In the name of God the beneficient and the merciful

Does combining physiotherapy with Botulinum toxin type A injections improve the management of children with spastic cerebral palsy?

A Thesis Submitted for the Degree of Doctor of Philosophy in the Faculty of Biomedical and Life Sciences

Division of Neuroscience and Biomedical systems

By

Abeer Ali Flemban

B.Sc. (Physical Therapy)

King Saud University, Riyadh.

2007

Declaration

I declare that this thesis is of my own composition and that the research described here in was performed entirely by myself except where expressly stated.

Abeer Ali Flemban

2008

Acknowledgements

First and most of all, person must thank God for all grace and guidance in this life. I am extremely thankful to Almighty Allah, who rewarded my effort in successful accomplishment of this piece of work. My special praise for Holy Prophet, Mohammed (may peace and the mercy of Allah be upon him), who is ever, a torch of guidance for humanity as a whole.

Thanks must also go for all those people who help, guide and encourage me in research field or social life. Chief amongst all is my supervisor, Dr Ron Baxendale. For his guidance and encouragement throughout the completion of this work.

I feel a matter of great pleasure to express my deep sense to Dr Hassan Shakfa for his kind help and hospitality in Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre in Saudia Arabia.

Also my pleasure to thanks Mr. Ian Watt. For his help and assistance.

I am grateful to Ministry of Labour and Social affair, Kingdom of Saudi Arabia for financial support.

Finally, I am indebted a special thank-you to my mother, sisters, brothers, and all my family for continued pray, and support through all my life.

Last thanks to my lovely kids Shima, Ibrahim, Marya and Noor for their interesting and enjoyable accompaniment in my scientific journey.

Dedication

To my husband

Dr Mohammed Bajunaid

Our dream becomes true.

Abstract

Cerebral palsy (CP) affects around every one in 500 children born. It isn't a particular illness or disease, but an umbrella term used to describe a physical condition that affects movement as a result of injury to the brain. There are several types of CP, the main ones being spastic, athetoid and ataxic. Despite medical advances, there is no cure for CP but there are ranges of treatments from drugs to Botulinum toxin type A injections, massage therapy to surgery. The aim of this study is to look at two of these treatments, namely Botulinum toxin type A injections and physiotherapy to treat spastic CP.

Botulinum toxin is widely used to reduce muscle tone in the treatment of spasticity in children with cerebral palsy. The aim of the study is to compare the effects treatment with Botulinum toxin type A and Botulinum toxin type A with additional physical therapy in the management of a group of children with cerebral palsy.

Experiments were done at The Prince Sultan Hospital and Al-Hada Armed Forces Hospital in Saudi Arabia. The local Ethics Committee approved the protocol. 47 children were recruited. All had cerebral palsy, diplegia, spasticity of the ankle planter flexors and significant gait abnormalities due to dynamic equinus foot deformity. They were divided into two groups. Both groups had their Gross Motor Function assessed one week before injection and at 4 and 6 weeks after injection. Additional measurements of range of movement and stiffness at the ankle and soleus electromyograms were recorded

The soleus EMG was silent during ankle dorsiflexion in 20 children four weeks after injection of Botox. The EMG had returned six weeks after injection in every child. The Gross Motor Function Measurements were not significantly different in

the two groups before the injection (p=0.23). The measurements improved significantly over the next six weeks in both groups (p<0.001). The magnitude of the improvement was greater in the group, which received Botulinum toxin type A and physical therapy (means 57.2 + 8.90 before, 64.9 + 9.78 after. Mean + SD) than in the group which received Botulinum toxin type A alone (59.5 + 11.0 before, 62.4 + 11.3 after Mean + SD).

Conclusions

1. . The Treatment allocation provided groups, which were comparable pre-treatment in terms of baseline GMFM.

2. . Both treatments showed evidence of improvement in GMFM over the period of the study and particularly at 52 weeks.

3. . Treatment 2 showed a significant average advantage in GMFM over Treatment 1 at all times in the study.

4. . This advantage in average GMFM increased from 4 through to 52 weeks with a clear and significant difference between 4 and 52 weeks.

5. . This average advantage appeared to increase the higher the child's baseline GMFM.

List of Contents

Chapter1

Literature Review

Chapter 2

General Methods

Chapter 3

Results

Chapter 4

Discussion

List of Tables

Table

List of Figures

Figure:

Abbreviations

CNS**: Central nervous system.**

CP**: Cerebral Palsy**

ES**: Electrical stimulation**

EMG**: Electromyogram.**

GMFM**: Gross motor function measurement.**

BTX-A**: Botulinum Toxin type A**

LL**: Lower limb.**

AFOs**: Ankle foot orthoses.**

SD**: Standard deviation of mean.**

NDT**: Neuro developmental therapy.**

PROM**: Passive range of motion.**

Chapter 1

Introduction

1. Introduction and Rationale

Cerebral Palsy is and will remain a significant problem. In developed countries, cerebral palsy is the most common cause of physical disability in childhood. Its incidence is about 2 to 2.5 per 1000 live births (Pharoah, Cooke, Johnson, King and Mutch, 1998). One of the most disabling aspects of cerebral palsy is the development of spastic hypertonia. Estimates suggest the incidence of spastic hypertonia is as high as 60% in those who suffer from cerebral palsy (Levitt, 1995). There are many ways of classifying cerebral palsy. The simplest is according to distribution and number of affected limbs. Spastic diplegia is the most common type of juvenile cerebral palsy; hemiplegia and quadriplegia are less common (Levitt, 1995). Neuromuscular deficits found in cases of cerebral palsy include: a loss of selective motor control, abnormal muscle tone leading to an imbalance between agonist and antagonists muscles, impaired coordination, sensory deficits and weakness. The ability to maintain postural control is critical for the activities of daily life. Control of posture and balance is automatic in healthy subjects; it is often a challenging goal for children with cerebral palsy.

Researchers have shown that children with cerebral palsy have a reduced ability to adapt their postural control to changing task and environment demands (Butler, 1998). These postural impairments affect the ability to respond to challenges to balance efficiently and effectively. There are four

principal contributing factors: these include velocity dependent increases in tonic stretch reflexes, muscle weakness, excessive co activation of antagonist muscles and increased stiffness around joints (Gage, 1991).

The increased muscle tone in cerebral palsy 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 deformity (Gage, 1991). Calf muscle spasticity is one major factor that can interfere with normal walking by preventing heel strike.

A common goal of treatment of children who have cerebral palsy is to increase the functional capacity and relieve discomfort. The approach to treating spasticity is usually multi-modal. Physical therapy is a component of anti-spasticity regimens. It is usually combined with surgical interventions and pharmaceutical treatments. It is open to debate which of these is most effective either alone or in combination. This study will examine the effectiveness of combining physical therapy with botulinum toxin A in the treatment of spasticity

1.1. Characteristics of Cerebral Palsy

Cerebral palsy is a disorder of movement and posture caused by a non-progressive abnormality of the immature brain. The brain damage that causes cerebral palsy also may produce a number of other disabilities (Kurtz, 1992). It is a commonly used name for a group of conditions characterized by motor dysfunction due to brain damage early in life. It is due to abnormal development of the brain, anoxia, intra-cranial bleeding, trauma and infection (Levitt, 1995). Although the brain continues to grow into early adulthood, the crucial events of its development occur during intrauterine life and early childhood (Kurtz, 1992). The key stages in brain development are illustrated in figure 1.1

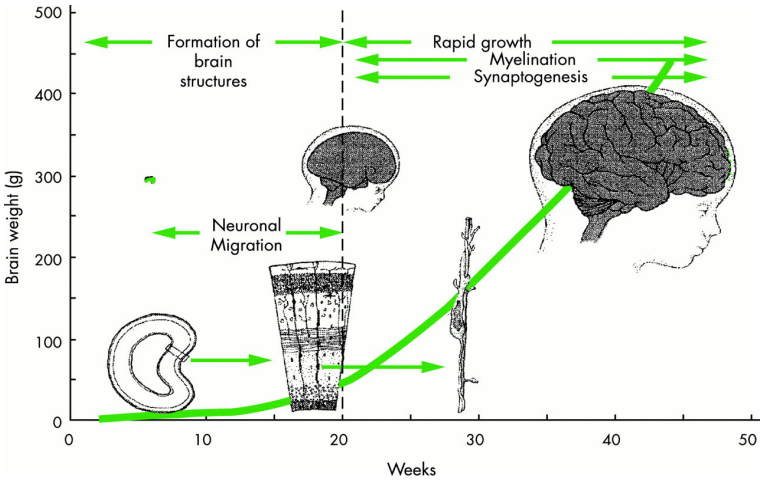


Figure 1.1

Brain development during gestation and early postnatal life. Injuries between 15–22 weeks gestation result in neuronal migration defects. After about 22 weeks gestation, the oligodendrocytes are vulnerable to injury and white matter wasting periventricular leucomalacia with associated expansion of the lateral ventricles is the dominant clinical pattern. Adapted from Lin, 2003.

