerebral palsy and adults with acquired brain injury. In particular, for children with cerebral palsy, delayed serial casting after BTXA injection compared to immediate serial casting had a significantly better effect on spasticity at 3 and 6 months after treatment in a pilot study of 12 children (123).

8.3.3. Orthopedic surgery

Orthopaedic surgery has an important role in the treatment of the musculoskeletal deformities and contractures present in the child with CP. The widely accepted principle is the single event multi-level surgery. One of the roles of BTXA therapy is to avoid multiple operations in order not to weaken muscles excessively and to protect children from multiple admissions in hospital. The challenge is to time the surgery correctly for the individual child in order to avoid going back. Perioperative BTXA injections may help to reduce spasticity-induced post-operative pain and to ease the rehabilitation process. BTXA injection may also help to confirm surgical indications: if the patient deteriorates functionally after injecting the target muscles, any planned surgery to these muscles should be approached with caution (123).SDR may reduce spasticity in selected individuals. There is a role for BTXA therapy in the long-term follow-up of SDR in many children (125).

8.3.4. Health-Related Quality of Life of children with CP

The impact of botulinum A toxin on the health-related quality of life(QoL) of children and their caregivers is as important as the clinical effects of botulinum toxin. There are several instruments available to assess QoL of children with CP. Two well established and often used instruments are the Child Health Questionnaire (CHQ) and the KIDSCREEN. (126,127)

The Cerebral Palsy Quality of Life for Children (CP QOL-Child) is the first health condition-specific questionnaire designed for measuring QOL in children with cerebral palsy. This questionnaire is useful for evaluating interventions designed to improve the lives of children and adolescents. The CP QOL - Child was first designed to assess the QOL of children with cerebral palsy aged 4-12

years and an adolescent version, the CP QOL – Teen has recently been developed for adolescents aged 13-18 years. The questionnaires have been designed by Australian and international researchers in collaboration with many children and adolescents with cerebral palsy and their parents.(128,129)

Third chapter: Effectiveness of botulinum toxin injections in the management of spasticity in children with CP

1. Outcomes of BTXA injections in children with spastic CP

In the past 2 decades, numerous trials have assessed the effectiveness of BTXA injections on motor function in children with CP. (130-137) While several studies found statistically significant beneficial effects (130,132,135,137) others failed to demonstrate benefits.(133,134)

In 2010, a Cochrane systematic review assessed the effectiveness of BTXA alone or in combination with occupational therapy for upper-limb treatment in children with CP. Ten randomized controlled trials (RCTs) were included. An analysis of data showed that a combination of BTXA and occupational therapy is more effective than occupational therapy alone in reducing impairment and improving activity-level outcomes, but not for improving quality of life or perceived self-competence. When BTXA was used alone there was moderate evidence that it was not effective. (131)

Several systematic reviews also analyzed the effectiveness of BTXA therapy in the management of lower-limb spasticity and gait in children with CP.(132-134) In 2001, Boyd and Hays (132) summarized results of 10 RCTs and found evidence for a moderate, dose-dependent treatment effect of BTXA on gait and lower-limb function. Koog and Min (133) reviewed 15 RCTs and reported less-favourable results. When botulinum injection was compared with a non-sham control, it was effective in improving muscle tone, ankle range of motion, gross motor function, and gait speed; however, when sham injection was used as control, botulinum injection had affected gross motor function only when measured after 4 months. Koog and Min (133) suggested that BTXA might not be as effective as commonly believed and might be overprescribed for CP patients. Recently, Ryll et al (134) systematically reviewed 8 RCTs in order

to assess treatment effects of BTXA on gait of children with CP. When compared with physiotherapy alone, adding BTXA treatment had a moderate positive effect after 2 to 24 weeks of follow-up. This effect was not demonstrated when BTXA treatment was compared with casting alone.

In another recent studies (138-140), BoNT-A injection is proved to be a treatment method that effectively reduces focal spasticity. It should be kept in mind that whichever method is applied to reduce spasticity, rehabilitation therapy is essential, and the functionality of the obtained relaxation depends on the rehabilitation work.

2. Impact of the injection technique

Studies have shown that the use of localization techniques such as EMG, ES, or US guidance in addition to anatomic localization would improve accuracy of identification of target muscles. In addition to this studies, others have demonstrated the superiority of each modality over anatomic guidance in isolation, however we still lack of studies investigating clinical outcomes achieved with each different technique independently.

Several studies have evaluated the accuracy of needle placement by using anatomic landmarks and palpation in isolation compared to the use of other guidance techniques.

First, the accuracy of anatomic localization using dissection was evaluated by Schnitzler and colleagues in the medial and lateral gastrocnemius muscle of cadaver limbs as performed by physicians, including Physiatrists and “Medical Specialists.” (141) Following insertion of the needle into the muscle, the physicians injected 1.5 ml of ink into the muscle. The cadaver limbs were

dissected by an orthopedic surgeon and an anatomist to determine if the injection was into the target muscle. The results showed that only 43% of injections were successfully place into the appropriate muscle belly, with 37% of injections being too deep and actually in the soleus muscle, and nearly 20% were too superficial. In another study, Yang and colleagues evaluated the accuracy of needle placement using anatomic localization in children with spastic cerebral palsy (CP), the children underwent injections into the gastrocnemius muscles. (142) The authors found that the needle was placed accurately into the gastrocnemius muscle in 78.7% of cases, with the highest accuracy being with needle insertion in the medial gastrocnemius (92.6%) and the lowest accuracy in the lateral gastrocnemius (64.7%). These investigators reported that the lateral portion of the gastrocnemius was thinner than the medial gastrocnemius, resulting in a higher rate of misplaced needle. (141)

2.1. Anatomic Localization versus Ultrasound:

Boon and colleagues investigated the accuracy of anatomic localization compared to US guided localization in cadaver limbs. (143) This study had the particularity that the two investigators had different training levels (one experienced attending physician and the other a resident in PMR). Overall these investigators reported a 39% accuracy rate using the anatomic guidance method, compared to a 96% accuracy rate with ultrasound guidance. When accounting for level of experience on placing the wire into the correct muscle or just deep to that muscle (indicating correct trajectory of insertion), it was noted that the experienced physician had an accuracy rate of 82% when performing non-guided placements compared to a 50% accuracy rate in the resident physician. Another study included adult patients with upper extremity spasticity from

stroke or traumatic brain injury explored the accuracy of anatomic localization of upper limb muscles. (144) The measurements of the sites determined by US guidance were compared with the standard injection sites based upon the Delagi and Bickerton methods.(145,146) The findings of this study confirmed that there was a statistically significant difference between the proposed injection sites per Delagi and Bickerton methods and the actual optimal injections sites as determined using ultrasound guidance for the musles. Based on these findings, the investigators recommended the use of US guidance for muscle localization in children and adults with upper extremity spasticity.(143)

2.2. Anatomic Localization versus EMG Guidance:

Molloy and colleagues evaluated the accuracy of muscle localization in adults with focal upper extremity dystonia using anatomic guidance versus EMG guidance. (147) These investigators reported that without EMG guidance only 37% of needle placement attempts reached the target muscle, however they were verifying placement within the target muscle using EMG feedback rather than visual verification with ultrasound or CT as described in the previous studies. Although these findings are of great importance, we still lack of studies comparing anatomic localization and EMG guidance BTX a injections in children with CP.

2.3. Anatomic Localization versus Electrical Stimulation Guidance:

Chin and colleagues investigated the accuracy of needle placement within target muscles using anatomic guidance versus ES in children with cerebral palsy.(148) The investigators first inserted a Teflon-coated insulated needle into the target muscles using anatomic guidance and palpation of the muscle bellies, as well as passive muscle stretch to confirm needle placement. These

investigators determined that the accuracy of manual needle placement using anatomic guidance alone was 78% in the gastroc-soleus, 67% in the hip adductors, 46% in the medial hamstrings, 11% in the tibialis posterior, 62% in the biceps brachii, 35% in the adductor pollicis, 22% in the pronator teres, 16% in the flexor carpi ulnaris and 13% in the flexor carpi radialis. Based upon these results the investigators recommended that physicians injecting BoNT should consider the use of ES or other guidance techniques in all muscles except gastroc-soleus.(148)