A recent consensus definition of cerebral palsy is: “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 (Mutch, Alberman and Hagberg, 1992). This definition will be used throughout this thesis.

In some cases the cause of the brain damage is known, but in many others it is not. However varied the aetiological factors may be the resulting abnormality of the central nervous system is not progressive. The clinical features appear to progress but this apparent progression is due to the effects of the child’s development (Davis and Barnes, 2000).

1.2. The prevalence of cerebral palsy

Worldwide, the prevalence of cerebral palsy is reported to be between 2 – 2.5 per 1000 live births according to many studies (Kuban and Levition, 1994, SCPE, 2002). The incidence of cerebral palsy in United Kingdom is 2.4 per 1000 (SCPE, 2002). It varies between 1.5 and 1.8 per 1000 in the USA (UCP, 2002). It is 1 per 1000 in France and 1.7 per 1000 in Sweden. The literature available on CNS diseases of children in Saudi Arabia is limited to papers by Al-Naquib (1988), Al-Asmari, Al Moutaery, Akhdar and Al Jadid (2006). A population survey on the prevalence of child disability in Saudi Arabia found the rate to be 1.2 per 1000 and this accounts for 0.04% of the total population (Ansari, Sheikh, Akhdar and Moutaery, 2001).

Pharoah et al (1998) reported on the epidemiology of cerebral palsy in England and Scotland. They found 1649 cases of cerebral palsy in 789,411 live births, a cerebral palsy prevalence of 2.1 per 1000 neonatal survivors. All cases of cerebral palsy born between 1984 and 1989, to mothers resident in the area, were included.

1.3. Aetiology

50% of children with cerebral palsy are born prematurely. Premature babies have a higher risk in part because their organs are not yet fully developed. This increases the risk of cerebral palsy. The occurrence of cerebral palsy is much more common in premature infants with a birth weight below 1.5 kilograms. Twins and small for gestational age infants also have a higher than normal risk of cerebral palsy (Hagberg, Hagberg and Olow, 1982).

The aetiologies of cerebral palsy are varied and can occur either pre-natally or post-natally (Koman, Mooney, Smith, Goodman and Mulvaney, 1993). The causes of cerebral palsy during the first trimester of pregnancy include developmental brain abnormalities, intrauterine infections, exposure to radiation, exposure to drugs, and chromosomal abnormalities. In later pregnancy, placenta abruption and other abnormalities in the fetal-placental unit place the child at risk. Later still, complications during labour and delivery also are risk factors. In early childhood neonatal illness such as meningitis, head trauma, and poisonings become important causes (Paneth, 1986).

The most common causes of cerebral palsy are listed in table 1.1. (Kurtz, 1992).

Causes of cerebral palsy	
Labour and delivery	Pre-eclampsia Complications of labour and delivery
Prenatal 1st trimester:	Genetic syndromes Chromosomal abnormalities e.g. Down's Syndrome Brain malformations
2nd-3rd trimester:	Intrauterine infections Problems in fetal/placental functioning
Perinatal:	Sepsis/central nervous system infection Asphyxia Prematurity
Childhood	Meningitis Traumatic brain injury Toxins

Table 1.1.

The most common causes of cerebral palsy adapted from Hagberg and Hagberg (1984).

1.4. Classification

Many classification system of cerebral palsy exist. A simplified three-group model: Pyramidal, Extrapyramidal and Mixed Type was suggested by (Kurtz, 1992).

1.4.1. Pyramidal.

Children with the pyramidal form of cerebral palsy have experienced damage to their motor cortex or to the pyramidal tract. Damage to any part of this pathway leads to spasticity (Kurtz, 1992).

1.4.2. Extrapyramidal.

In this type, the damage occurs to the pathways outside the pyramidal tract. These extra-pyramidal tracts pass through the basal ganglia or emanate from the cerebellum. The most common type of extrapyramidal cerebral palsy is called athetoid cerebral palsy. The clearest clinical sign of extrapyramidal cerebral palsy is variable resistance to imposed movement. The limb initially appears rigid but this disappears with pressure. Muscle tone may vary from one time to another (Denhoff & Robinault, 1960).

1.4.3. Mixed-type cerebral palsy:

The mixed-type of cerebral palsy includes elements of both the pyramidal and extrapyramidal forms. The most common types of mixed cerebral palsy are athetoid and spastic hemiplegic and athetoid and spastic-diplegic (Whyte and Glenn, 1990).

1.5. Topographical classifications

In addition, topographical classifications are frequently used.

Quadriplegia indicates involvement of the four limbs. It has the worst prognosis. The patients are much more likely to suffer from mental retardation and to be affected by seizures. They commonly suffer from visual or auditory deficits (Eiben and Crocker, 1983).

Triplegia involves three limbs.

Diplegia involves all four limbs but the legs are more affected than the arms. Diplegic patients resemble quadriplegic patients but the important difference is that diplegic children can walk with assistance (Levitt, 1995).

Paraplegia: involves both legs but the arms are unaffected.

Hemiplegia: involves one side of the body. In general, the arm is more severely involved than the leg.

Monoplegia: Affects one limb.

This classification is illustrated in Figure 1.2.

1.6. Dyskinetic Cerebral Palsy

Dyskinetic cerebral palsy is characterized by abnormalities in muscle tone that involve the whole body. Usually the patterns of muscle tone change from hour to hour and day to day. These children will often exhibit normal muscle tone or decreased tone while asleep and rigid tone while awake (Levitt, 1995).

1.7. Ataxic Cerebral Palsy

Ataxic Cerebral Palsy is characterized by a lack of coordination and balance due to damage to the cerebellum (Whyte and Glenn, 1990). Its main motor characteristics are: poor fixation of the head, trunk, shoulder and pelvic girdles, disturbances of balance (Levitt, 1995).

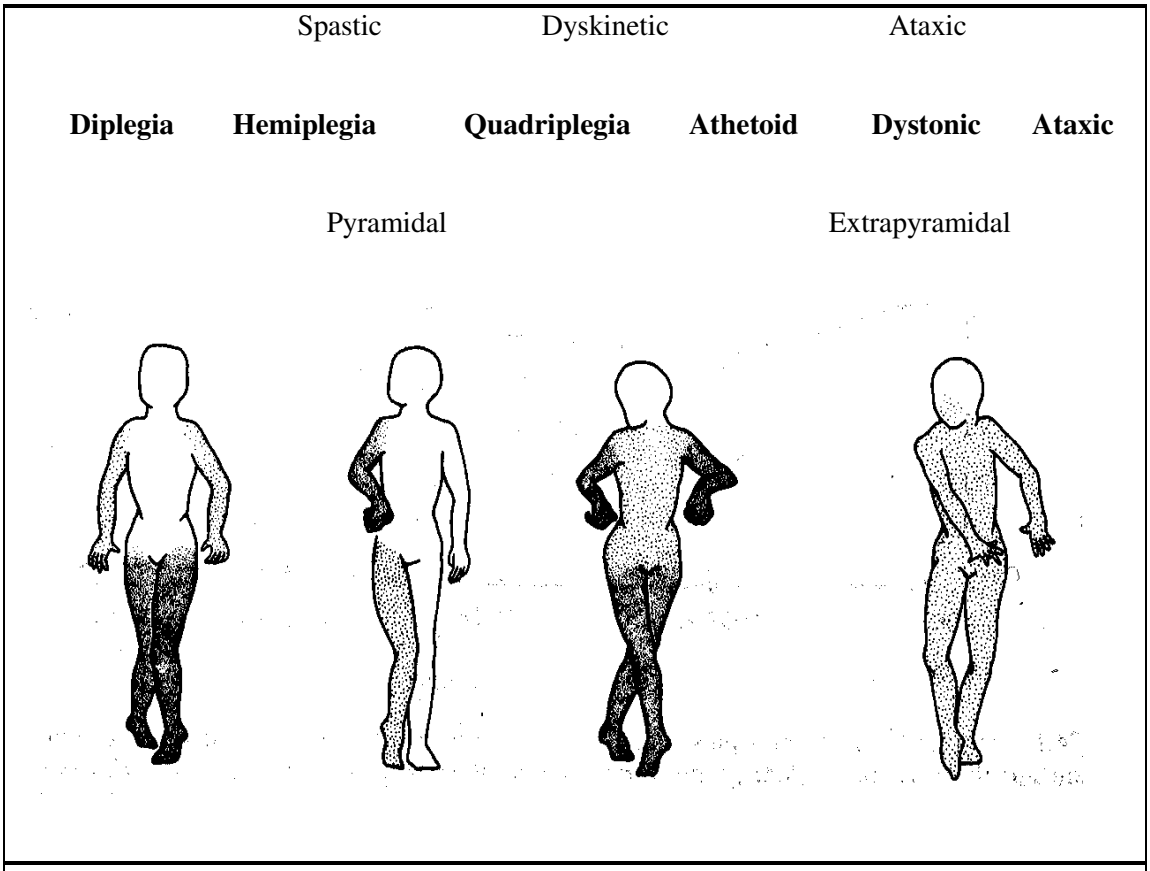


Figure 1.2.
Different regions of the brain are affected in various forms of cerebral palsy. The darker the shading, the more severe the involvement. (Adapted from Children with disabilities. By Mark L. Batshaw, M.D.1992)

1.9. Spasticity

Spasticity in patients can arise from a multitude of lesions that may include the sensorimotor cortical areas and their descending tracts, motor centres in the brainstem and their descending pathways, and finally the spinal cord itself. The severity of spasticity, its distribution and the magnitude and type of reflex responses depend heavily on the precise localization and combination of lesions as well as on the time since the lesion developed. In the large majority of cases, spasticity develops gradually within months after a lesion; less frequently, muscular hypertonia is present immediately as in the human cases of deceleration (Walshe, 1923).