In another study by Picelli and colleagues, the accuracy of needle placement using anatomic landmarks was compared to the needle placement with ES guidance. (149) In this study adult patients underwent BoNT injection into two sites at each head of the gastrocnemius muscle. The first group received injections with the use of anatomic localization in isolation, while the second group received injections with the use of ES guidance. The accuracy of needle placement, as well as muscle thickness at each site, was determined by ultrasound evaluation. Overall, the needle placement in the medial gastrocnemius was more accurate for both groups (92% accuracy) compared to needle placement in the lateral gastrocnemius (79% accuracy). Needle localization into the lateral gastrocnemius using ES guidance demonstrated significantly higher accuracy (87% accuracy) compared to anatomic localization alone (64% accuracy); however there was no significant difference between the accuracy of injections techniques in the medial gastrocnemius (88% accuracy for anatomic localization versus 92% accuracy for electrical stimulation guidance).(149)

In a recent study (150), ultrasound-guided botulinum toxin injection according to innervation zones of the muscles improved lower limb spasticity and motor functions in children with cerebral palsy. BoNT-A injections are commonly used in recent years for treatment of focal spasticity.

2.4. Impact of dose variations

Lower limb

Satila (151) evaluated the effect of individually adjusted doses in a clinical setting of treating equinus gait in CP children to compare between low and high doses of botulinum toxin. The results stated that the use of high doses did not bring better effects compared with lower doses, which was in accord with the hypothesis whereby no better improvement in passive ROM and gait pattern is to be obtained with doses over 6 U/kg per gastrocnemius-soleus muscle.

in 2002, Polak and Baker (152) studied the results of both high and low doses in gastrocnemius muscle, they found most pronounced change in the muscle length with doses between 20 to 24 U/kg of DysportR. This corresponds to approximately 5 to 6 U/kg of BotoxR. In the studies in question the beneficial effect seemed to plateau or even decline with higher doses, only increasing the rate of adverse events. Further, Bakheit and colleagues (153) also noted that children receiving a moderate dose of BTXA (10 to 40 U/kg DysportR; approximately 2.5 to 10 U/kg of BotoxR) benefited the most, but that doses over 40 U/kg did not yield better results. The findings of this studies combined suggest that an optimum dose per muscle exists, after which the effect does not increase in a given muscle. Nevertheless, children may require relatively higher doses than adults. Ma and colleagues (154) studied the density, distribution and morphometry of NMJs in the biceps and gastrocnemius muscles of juvenile (1-

month-old) and adult (6-month-old) rats. They found that while the NMJs are of smaller size in juveniles their density within the muscle is higher than in adults (4 times greater in gastrocnemius and 2.6 times greater in biceps).

Upper limb

Corry and associates(155) studied the use of high doses corresponding to (4-7 U/kg BotoxR or 8-9 U/kg DysportR), they found minimal change in grasp-and-release and fine motor functions despite a reduction in muscle tone at elbow and wrist and an increase in elbow and thumb extension. Fehlings and colleagues (156) studied the effectiveness of low doses (2-6 U/kg BotoxR), they showed no significant difference between treatment and control groups in passive ROM, spasticity scores or grip strength, but on the other hand improvement in function as assessed by the QUEST and the Self Care Domain of the PEDI.

In 2007, Kawamura and colleagues compared high and low doses in the upper limbs of spastic CP children (100). The doses in the higher dosage group were twice those of the lower dose group. Their study showed no differences between treatment groups in MACS and grip strength. As a conclusion, the authors recommended the following doses: biceps brachii 1 U/kg, wrist/finger flexors 1.5 U/kg (as total), brachioradialis and pronator teres 0.75 U/kg and adductor/opponens pollicis 0.3 (total max. dose 10 U).