Spasticity has been defined as a motor disorder characterized by a velocity-dependent increase in tonic-stretch reflexes with exaggerated tendon reflexes. This results from hyperexcitability of the stretch reflex and is one component of the upper motor neuron syndrome (Lance, 1980).

Electromyography has been used successfully to give objective and quantitative assessment of reflex excitability and to study the efficacy of drugs used to reduce spasticity (Delwaide et al., 1985), (Basmajian, 1974). Spasticity can lead to significant physical problems including spasms, restricted range of movement, pain and contractures, as well as functional difficulties including the maintenance of personal hygiene (Davis and Barnes, 2000).

Clinicians tend to concentrate on positive features of the upper motor neurone syndrome like spasticity, clonus, hyper-reflexia and co-contraction. However, negative features such as weakness, loss of selective motor control and sensory impairment can cause more disability (Graham, Aoki, Autti-Rämö, Boyd, Delgado, Gaebler-Spira, Gormley, Guyer, Heinen, Holton, Matthews, Molenaers, Motta, Garcia Ruiz and Wissel, 2000). Flett concurs with this view, suggesting that eliminating spasticity enables the cerebral palsy child to utilise their selective motor control more effectively and functionally (Flett, 2003).

In 2004 Lieber et al acknowledged that the basic mechanisms underlying the functional deficits that occur after the development of spasticity are not well understood and that with a few notable exceptions, the properties of skeletal muscle have largely been ignored. However it is becoming increasingly clear that there are dramatic changes within skeletal muscle as well as in the nervous system. Although our current understanding of spasticity is incomplete, it is now acknowledged that spasticity has both neurophysiological and musculoskeletal components (Lieber, Steinman,

Barash and Chambers, 2004). They suggest that this is why therapeutic interventions involving stretching, casting, splinting, neurectomy, intrathecal baclofen, botulinum toxin A and electrical stimulation have proved to be only partially effective.

Even less clear are the mechanisms, which lead to a slowly developing spasticity. In view of the heterogeneity of the 'spastic' condition in man, it is not surprising to note that there is no unique model, which would satisfy all clinical signs and symptoms. The problem of late changes typically found in patients with human spasticity is a key issue in future studies of spasticity.

After Botulinum toxin-A injection the nerve sprouting and muscle re-innervations lead to functional recovery within 2 to 4 months (Rosales, 1996). There is evidence that partially functional neuromuscular junctions are re-established within 4 weeks (Angaut-Petit, Molgo, Comella, Faille and Tabit, 1990). The periods of clinically useful muscle relaxation is usually 12-16 weeks (Graham et al, 2000, Duchen and Strich, 1968). The nature and the precise role of the mechanisms which have been discussed in previous studies sprouting and hypersensitivity of denervate structures – are still poorly understood (Wiesendanger, 1985).

Spasticity has been defined as follows: "spasticity is a motor 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 neuron syndrome" (Lance, 1981). In the clinical diagnosis of spastic syndromes, reflexes evoked from the skin play an important role. One of them, the sign of Babinski, is undoubtedly the most reliable and sensitive indicator of a descending tract lesion. Surprisingly enough, the significance of such a first rank sign for the pathophysiology of spasticity is still obscure: probably most neurologists

understand spasticity as a state of exaggerated stretch reflex (Meinck, et al.1985).

1.9.1 Spastic Diplegia

This study will focus on spastic diplegia. Severe spasticity can interfere with a child's normal functioning, motor and speech development, and comfort. Spasticity can be painful, especially if joints are pulled into abnormal positions or if range of motion is limited (Whyte and Glenn, 1990).

It primarily affects the legs, although there may be considerable asymmetry between the two sides. The tension in the spastic muscles during development often leads to bony deformities. The most significant problem in spastic diplegia is a lack of stability in standing and walking. Even after surgical treatments to correct the muscle imbalances, children with this condition need walking aids to correct deficiencies in balance.

1.9.2. Mechanical Changes in Spastic Muscle

There is no clear consensus regarding whether muscle cells from patients with spasticity have normal properties. This lack of consensus is due to the paucity of objective data regarding the mechanical, physiological or biochemical properties of spastic muscle (Frieden and Lieber, 2003).

Foran, Steinman, Barash, Chambers and Lieber (2005) assert that ‘spastic’ muscles are altered in a way that is unique among muscle plasticity models and inconsistent with simple transformation due to chronic stimulation or use.

They make the case for the following alterations in spastic muscle:

1) Altered muscle fibre size and fibre type.

2) Proliferation of extra-cellular matrix.

3) Increased spastic muscle cell stiffness, and to a lesser extent spastic muscle tissue.

4) Inferior mechanical properties of extra-cellular material, compared to normal muscle

Examples of these changes are shown in figure 1.3. the figure on the left (a) shows normal muscle fibers for a child, it shows light stained type fibers, tightly packed fibers .

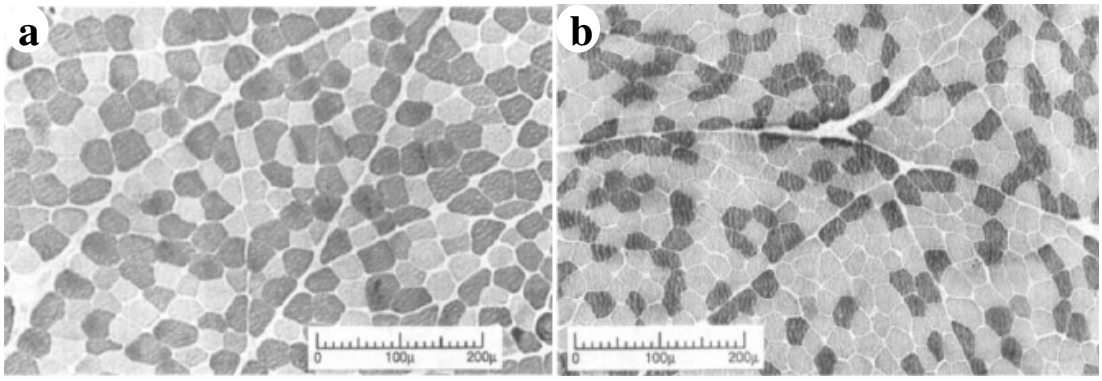


Figure 1.3
Comparison spastic muscle and control –altered proportions of muscle fibre type

Skeletal muscle stained with ATPase, pH 9.4. Type 2 fibres are dark. (a) Biopsy of the peroneus brevis muscle (x50) from a 7-year-old control subject. (b) Biopsy of the lateral gastroenemius muscle (x50) from a 5-year-old subject with cerebral palsy. Adapted from Rose J, 1994

These authors suggest that collagen may be involved in increases in the muscle stiffness observed in spasticity and that its accumulation contributes

either directly or indirectly to the development of contractures and secondary bony abnormalities thus playing a major role in mobility problems observed in cerebral palsy.

Other studies have shown that although spastic muscle contains a larger amount of extracellular matrix within it, the mechanical strength of that material is poor compared with that of normal muscle (Lieber et al, 2004).

1.9.3. Spastic muscle Response to Stretch

More recently it has been shown that only part of the resistance of spastic muscles to stretching can be attributed to increase a reflex contraction; much is due to the intrinsic stiffness of the muscle itself. This resistance has three components: passive muscle stiffness, neurally mediated reflex stiffness, and active muscle stiffness. Of these, increased passive mechanical stiffness accounts for nearly all of the increase in limb stiffness (Lieber et al, 2004).

1.10. The methods of measurement of spasticity

A number of assessment scales are used to assist the diagnosis of spasticity and to measure its severity. The scales measure the resistance to passive muscle stretch or the joint range of motion. These clinical rating scales all suffer from a subjective component of the assessment of spasticity. There is no absolute standard of measurement.

1.10.1. The Ashworth Scale

The original Ashworth scale and it is modified version (Bohanon and Smith, 1987) both attempt to measure the severity of muscle hypertonia using clinical assessment scales. The modified Ashworth scale has 6 grades: see table 1.2.