Impact of age

Spasticity most commonly develops within the first few years of life in children with CP. Therefore, BTXA treatment is recommended at 2 to 6 years of age, when gait patterns and motor function are still flexible. Desloovere et al

(135) demonstrated that BTXA injections delay and reduce the frequency of surgical procedures and result in a favourable gait pattern at 5 to 10 years of age. Similarly, Molenaers et al (130) reported that BTXA treatment can delay and reduce the need for surgery in the follow-up of children with CP, provided that the treatment is started while gait patterns are still flexible. A recent study (157) on children with CP treated with BTXA included children with a mean age of 6 years who were followed up for a year. Results demonstrated larger reduction in spasticity and better functional prognosis after BTXA injection in younger children. More recently, the authors found that the best clinical effectiveness was observed for children under 6 years old (53%) and over 12 (57%). They found an overall functional improvement in 24% of the children. The best results were obtained in the GMFM category E – ‘‘Walking, Running, and Jumping’’, with a global value of 34% and a value of 55% of functional improvement in the children under 6 years of age (Fig.26). These results were in agreement of the results of previous studies. That this effectiveness is also better in children over 12 than in children from 6 to 12 years old was more surprising. This can probably be explained by the fact that many of the children over 12 had already had musculo-tendinous surgical treatments in their lower limbs, which helped the practitioner target more precisely the muscles to be injected, with higher doses per muscles than those that could be injected with multi-site injections for which the total dose set by the AMM must be distributed among several muscles.

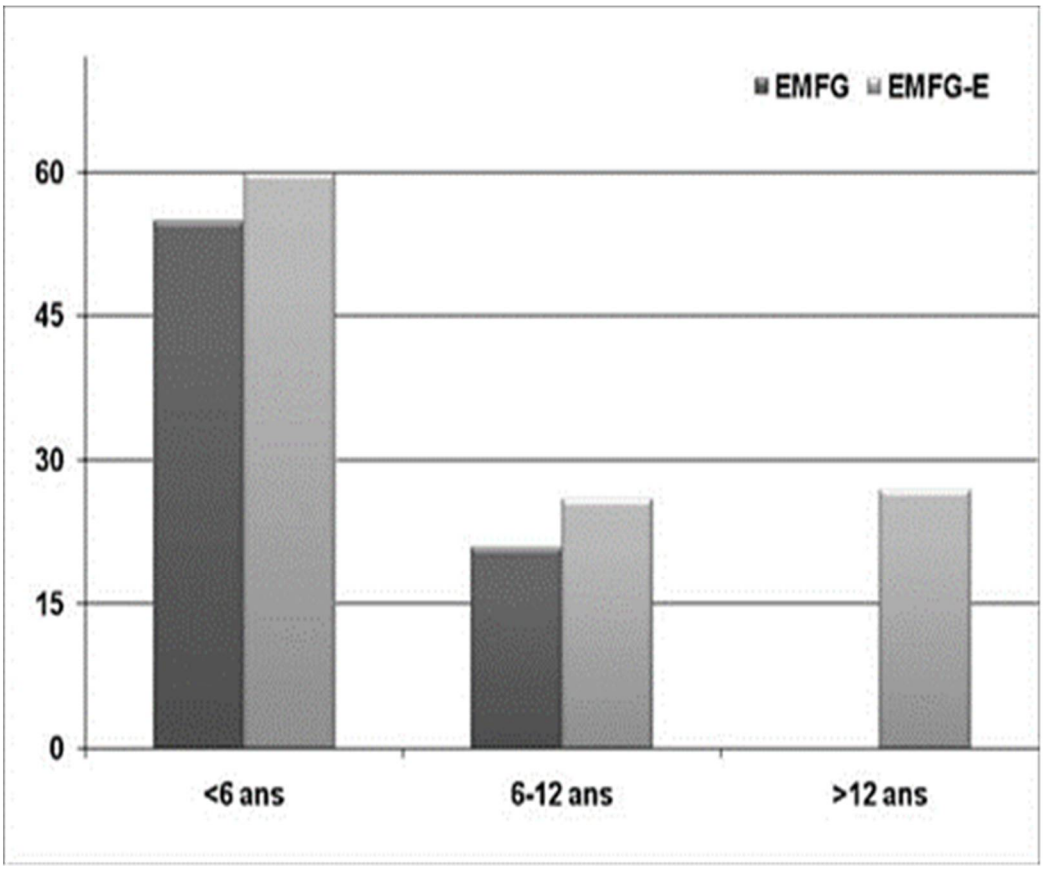

Figure 28: Effectiveness of botulinum toxin expressed by % of treated children, assessed by global EMFG-88 and category E (Walking, Running, and Jumping) among several age groups.(157)

Conclusion

This survey identified several areas influencing the effectiveness and outcomes of botulinum toxin injections in children. Each of these areas deserves attention and examination as these all have implications for the overall safety and clinical effectiveness of botulinum toxin injections in pediatric patients.

In these studies, the children were between 1 and 17 years. We found that the optimal time to treat spasticity with BTXA appears to be between 2 and 6 years to coincide with the child motor development and learning to walk. This can be explained by the fact that the fibrotic and retractile phenomena are less significant in young children, thus permitting the anti- spastic effect of the toxin to be revealed more easily. It also seems that motor development is greater during this period, so eliminating the problematic spasticity has a rapid influence on overall motricity.

As a whole in this review, we can conclude that the use of high doses did not bring better effects compared with lower doses, which is in accord with the hypothesis whereby no better improvement in passive ROM and gait pattern is to be obtained over 6U/kg per gastrocnemius –soleus muscle. This can be explained by the saturation of neuromuscular junctions and spread of the remaining toxin into adjacent muscles. The beneficial effect of BTX type A seems to plateau or even decline with high doses, leading to the increase of the rate of adverse events.

Based on the results of this survey, the majority of pediatric physiatrists are splitting the dose of onabotulinumtoxinA throughout the muscle with a much smaller percentage trying to avoid spread of the toxin overflow into neighbouring structures and the systemic circulation leading to serious adverse effects. The great majority of adverse events are mild, occur within 3-4 weeks

(by the first assessment), and are transient and resolve within a couple of weeks. Symptoms most frequently reported are leg pain or bruising, clumsiness, fatigue because of transient weakness, and flu-like symptoms. Incontinence may also be noted and it causes generally a major degree of parental anxiety but it resolves fully and quickly in all children. Although all this effects seem to be moderate, serious systemic adverse events can occur in 1 to 2 % of the children. All the studies suggest that high doses over 6 U/kg bodyweight are associated with increased odds of adverse effects. The risk of serious adverse effects is also interrelated with the GMFCS level and the presence of pre-existing medical comorbidities. It is difficult to interpret probable side-effects in more severely involved patients. This patient group is inclined to bulbar symptoms, pre-existing gastro-esophageal reflux and frequent infections such as pneumonia, and caution with BTXA treatments is recommended to protect them from potentially fatal adverse events.

There is no consensus about the technique used to define the BTXA injection site. In deep muscles, ultrasound, invasive electrical stimulation (ES) and needle electromyography (EMG) are used. Except for the latter, these techniques do not locate NMJ exactly. For superficial muscles, manual palpation and anatomical guidance are recommended. Ultrasound is more and more recognized as a useful and essential localization technique, it may lead to improved efficacy and safety of BTXA injections in children with CP and therefore help reducing the required dose of the medication. The main limitation of this technique is that it is operator dependent; it needs experience, training and access to the equipment. For the purpose of facilitating and perfecting US guided injections, we assembled information from recently published studies, in

the form of a sonographic guide including the most frequent clinical patterns and dosing guidelines for both onabotulinum toxin A and abobotulinum toxin A. As increasing numbers of physicians gain experience, training, and access to ultrasound for procedural guidance, the number of clinicians using ultrasound for BTXA therapy will clearly increase.

Ideally, BTXA injection must be associated with a specific, personalized rehabilitation program (adjunct therapies). A large heterogeneity of practices concerns adjunct therapies after BTXA injections to optimize the results. Although BTXA treatment is highly recommended to treat focal spasticity in children with CP (and by extrapolation to treat focal spasticity in children), no clear data are available to provide recommendations for the optimal adjunct therapies after such treatment.