Grade 0 = no increase in muscle tone. Grade 1 = slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion (ROM) when the affected part is moved in flexion or extension/abduction or adduction. Grade 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the reminder (less than half) range of motion (ROM) Grade 2=more marked increase in muscle tone through must of ROM, but affected part easily flexed Grade 3=considerable increase in muscle tone, passive movement is difficult. Grade 4=affected part rigid in flexion and extension, abduction or adduction.
Table 1.2. The modified Ashworth scale (Bohanon & Smith, 1987)

1.10.2. Pendulum test

The pendulum test is a biomechanical method of evaluating muscle tone by using gravity to provoke muscle stretch reflexes during passive swinging of the lower limb (Fowler, Nwigwe and Wong, 2000). The oscillations of the knee are affected by spasticity of the quadriceps and hamstring muscles and this effect can be seen with the naked eye (Graham, 2000). The pendulum test was described almost 50 years ago but has not been assessed as a clinical tool in children who have spastic CP.

1.10.3. Spasm score

Spasm score is a simple scale for recording the frequency of muscle spasms (Middel, Kuipers-Upmeijer, Bouma, Staal, Oenema, Postma, Terpstra and Stewart, 1997). See table 1.3.

The Spasm Scale
0 = no spasms. 1 = mild spasms induced by stimulation. 2 = infrequent spasms occurring less than once per hour. 3 = spasms occurring more than once per hour 4 = spasms occurring more than 10 times per hour.

Table 1.3.
Spasm scale Evaluates the frequency of spasms with scores listed (Berrie Middel 1997)

1.10.4. The modified Tardieu scale

The Tardieu scale is a recent introduction to clinical practice (Boyed, Barwood, Baillieu and Graham, 1998). It assesses the range of motion of the ankle and knee: The dynamic component, R1 or angle of the overactive stretch reflex is defined at Tardieu velocity of stretch V3 and the slow PROM or degree of muscle contracture R2 is graded as the angle at V1. The score is recorded as R1/R2. Boyd found that a large difference between the two measures characterises a large dynamic component, which is likely to respond to BTX-A injections, whereas a small difference between R2 minus R1 means that there is predominantly fixed muscle contracture present. It does not seem to have been adopted widely.

1.10.5. Goniometry

Spasticity decreases the range of motion at joints. In more recent studies electrogoniometers make continuous measurements of the angle of a joint. The output of an electrogoniometer is usually plotted as a chart of joint angle against time (Whittle, 1996).

1.10.6. Neurophysiological Investigations

Electromyography (EMG) is the measurement of the electrical activity of a contracting muscle- the muscle action potential. One of the most useful textbooks on EMG is that by Basmajian (1974) Electromyography is sometimes used to distinguish muscle spasticity from a fixed contracture.

1.10.7. Gross Motor Function Measurement (GMFM)

The GMFM is commonly used to establish a baseline gross motor level and to detect change after interventions (Russell, Rosenbaum, Cadman, Gowland, Hardy and Jarvis, (1989), Leach, (1997), Yang, Chan, Chuang, Liu and Chiu, (1999), Russell, Avery, Rosenbaum, Raina, Walter and Palisano, (2000), Ubhi, Bhakata, Ives, Allgar and Roussounis, (2000), Linder, Schindler, Michaelis, Stein, Kirschner, Mall, Berweck, Korinthenberg and Heinen, (2001), Russell, Rosenbaum, Avery and Lane, (2002). It is a standardised observational instrument designed and validated to measure the change in gross motor function over time in children with cerebral palsy. The scoring key gives a general guideline. However, most of the items have specific descriptors for each score.

Scoring is based on a four- point scale for each item using the following key:

0 = does not initiate

1 = initiates

2 = partially completes

3 = completes

NT = not tested

“Does not initiate” is applied when the child is unable to begin any part of the activity. “Initiates” is applied when less than 10% of the task is completed. “Completes,” is applied when the task is completed fully. “Not tested” is used when an item has not been administrated or when a child refused to attempt it.

The test includes 88 items grouped in five dimensions: (A) Lying and Rolling; (B) Sitting; (C) Crawling and Kneeling; (D) Standing; (E) Walking, Running, and Jumping. Each item of the test is scored on a 4-point scale and percentage score is calculated for each dimension. The total score is obtained by calculating the mean of the five dimension scores. The total GMFM score and dimension scores collected at each evaluation was used in the analysis. See appendix number 4

The GMFM is used ever more frequently as an outcome measure to investigate functional benefit of various treatment regimes (Russell et al, (1989) Leach, (1997) Yang et al, (1999) Flett, Stern, Waddy, Connell, Seeger and Gibson, (1999) Russell et al, (2000) Ubhi et al, (2000) Boyd, Dobson, Parrott, Love, Oates, Larson, Burchall, Chondros, Carlin, Nattrass and Graham, (2001) Linder et al, (2001) Russell et al, (2002) Reddihough, King, Coleman, Fosang, McCoy, Thomason and Graham, (2002) Bottos, Azienda, Benedetti, Salucci, Gasparroni and Giannini, (2003) Mall, Heimen, Siebel, Bertram and Hafkemeyer, (2006)).

In this study I used goniometry, electromyography and GMFM but not the pendulum test or Ashworth scale because both spasticity and fixed contractures dampen the limb swing and the pendulum test, like the Modified Ashworth scale does not distinguish between reversible muscle spasticity and fixed contractures. (Bakheit, Pittock, Moore, Wurker, Otto, Erbguth and Coxon, 2001) The Modified Ashworth scale has a good reliability when used to measure upper limb spasticity but it is less reliable

when used for the measurement of spasticity in the lower limb (Sloan, Sinclair, Thompson, Taylor and Pentland, 1992).

Literature Review

1.11. The management of spasticity by Physical Therapy

Physical therapy may help children with cerebral palsy to learn better ways to move and maintain their balance. It may help children learn to walk, use their wheelchair, stand by themselves, or go up and down stairs safely. Children may also work on skills like running, kicking and throwing a ball or learning to ride a bike (Jones, 1987). Appropriate muscle tone is necessary to increase mobilization, prevent postural abnormalities, provide independence in daily living activities and accelerate walking speed. Various methods including neurodevelopmental therapy, physical exercise, electrical stimulation, orthoses and splints, biofeedback and cold applications, are used for the management of spasticity. Physical therapy includes daily stretching exercises to maintain the full range of motion for the affected muscles. In mild spasticity, this may be the only treatment needed, while in severe spasticity, it is a part of the full therapy plan (Cherry (1980), Kluzik, Fetters and Coryell (1990), Whyte and Glenn (1990), Girolomi and Champell (1994), Barry (1996), Levitt, (1995)).

See appendix 1 for more details about Physical Therapy.

1.11.1. Neurodevelopmental Therapy

Neurodevelopmental Therapy (NDT) is based on the principles of normalization of postural tone, inhibition of abnormal reflexes, and the facilitation of appropriate developmental reflexes, equilibrium responses, and postural reactions (Bly, (1991), Bobath and Bobath, (1984)). The aim of treatment is to improve corrective and balance reactions and muscle tone,

to decrease excessive muscle tone and to improve posture (Bobath, (1980) Perin, (1989) Valvono and Long, (1991) Leach, (1997)).

1.11.2. Therapeutic Exercises

Resistive exercises and both passive and active stretching, can be used with children with cerebral palsy after Botulinum toxin type A injections. The goals of these exercises include maintaining or regaining the range of motion in order to prevent contractures and maximize functions and enhance motor skills. Joint and soft tissue mobilization can be effective additional measures to enhance mobility once the spasticity is decreased by Botulinum toxin type A (Cherry (1980), Humphrey (1985), Harris and Lundgren (1991), Leach, (1997), Levitt, (1995)).

1.11.3. Use of splints, plaster casts, and orthoses

The use of casts has become increasingly popular as an adjunct to more traditional methods of managing spasticity (Smith and Harris (1985), Hanson and Jones (1989)).

Physiotherapy combined with the use of splints and plaster casts can prevent the development of fixed contractures. These treatments may preserve the optimal length of muscle and the range of motion. They may improve gait and weight bearing and also improve functional hand use (Bertoti, (1986), Smelt (1989), Yasukawa, (1990)). The application of plaster casts is an effective treatment method in the short-term management of spasticity and is especially valuable when it is started early before the onset of contractures (Nuzzo (1980), Bakheit, (2001)). The main disadvantage of plaster casts is that they limit the functional use of the limb and the immobilisation may cause disuse muscle atrophy (Bakheit, 2001). Orthotic intervention in ambulatory children with spastic cerebral palsy is intended to prevent deformity, achieve a stable base, improve dynamic efficiency of gait and aid

achievement of motor function (Buckon, Thomas, Huston, Moor, Sussman and Aiona, 2001). Orthoses are designed to provide joint stability, to hold a joint in a functional position and to keep tight the stretched muscles (Flett, 2003).