Specific factors were found to be associated with lower quality of life in certain domains, e.g. pain is associated with less QoL in the physical and psychological well-being and self-perception domains. Greater limitations, on the other hand, lead to higher or lower QoL depending on the domain. However, impairment and pain can only explain a small amount of variance in QoL, which is therefore likely to be largely determined by social and environmental factors. Unfortunately, social and environmental factors can differ significantly between countries, and we can say that in our particular context, in Morocco, we still lack of CP institutions that can take care of these children and provide the best care for them and their caregivers.

There is no established surveillance program for children with CP generally or specifically children with CP having BTXA injections in our hospital, in order to reach that, we developed a simplified surveillance book for the child, to ensure the surveillance, evaluate the effectiveness of the injections, evaluate adverse events and present a source of data in further studies.

In conclusion, Treatment of spastic-movement disorders in children with CP requires an interdisciplinary team approach with a range of treatments. There is evidence that BTXA is effective in reducing spasticity and improving motor function. The correct choice of target muscles and the choice of the most accurate localization technique, are the key for an effective and successful injection. Prior to and following every injection, individualised assessment is essential, and should be part of an integrated approach that will support the achievement of motor milestones. To this end, goals should be set for each injection cycle and for the long-term. Detailed information describing expected functional improvements after treatment, must be communicated to families in useful, understandable terms to ensure that they enter into treatment with truly informed consent. For the parents, the high cost of this treatment represent a limitation for its use and implies to a restriction on the frequency of treatment.

It is important to know that long-term BTXA treatment cannot always prevent the development of secondary deformities such as lever-arm dysfunctions (due to underlying weakness, lack of good selective motor control etc.). These secondary problems can then be successfully addressed by orthopedic surgical corrections with good long-standing outcomes. In the management of children with cerebral palsy, BTXA treatment and surgical intervention can be viewed as complementary rather than mutually exclusive, and may be used concurrently or sequentially to increase the benefit.

Clinical implications and suggestions for further studies

Physicians who perform BTXA injections for spasticity management in their patient populations have several options for injection techniques as discussed above. Anatomic localization in isolation is likely to be the least accurate injection method in adults and children, as demonstrated by the aforementioned studies. EMG, ES, and US guidance are modalities that are available to physicians to accurately identify target muscles. With appropriate training and repeated use, a physician may develop the most accurate muscle targeting using ultrasound guidance with or without EMG and ES, as this modality allows for direct visualization of needle tip location. Equipment cost, however, and the steep learning curve required to become proficient in US technique may make this method less favorable to some physicians.

We found that there remains significant variability within pediatric physiatrists in many dimensions of this common procedure like doses, number of injection sites and the localization technique. As a result, patients and families likely experience significant practice variability of botulinum toxin injections among pediatric physiatrists.

This study highlights the need for additional research in the following areas: comparing outcomes of botulinum toxin injections in pediatrics by dosing, formulation, dilution, localization, as well as taking into consideration any adverse events and procedure tolerance. It is also important to identify the underlying factors influencing variability as well as the motivators that influence the decision regarding these variables. Future research in these areas are necessary to optimize practice and obtain the best outcomes for patients receiving neurotoxin injection.

Finally, since the approach to treating cerebral palsy is multidimensional and involves surgical and medical specialties, it is important to encourage scientific research in some promising fields such as stem cells therapy, it appears that stem cell therapy improves symptoms in patients with CP by helping motor development.

Résumés

Résumé

Titre: la toxine botulique (A) dans la prise en charge de la spasticité dans la paralysie cérébrale de l'enfant

Auteur: SERGHINI Niâma

Les mots clés: paralysie cérébrale, spasticité, enfants, toxine botulique, échographie.

La spasticité est un symptôme courant et invalidant chez les enfants atteints de paralysie cérébrale (PC). Le traitement par toxine botulique représente une partie importante de la gestion multimodale de la spasticité.