Ankle foot orthoses (AFOs) are commonly prescribed for children with cerebral palsy to improve their walking abilities and to prevent the development of deforming contractures. They also allow for greater ease in performing tasks like stair climbing and rising from the floor (Rethlefsen, Dennis, Forstein, Reynolds, Tolo and Antonelli, 1995). Dorsiflexion will allow stretching of the Achilles tendon, which may result in reduced spasticity of the triceps surae muscle (Middleton, Hurley and Mcllwain, 1988).

1.11.4. Cryotherapy

The effect of the cryotherapy is usually modest lasting one hour, because of this cryotherapy has limited clinical value in the management of spasticity. The immersion of the spastic limb into cold water (t=7ºC) or the application of ice packs onto the muscle for 20 to 30 minutes usually results in noticeable reduction in the muscle tone (Bakheit, (2001), Kathleen, (1997)

1.11.5. Electrical Stimulation

Electrical Stimulation of the neural structures has been shown to reduce tone in spastic muscles. Clinical improvement in spasticity and reduction in painful muscle spasms may occur following spinal cord stimulation, transcutaneous electrical nerve stimulation and cerebellar stimulation. However, this form of treatment is not widely used (Seib, Price, Reyes and Lenhmanan, 1994). The effect of electrical stimulation is usually transient. In some patients the beneficial effect may last six hours or more (Bakheit et al, 2001, Leach, 1997).

1.11.6. Neurosurgical treatment of spasticity

A number of neurosurgical procedures have been used to treat cerebral palsy. These include implantation of cerebellar or dorsal column stimulators and performing of dorsal rhizotomies (Park & Owen, 1992). In children who have adductor contractures, the use of selective anterior branch obturator neurotomies may be beneficial. Stereotactic surgery is also used but has limited success (Henry, 1997). Spellman and Van Manen reviewed 28 patients with cerebral palsy, with a mean of 21 year's postoperative follow-up. They found good results in patients with moderate to severe dyskinetic cerebral palsy but poor results in those patients with quadriplegia or diplegia with spasticity (Henry, 1997).

Selective posterior rhizotomy is a relatively new neurosurgical procedure designed to reduce spasticity in cerebral palsy children (Berman, Vaughan and Peacock, 1990) Contraindications include muscle weakness especially postural muscle (Henry, 1997).

1.11.7. Orthopaedic surgery

Most of the surgery performed on patients with spasticity takes place at the muscles or the tendons. Orthopaedic surgeons can lengthen, release or transfer a contracted or spastic muscle (Henry, 1997). Common surgical procedures for the correction of equinus deformity in cerebral palsy have included gastrocnemius lengthening and achilles tendon lengthening. It is not clear which of these methods is more effective for increasing the excursion of the ankle joint (Etnyre, Chambers, Scarborough and Cain, 1993).

A previous study compared the effects of different methods of surgical correction of equinus gait in children with spastic cerebral palsy. This study showed that surgical intervention resulted in significant improvement of

velocity, cycle time, and stride length (Etnyre et al, 1993) Overall, the aims of surgery are to reduce established deformity, improve cosmesis, improve gait pattern and reduce the energy cost of walking (Flett, 2003).

1.11.8. Drug therapy

Neuromuscular blockade can be used to interrupt the function of the nerve, the neuromuscular junction, or the muscle. This blockade may be achieved by chemical alteration of peripheral muscle activity, thus weakening the treated muscles by selective paralysis, denaturing of muscle fibres, or partial denervation (Koman, James, Mooney and Beth, 1996).

Neuromuscular blockade balances agonist-antagonist forces by diminishing stretch reflexes through neural destruction and blocking of nerve transmition with 4% to 6% phenol, alcohol or local aenesthetic.

1.11.9. Alcohol

Ethyl alcohol nonselectively denatures protein and disrupts myoneural junctions. It causes retrograde Wallerian degeneration of peripheral nerves. It is used for peripheral nerve blocks and intrathecal blocks (Koman et al, 1996).

1.11.10. Phenol

Like alcohol, phenol denatures the protein in the injected area (Koman et al, 1996). Destructive treatments using phenol nerve blocks are inappropriate in the management of children who have a maturing nervous system (Ubhi et al, 2000). Complications after phenol usage include skin and muscle necrosis and muscle atrophy, paraesthesias, wound infection, and commonly, post-injection pain.

1.11.11. Local anesthetic agents

Local anesthetics block both afferent and efferent axons. The onset of action is within minutes and duration of action varies between one and several hours. A short-acting anesthetic can also serve as preparation to casting or as an analgesic for intramuscular injections of other antispastic treatment. Unfortunately, such medications have limited usefulness in improving muscle tone in children with cerebral palsy.

1.11.12. Baclofen

Baclofen, an agonist of γ-aminobutric acid-β receptors (GABA), is effective in the treatment of spasticity and is currently the most widely used antispasmodic drug (Ordia, Fischer, Adamski and Spatz, 1996). Baclofen can be administered orally or intrathecally. It is better known for its efficacy in reducing spasticity in adult subjects. It is most effective for treating spasticity of spinal rather than central cerebral origin (Flett, 2003). The main adverse effects of baclofen are neuropsychiatric and include respiratory depression, excessive sedation, fatigue, dizziness, convulsions, mental confusion, and hallucinations (Katz, 1988).

1.11.13. Diazepam

Diazepam is the most commonly used benzodiazepine in the treatment of spasticity. In clinical practice, diazepam is frequently used as an adjunct to baclofen in treating spasticity and is less commonly used on its own. Adverse effects of its use include sedation and cognitive impairment. In addition, there is the potential for dependence to develop. A withdrawal syndrome is associated with the benzodiazepines and abrupt cessation of diazepam has been associated with seizures (Kita and Goodkin, 2000).

1.11.14. Tizanidine

Tizanidine is an imidazole derivative and is a centrally acting α_2-adrenergic agonist that inhibits the release of excitatory amino acids in spinal interneurones. Tizanidine has potent muscle relaxing properties in animal models of spasticity and it suppresses polysynaptic reflexes in the spinal cat.

In placebo controlled trials, tizanidine has been shown to reduce muscle tone and frequency of muscle spasms in both patients with muscle spasm and spinal cord injury. Although tizanidine was found to reduce spasticity without altering muscle strength, it has shown no consistent positive effect on functional measures (Coward (1981), Kita and Goodkin, (2000)).

1.11.15. Dantrolene

In contrast to baclofen and diazepam, dantrolene acts directly on muscle and reduces tone by inhibiting the release of calcium from the sarcoplasmic reticulum (Whyte and Robinson, 1990). Placebo controlled trials of dantrolene show effective reductions of muscle tone and hyper-reflexia. Spasticity was slightly better controlled with dantrolene than with diazepam. Because its site of action is peripheral, the most common adverse effect of dantrolene is muscle weakness. For this reason, dantrolene may be most appropriate for those patients who are non-ambulatory with severe spasticity. Other adverse effects include drowsiness, diarrhoea and malaise (Kita and Goodkin, 2000).

1.11.16. Gabapentin

Gabapentin was first introduced in 1994 as a new treatment option for patients with partial seizures. It is structurally similar to GABA. It is easily

absorbed, reaching peak plasma concentrations in 2 to 3 hours. It is not protein bound. It does not undergo metabolic degradation, and is excreted unchanged in the urine. It is well tolerated in dosages up to 3600 mg/day. Recent studies and reports have suggested it might be effective as another tool in treating spasticity but further studies will be necessary to confirm efficacy (Dunevsky and Pere, 1998).

1.11.17. Botulinum Toxin-A in the treatment of cerebral palsy.

The toxin is produced by Clostridium botulinum and its ingestion can produce botulism, a rare and often fatal paralytic illness. Injection of Botulinum toxin type A into muscle causes chemical denervation and focal paralysis (Flett, 2003). Botulinum toxin type A is easy to administer. It diffuses readily into the muscle. It should be painless and it can be given without anaesthesia (Bakheit, 2001). The main indication for Botulinum toxin type A use is abnormally increased dynamic muscle tone. The action of Botulinum toxin type A is known to be relatively long lasting and when used in conjunction with other conservative non-surgical treatment, it can be used for years without necessarily losing efficacy (Flett, 2003).

The clinical effects of botulinum toxin have been recognised since the end of the 19th century (Davis and Barnes, 2000). Botulinum toxin type A has many clinical uses varying from cosmetic to clear clinical applications. Scott et al first used Botulinum toxin type A in 1973 as therapeutic treatment for the correction of strabismus. It has been used in many other conditions including improve upper extremity function (Wall, Chait, Temlett, Perkins, Hillen and Becker, (1993); Bakheit.et al, (2001)).

Botulinum toxin type A has been used to reduce the spasticity by blocking neuromuscular transmission. The net effect of neuromuscular blockade is complete or partial paralysis of the target muscle(s) while leaving antagonist

muscle(s) unaffected (Koman et al, 1996). The first clinical trials of Botulinum toxin type A in patient with cerebral palsy was carried out in 1987 in the United States (Koman, Mooney, Smith, Goodman and Mulvaney, 1993). Since then many groups have investigated if Botulinum toxin type A treatment can be used in cerebral palsy try to improve walking (Koman, Smith, Tingey, Mooney, Slone and Naughton (1999), Ubhi et al, (2000), Koman et al, (1993), Cosgrove, Corry, and Graham (1994), Sutherland, Kaufman, Wyatt and Chambers (1999), Bottos et al, (2003), Flett et al (1999), Koman, Mooney, Smith, Goodman and Mulvaney (1994), Corry, Cosgrove, Duffy, Taylor and Graham, (1999)).

Botulinum toxin type A also used as an adjuvant therapy in the management of dynamic contractures or spasticity (Wall, Chait, Temlett, Perkins, Hillen and Becker (1993); Koman et al, (1993); Cosgrove et al, (1994); Flett et al, (1999); Sutherland et al, (1999); Yang et al, (1999), Ubhi et al, (2000), Linder et al, (2001), Baker, Jasinski and Maciag (2002), Fragala, O'Neil, Russo and Dumas (2002)).

Botulinum toxin type A injections have also been used to improve gross motor function in children with cerebral palsy (Yang et al, (1999), Reddihough et al, (2002)) and to increase muscle length (Thompson et al, (1998), Eames, Baker, Hill, Graham, Taylor and Cosgrove, (1999)). BTX-A has also been used to facilitate positioning and hygiene (Koman et al, 1993), to delay surgery, (Flett, (2003); Graham et al, (2002); Ubhi et al, (2000)), and to facilitate or replace bracing (Koman et al, 1996). In addition, it used as a diagnostic aid to determine the efficacy of surgery (Koman et al, 1993).

The use of Botulinum toxin type A is inappropriate or inadvisable in the management of fixed contractures and in the presence of certain specific neuromuscular diseases in which a patient is being treated with medications that may exaggerate the response to neuromuscular blocking agent, in

muscle(s) that did not respond to alcohol or phenol injections and in the presence of antibodies to Botulinum toxin type A (Koman, 1994).

1.12. Pharmacology of Botulinum toxin type A

Now that the efficacy and safety of Botulinum toxin has been demonstrated, there has been continuing interest in its use. Of the 8 immunologically distinct serotypes (types A, B, C1, C2, D, E, F and G), the only types currently in clinical use are Botulinum toxin type A and Botulinum toxin type B (Flett, 2003). Botulinum toxin type A is a large molecule with a high specific binding coefficient. It spreads in tissues through local diffusion. Therefore, distant clinical effects and functional involvement of adjacent muscle groups are not apparent at doses lower than 6 U/Kg of Botulinum toxin type A body weight (Scott, 1981).

Botulinum toxin type A acts by interfering with presynaptic acetylcholine release at motor nerve terminals. It does not destroy nerve endings, nerve terminal or neuromuscular junctions (Wall et al, 1993). Injection of Botulinum toxin type A into selected muscles, therefore, produces dose-dependant chemical denervation resulting in reduced muscular activity (Borodic, Ferrante, Pearce and Smith, 1994). Its effect is reversible (Scott, 1981).

Nerve sprouting and muscle re-innervation lead to functional recovery within 2 to 4 months (Rosales, 1996). There is evidence that partially functional neuromuscular junctions are re-established within 4 weeks (Angaut-Petit, Molgo, Comella, Faille and Tabit, 1990). The periods of clinically useful muscle relaxation is usually 12-16 weeks (Graham et al, 2000). (Duchen and Strich, 1968). Botulinum toxin type A appears to denervate fast-twitch muscles (e.g. gastrocnemius) for longer periods than slow-twitch muscles (e.g. soleus) (Koman et al, 1996).

1.13. Dose of Botulinum toxin type A

There is no consensus in either paediatric or adult practice about the "correct" dose of Botulinum toxin type A to treat spasticity. The dose is generally determined by the size of the muscle to be injected. The aim is to achieve a clinical response without excessive weakness or systemic side effects (Carr, Cosgrove, Geringrass and Neville, 1998). A dose of 20-120 U of botulinum toxin type A(or the equivalent dose of Dysport) for large muscles and 2.5-40 U for smaller ones seems to be effective in the treatment of both spasticity and rigidity (Gordon, 1999).

The accepted safe maximal dosage of botulinum toxin type A is 6 U/Kg body weight. In previous studies of Botulinum toxin type A as a treatment for cerebral palsy, the minimum dose that appeared to be required for focal muscle weakness 1 to 2 units of toxin per kilogram of body weight per major muscle group injected (Koman et al, 1993).

One study has investigated the dose-response relationship of Botulinum toxin type A in the treatment of children with cerebral palsy (Carr, 1998). The effects of high (200 units per leg) and a low-dose (100 units per leg) doses were compared in 33 patients with CP. The results of this study indicated that doses of 200 Botulinum toxin type A distributed in 4 to 5 muscles per leg are more effective and equally safe compared to 100 units distributed per leg in treating spastic gait pattern in CP. Longitudinal gait parameters improved more significantly only in patients with high dose treatment. Additionally, analysis of variance showed dose dependency of Botulinum toxin type A on gait velocity and stride length. The authors found a dose dependent response in knee flexor muscle tone, walking speed, and stride length without increase in systemic effects. Some clinicians recommend a maximum of 900 units of Dysport and 300 units of Botulinum toxin type Ain the older child (Carr, 1998).

Some studies have suggested that the highest doses of Botulinum toxin type A not only resulted in more adverse events, but they were also associated with less therapeutic responses and in some cases, functional deterioration (Bakheit et al, 2001). The total dose of toxin per treatment session, rather than that calculated on the basis of body weight, correlated with the incidence of adverse events and functional improvement or deterioration. This would be explained by the fact that the number of neuromuscular junctions in a muscle may be more important for the clinical response to the toxin than its absolute body weight (Bakheit et al, 2001).

1.14. BTX-A combined with Physical Therapy

Physical therapy programme after Botulinum toxin type A injection remains central to treatment. It has been suggested that targeted motor training may prolong the benefit of Botulinum toxin type A (Graham, et al, 2000). Most studies recommend physical therapy after Botulinum toxin type A treatment (Fragala et al, 2002). However the most effective physical therapy programme is not known. Intensive physiotherapy treatment is currently the standard management following Botulinum toxin type A in cerebral palsy children in the hope of providing improved long-term benefit (Ubhi et al, 2000).

1.15. Effect of Botulinum toxin type A on muscle tone and walking

The basic use of Botulinum toxin type A is as an adjuvant therapy in the management of dynamic contractures or spasticity (Jefferson, 2004). Koman et al first described the use of Botulinum toxin type A in children with cerebral palsy in an open-label study of 27 children with dynamic deformities. They noted that the Botulinum toxin type A action appeared to last longer in more active patients. They also found a reduction in spasticity within 12 to 72 hours after injection. It lasted for 3 to 6 months without

major adverse effects. These authors postulated that adjuvant therapy with Botulinum toxin type A might delay orthopaedic surgery (Koman et al, 1993).

The previous study demonstrated that very low doses of Botulinum toxin type A (0.5-1 U/Kg of body weight / muscle) combined with rehabilitation therapy (stretching exercises, therapeutic facilitation exercises, and plastic ankle and foot orthoses) decreased spasticity and improved gait in cerebral palsy children. The long-term effect of this combination of treatments suggest that the initial effects were likely to be the result of a direct Botulinum toxin type A blockade of neurotransmission but that sustained effect resulted from long-lasting compensatory mechanism (Suputtitada, 2000).

Cosgrove et al investigated the changes in sagittal plane kinematics using electrogoniometer in a group of 26 patients who had dynamic contractures of the lower limb interfering with positioning or walking. Patients received Botulinum toxin type A injections to the gastrosoleus, tibialis posterior and hamstring muscles. A reduction in muscle tone occurred within 3 days of the injections and lasted from 2 to 4 months (Cosgrove et al, 1994). Their study was the first to report that gains in dorsiflexion after calf injection. Improvements were less in older subjects, probably because of the gradual development of fixed contractures. In the study, improvement was noted in such parameters as ankle dorsiflexion in stance and swing and knee extension in stance and swing following injection of the calf muscles and hamstrings respectively (Cosgrove et al, 1994). Sutherland, Kaufman, Wyatt hgand Chambers, (1996) investigated the effect of treating 26 cases of dynamic equinus with injection of Botulinum toxin type A into the gastrocnemius. They found increased walking velocity, increased step length and increased stride length at following compared with baseline values. During swing,

there was an increase in ankle dorsiflexion; this active movement mediated by the ankle dorsiflexors, allowed ground clearance in the swing phase of the gait cycle. Koman et al, (1993) injected the paraspinal and lower limb muscles. They found decreases in tone and improvement in positioning and gait. Sutherland et al, (1996) reported gait improvement in foot rotation, step length, and dorsiflexion after calf injection. Ubhi et al, (2000) reported improvement in the physician rating scale in 48% of children treatment with Botulinum toxin type A compared to 17% of those treated with placebo. The improvement of equinus foot position in 50-60% of patients without significant morbidity.