Objectif: Le but de cette thèse était de présenter une revue de la littérature sur les résultats de l'injection de toxine botulique de type A (BTXA) pour la prise en charge de la spasticité chez les enfants atteints de PC, ainsi que les variables pouvant influencer les résultats de l'injection tels que l'âge, le dosage et principalement la technique de localisation des muscles cibles.

Méthodes: Les bases de données électroniques ont été explorées depuis la date la plus ancienne disponible jusqu'à juin 2018. Les critères d'inclusion consistaient en études avec des enfants âgés de 17ans ou moins, atteints de la forme spastique de PC, recevant un traitement par BTXA.

Résultats: La recherche a abouti à un total de 224 études, dont 32 répondaient aux critères d'inclusion.

Conclusion: il est évident que la spasticité peut être limitée en appliquant une approche thérapeutique multiniveau intégrée au BTXA. Nous avons constaté que l'utilisation de doses élevées n'entraînait pas de meilleurs effets par rapport à des doses plus faibles, l'âge optimal pour l'injection semble être compris entre 2 et 6 ans, la palpation anatomique est la technique la moins précise et l'échographie semble être la meilleure option pour garantir l'efficacité et la sécurité de l'injection. Cependant, des études plus systématiques sont nécessaires pour montrer des preuves suffisantes de la technique de localisation par échographie par rapport à d'autres techniques telles que la stimulation électrique et l'électromyographie.

Abstract

Title: Botulinum toxin type A in the management of spastic Cerebral palsy in children

Author: SERGHINI Niâma

Keywords: cerebral palsy, spasticity, botulinum toxin, ultrasound, children.

Spasticity is a common and disabling symptom for many children with cerebral palsy. Botulinum toxin type A (BTXA) treatment has become very popular in the last years; it represents an important part of the multimodal management of spasticity in children with CP.

Aim: The aim of this thesis was to present a review of the literature on the outcome of BTXA injections for the treatment of spasticity in children with cerebral palsy (CP), and the variables that may affect the outcome of injection such as age, dosage and essentially the localization technique of target muscles.

Methods: Electronic databases were searched from the earliest available date to June 2018 using a combination of subject headings and free text. Inclusion criteria consisted of studies with children aged between 2 and 17 years, with spastic CP, receiving BTXA treatment,.

Results: The search resulted in a total of 244 studies, of which 32 met the inclusion criteria.

Conclusion: we can conclude that there is clear evidence that the spasticity in children with CP can be limited by applying an integrated multi-level BTX-A treatment approach. We found that the use of high doses did not bring better effects compared with lower doses; the optimal age for injection appears to be between 2 and 6 years, anatomic palpation is the less accurate technique and ultrasound appears to be the best option to guarantee efficacy and safety of the injection. However, more systematic studies are necessary to show sufficient evidence for the ultrasound localization technique in comparison with other techniques such as electrical stimulation and Electromyography.

خلاصة

عنوان الأطروحة: توكسين البوتولينوم A في تدبير التشنج العضلي عند الأطفال المصابين بالشلل الدماغي.

المؤلف: السرغيني نعمة.

الكلمات الأساسية: الشلل الدماغي، التشنج العضلي، الأطفال، توكسين البوتولينوم، الإيكوغرافيا.

التشنج العضلي هو عرض شائع وعائق للعديد من الأطفال المصابين بالشلل الدماغي. أصبح علاج توكسين البوتولينوم أكثر شعبية في السنوات الأخيرة، وهو يمثل جزأ مهما في الإدارة المتعددة الأطراف للتشنج.

الهدف: كان الهدف من الأطروحة تقديم مراجعة للأبحاث حول نتائج حقن لعلاج التشنج لدى الأطفال المصابين بالشلل الدماغي، والمتغيرات التي قد تؤثر على نتائج الحقن مثل العمر، الجرعة وخاصة تقنية توطين العضلات المستهدفة.

الطريقة: تم البحث في قواعد البيانات الإلكترونية من أقدم تاريخ متاح إلى يونيو 2018. تضمنت معايير الاشتمال دراسات للأطفال المصابين بالشلل الدماغي الذين تتراوح أعمارهم بين 1 و17 سنة، ذوي مستويات، ويتلقون علاج ().

النتائج: أسفر البحث عن 244 دراسة، منها 32 استوفت معايير الاشتمال.

الخلاصة: يمكننا أن نستنتج أن هناك أدلة واضحة على أنه يمكن الحد من التشنج العضلي من خلال تطبيق علاج متكامل متعدد المستويات يشمل (). وجدنا أن استخدام جرعات عالية لم يجلب أثار أفضل مقارنة مع جرعات أقل، العمر الأمثل للحقن يتراوح بين 2 و6 سنوات، تقنية الجس هي الأقل دقة بينما تقنية الإيكوغرافيا هي أفضل خيار لضمان فعالية وسلامة الحقن. مع ذلك، هناك حاجة لمزيد من الدراسات المنهجية لإظهار أدلة كافية لتفوق الإيكوغرفيا على التقنيات الأخرى مثل التحفيز الكهربائي والتخطيط الكهربائي العضلي.

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Serment d' Hippocrate

Au moment d'être admis à devenir membre de la profession médicale, je m'engage solennellement à consacrer ma vie au service de l'humanité.

- *Je traiterai mes maîtres avec le respect et la reconnaissance qui leur sont dus.*
- *Je pratiquerai ma profession avec conscience et dignité. La santé de mes malades sera mon premier but.*
- *Je ne trahirai pas les secrets qui me seront confiés.*
- *Je maintiendrai par tous les moyens en mon pouvoir l'honneur et les nobles traditions de la profession médicale.*
- *Les médecins seront mes frères.*
- *Aucune considération de religion, de nationalité, de race, aucune considération politique et sociale ne s'interposera entre mon devoir et mon patient.*
- *Je maintiendrai le respect de la vie humaine dés la conception.*
- *Même sous la menace, je n'userai pas de mes connaissances médicales d'une façon contraire aux lois de l'humanité.*
- *Je m'y engage librement et sur mon honneur.*

قسم أبقراط

بسم الله الرحمان الرحيم

أقسم بالله العظيم

في هذه اللحظة التي يتم فيها قبولي عضوا في المهنة الطبية أتعهد علانية:

- بأن أكرس حياتي لخدمة الإنسانية .
- وأن أحترم أساتذتي وأعترف لهم بالجميل الذي يستحقونه .
- وأن أمارس مهنتي بوازع من ضميري وشرفي جاعلا صحة مريضي هدفي الأول .
- وأن لا أفشي الأسرار المعهودة إلي .
- وأن أحافظ بكل ما لدي من وسائل على الشرف والتقاليد النبيلة لمهنة الطب .
- وأن أعتبر سائر الأطباء إخوة لي .
- وأن أقوم بواجبي نحو مرضاي بدون أي اعتبار ديني أو وطني أو عرقي أو سياسي أو اجتماعي .
- وأن أحافظ بكل حزم على احترام الحياة الإنسانية منذ نشأتها .
- وأن لا أستعمل معلوماتي الطبية بطريق يضر بحقوق الإنسان مهما لاقيت من تهديد .
- بكل هذا أتعهد عن كامل اختيار ومقسما بشرفي .

والله على ما أقول شهيد .

المملكة المغربية
جامعة محمد الخامس بالرباط
كلية الطب والصيدلة
الرباط

سنة : 2020

أطروحة رقم: 31

توكسين البوتولينوم (A)
في تدبير التشنج العضلي
عند الأطفال المصابين بالشلل الدماغي

أطروحة

قدمت ونوقشت علانية يوم : / /2020

من طرف
السيدة نعمة السرغيني
المزدادة في 20 أكتوبر 1992 باكادير

لنيل شهادة

دكتور في الطب

الكلمات الأساسية : الشلل الدماغي؛ التشنج العضلي؛ الأطفال؛ توكسين البوتولينوم؛ الإيكوغرافيا

أعضاء لجنة التحكيم:

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