The Botulinum toxin type A injection into the hamstring muscles produces improvement in knee extension in gait without significantly reducing knee flexion. This increased muscle excursion may improve stretch of the relaxed muscle leading to its lengthening. The hip range of movement was also increased significantly at 12 weeks. Improvement of hip flexor activity may partly account for the significant increase in speed after the Botulinum toxin type A that arose as an increase in cadence and step length (Corry et al, 1999).

1.16. Effect of Botulinum toxin type A on muscle length

Eames and colleagues (1999) studied the change in gastrocnemius muscle length following Botulinum toxin type A injection in 39 children and correlated the pre-treatment dynamic component of spasticity with the magnitude and duration of the response. They found greatest change in muscle length two weeks following Botulinum toxin type A. One year after the injection 30% of injected muscles were longer than baseline. Botulinum toxin type A appeared to act on the dynamic element of a contracture and produced relatively small changes in absolute muscle length. Botulinum toxin type A injection in both short and adequate length muscles produced

muscle lengthening (Thompson et al, 1998). Botulinum toxin type A provides a useful way of controlling excessive muscular contraction in the spastic muscles injected. It follows that it is most effective in patients with dynamic muscle shortening which is localized to a few muscles (Graham et al, 2000). These observations clearly establish a link between the dynamic component of muscle shortening and the response to Botulinum toxin type A in terms of increase in muscle length during gait (Eames et al, 1999).

Botulinum toxin type A does cause a detectable lengthening of gastrocnemius muscle in ambulant children. The magnitude of this response varies and is related directly to the dynamic component present immediately before an injection. Repeated injections display similar correlation, the dynamic component being the important factor than the number of the injections. Children with hemiplegia and diplegia show similar response, but because children with diaplegia tend to show a greater degree of dynamic component, they tend to respond better to the injections. For most children, Botulinum toxin type A does not cause a long-term lengthening of gastrocnemius muscle, but does act to delay any shortening of muscle (Eames et al, 1999).

1.17. Effect of Botulinum toxin type A on joint Range of Motion (ROM)

Koman et al, (1993) and Cosgrove et al, (1994)) confirmed increases in the range of passive as well as active movements. For example, two open –label studies showed that reduction in calf muscle spasticity improved the passive ankle dorsiflexion.

Active ROM measured at the ankle shows significant increases after Botulinum toxin type A treatment, whereas passive ROM does not change (Ubhi et al, 2000). One possible explanation for the lack of effect of

Botulinum toxin type A on passive movement is that Botulinum toxin type A affects the “dynamic” spastic component as opposed to the range of passive movement, which encapsulates resistance, produced by muscle or joint connective tissue (Ubhi et al, 2000).

Fragala et al, (2002) studied impairment, disability and satisfaction outcomes after lower-extremity Botulinum toxin type A injections in seven children with cerebral palsy. All the children demonstrated an increase in passive range of motion and decrease in spasticity in at least some of the injected muscles. Six of the seven children demonstrated improvements in disability and parent satisfaction outcomes.

1.18. Effect of Botulinum toxin type A on energy expenditure

Ubhi et al, (2000) and Corry et al, (1999) carried out controlled trials of the effect of Botulinum toxin type A on energy expenditure during walking following Botulinum toxin type A injections into the hamstrings of children with cerebral palsy and crouch gait. The results were variable, but in some children there was a significant improvement in knee extension on kinematic studies and a significant decrease in energy consumption.

1.19. Use of Botulinum toxin type A in the upper limb

Upper limb spasticity frequently causes difficulties with activities of daily living. Severe hypertonia of upper limb muscles is a common complication in patients with an upper motor neurone lesion. Botulinum toxin type A has been used to reduce spasticity to the wrist and fingers in patients who have suffered a stroke (Bakheit et al, 2001).

Bakheit et al, (2001), Wall et al. (1993) were the first to report the use of Botulinum toxin type A in the upper limbs of five children with cerebral palsy. Injection into the adductor pollicus and rigid splinting led to

improvement in hand function. All cases were shown to improve in terms of both function and appearance. Friedman, Diamond, Johnson and Daffner (2000) found a significant decrease in upper limb spasticity when the elbow flexors were injected. Improvements were found with elbow and wrist extension and flexion at 1-3 months after the injection with Botulinum toxin type A in cerebral palsy children.

1.20. Effect of Botulinum toxin type A on functional activities

Linder et al, (2001) studied the effect of Botulinum toxin type A on motor function, using the Gross Motor Function Measure (GMFM), in twenty-five children with cerebral palsy and spasticity. They recorded a significant improvement of gross motor functions after twelve months of treatment. The improvement occurred in both ambulatory and non-ambulatory children.

Other previous studies also demonstrated that treatment with Botulinum toxin type A led to reduction in spasticity and improvement in functional performance in standing and walking (Botos et al, (2003), Ubhi et al, (2000)).

1.21. BTX-A use for post operative pain reduction

Many surgeons use Botulinum toxin type A during operations to reduce painful post-operative spasms and to protect the soft tissues from involuntary movement and spasms until healing occurs. Severe post-operative pain and spasm is often present after adductor-release surgery to treat or prevent hip dislocation in children with spastic cerebral palsy. Barwood, Bailiew, Boyd, Brereton, Low, Nattrass and Graham, (2000) showed that there may be an important clinical role for Botulinum toxin type A in reducing post-operative pain and analgesic requirement after hip

adductor release surgery in children with cerebral palsy. These authors found Botulinum toxin type A reduced the mean pain scores in 74% of cases (Barwood et al, 2000).

1.22. Botulinum toxin type A use in the treatment of drooling in children with C.P

In 2000 the first trial results, in adults with Parkinson's disease showed Botulinum toxin type A to be an effective treatment for drooling. No side effects were observed. The authors conclude that Botulinum toxin type A is an effective treatment for the common problem of drooling saliva in chronic neurologic disease (Pal, Calne, Calne and Tsui, 2000). Likewise Dogu, Aaydin, Sevim, Umit and Aral, (2004) showed an improvement in the mean rate of saliva secretion in the first week after Botulinum toxin type A injection into the parotid gland. Vaile and Finlay, (2006) suggested that Botulinum toxin type A inhibits saliva production. In a study of 45 school-aged children, Botulinum toxin type A injections significantly reduced salivary flow rate in the majority of children suffereing from cerebral palsy with severe drooling, demonstrating high response rates up to 24 weeks (Jongerius, Rotteveel, Limbeak, Gabreëls, Hulst and Hoogen, 2004).

1.23. Botulinum toxin type A use in the treatment of blepharospasm and dry eye

Botulinum toxin type A injections were effective in relieving blepharospasm but were not successful in treating dry eye syndrome. In the patients suffering from blepharospasm and dry eye Botulinum toxin type A is an effective treatment for reducing spasms (Horwath, Bergloeff, Floegel, Haller and Schmu, 2003).

1.24. Correlation between the effect of Botulinum toxin type A and age

The data on the relationship between the responses to Botulinum toxin type A and the age of patients are contradictory. Thompson et al, (1998) reported that there was no correlation between the patient's age and the response to Botulinum toxin type A injection. However Cosgrove et al, (1994) found an inverse relationship between the therapeutic response and the patient's age. Similarly, Graham et al, (2000) and Ubhi et al, (2000) found that treatment at an early age before the development of contractures produces better results and may prevent deformity, thus giving long term benefit and delay surgery. Eames and colleagues et al, (1999) have suggested that the age effect may be because of a change of the child's problems from dynamic to a fixed defect overtime as contractures develop. Graham (2000) found early treatment is preferable to give maximum response. Fragala et al, (2000) also found that young children benefited from Botulinum toxin type A injection more than older children.

1.25. Comparison of Botulinum toxin type A treatment with plasters casts

Flett et al, (1999) compared the effect of Botulinum toxin type A injection into the calf with the effect of serial casting. They found that the effects of the Botulinum toxin type A last longer than the effects of casting. Desloovere, Molenaers, Jonkers, Cat, De, Borre, Nijs, Eyssen, Pauwels and De Cock, (2001) found significant changes in the walking patterns of both groups with the most significant changes at the ankle joint. Children who received casts after injections demonstrated a slightly more pronounced benefit, mainly in the proximal joints. Botulinum toxin type A injections were of similar efficacy to serial fixed plaster casting in improving dynamic calf tightness in ambulant or partially ambulant children with cerebral palsy.

Botulinum toxin type A injections and serial casting have become an increasingly integral part of treatment for children with cerebral palsy over the past 10 to 15 years. The combined therapy shows a significantly greater increase in passive range of motion of the ankle joint in comparison to treatment with Botulinum toxin type A alone (Glanzman; Kim; Swaminathan and Beck, 2004). Similarly, patients who received both serial casts and Botulinum toxin type A show more sustained improvements in Gross Motor Function Measure scores (Bottos, 2003). Glanzman et al, (2004) found the combined treatment gave greater increases in passive range of motion of the ankle joint in comparison with Botulinum toxin type A alone.

1.26. GMFM as an outcome measure for the evaluation of Botulinum toxin type A treatment

The GMFM technique has been used in a variety of clinical and research situations. Its results are sensitive and reliable. Graham et al, (2000) reported that the GMFM is the most useful validated objective outcome measure. It is more appropriate for assessing children in the mid-range of disability. In children with mild disability the GMFM may not be sensitive enough to detect change. Similarly, assessment of children with severe disability and generalised spasticity with GMFM may not be very accurate.

Evidence of the responsiveness of the GMFM to change includes the findings that the mean GMFM scores of the children with cerebral palsy changed over 12 months and that the mean change scores were related to age and severity of motor disability (Russell et al, 2000).

In an open label prospective study Linder et al. (2001) demonstrated the value of the GMFM in the assessment of cerebral palsy children treated with Botulinum toxin type A and followed up for one-year. Bottos et al. (2003) also found a significant improvement of gross motor function in children treated with Botulinum toxin type A and plaster casts.

However, Baker et al demonstrated a clear improvement in the dynamic component in patients with diplegic cerebral palsy after treatment with Botulinum toxin type A, but not in the overall GMFM scores. It is also possible that the GMFM is not sensitive enough to detect the functional improvements that were subjectively reported. The GMFM is designed to assess whether patients can perform various functions but does not assess how well each function is performed. It is, therefore, unable to detect improvements in the quality of function (Baker, Jasinski and Tymecka, 2002).

Reddihough, King, Coleman, Fosang, McCoy, Thomason and Graham, (2002) in a randomized study found that there were no statistical differences between the Botulinum toxin type A and control groups, at 3 and 6 months post injection. However, in another study functional outcomes assessed by the GMFM showed a statistically significant improvement after Botulinum toxin type A use (Jefferson, 2004).

1.27. Adverse effects of Botulinum toxin type A

Botulinum toxin type A is a safe anti-spasticity agent but adverse effects of Botulinum toxin type A can occur locally as a result of larger than necessary doses in a single muscle producing significant transient focal weakness, or systemically because of more than enough total body dose to several muscles (Jefferson, 2004).

Ptosis is the most common problem after injections for blepharospasm and hemifacial spasm (Jitpimolmard, Tiamkao and Laopaiboon, 1998). Significant adverse events associated with Botulinum toxin type A injections are rare. Approximately 20% of patients, or families, report concerns over muscle weakness, cramping, pain or problem in coordination (Koman et al, (1993); Ubhi et al (2000); Koman, Brashear, Rosenfeld and Chambers (2001); Papadonikolakis et al, (2003)).

Rosalind, (2004) found that the adverse events of Botulinum toxin type A could occur locally as a result of excessive doses in a single muscle, but they occur infrequently and generally mild in nature. Pain around the injection site is the most commonly reported complaint, frequent falls from balance problems, and generalized weakness may also occur (Ubhi, 2000) and (Mall et al, 2006).

Other authors including, Sutherland (1999), Linder (2001), Papadonikolakis et al (2003), and Sarioglu, Serdaroglu, Tutuncuoglu and Ozer (2003) did not observe any side effects in the studied population.

1.28. Aims of the study

Cerebral palsy is large clinical problem. One of the main problems in reviewing the literature is the use of several assessment scales and many treatments used alone or combination.

The aim of this study is to examine whether the combination of physiotherapy with Botulinum toxin type A treatment improve the clinical outcomes as assessed by GMFM and ROM for patients with cerebral palsy more than Botulinum toxin type A injections alone.

Chapter 2

Methods

2.1. Study design

This project used an open label study design. Both the clinical staff and the patient's family were aware of the treatment delivered. Ultimately, it is not possible to blind either group to the nature of the treatment delivered since it is immediately obvious whether muscles have been paralysed.

This was a prospective study. Patients were allocated to receive Botulinum toxin type A alone or Botulinum toxin type A and physiotherapy. The experiments were conducted at The Rehabilitation Centre of The Prince Sultan Military Hospital in Al Hada and in the Centres of the Disabled Childrens' Association in Mecca and Jeddah, in Saudi Arabia. The same protocols were followed at each centre. In all, 47 children participated in the study. These three centres treat about 325 children and so the sample recruited represents a significant proportion of the available patient population.

The children in the study had cerebral palsy, diplegia, spasticity of the ankle planter flexors and significant abnormal gait because of lower limb spasticity predominantly affecting the calf muscles. This study assessed of the effects of Botulinum toxin type A alone and in combination with intensive physical therapy in the treatment of these children. The study extended over 12 months.

The design of the experiment was reviewed and approved by the local review committee. The oldest children in the study were 14 years and so were too young to give consent. The patients' parents were fully informed of the nature and purpose of the study. Their parents gave written consent to participation and at least one parent attended all treatment and testing sessions.

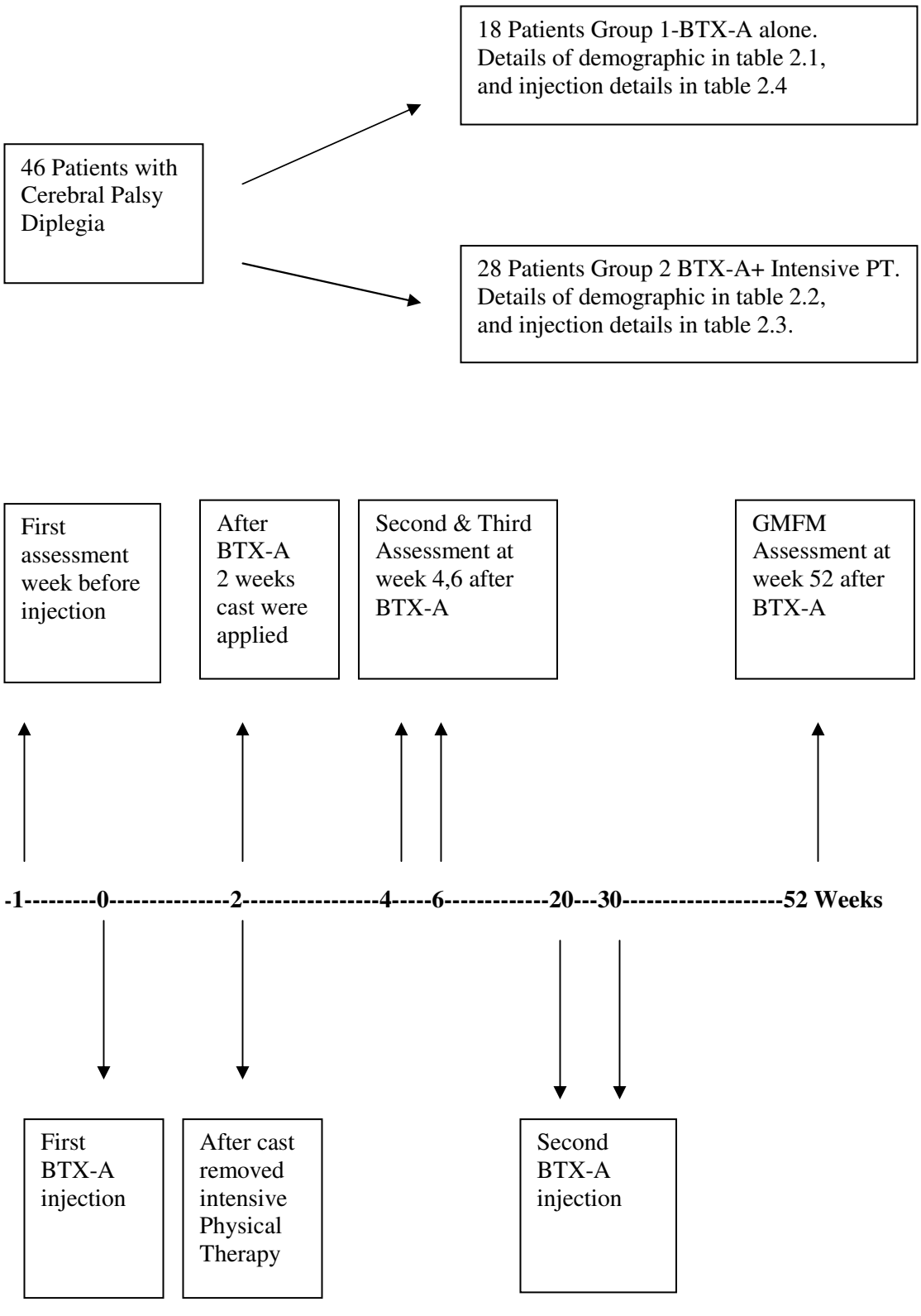


Figure 2.1. Scheme of study

The children were assigned to one of two groups: Group 1 received Botulinum toxin injections twice at six month intervals, their ankles were placed in plaster casts for 2 weeks after the first injection and they were fitted with medical shoes when the casts were removed. Group 2 received similar treatment with the addition of intensive physical therapy for 2 weeks after the removal of the casts. Additional information on the nature of these interventions will be given in sections 2.7.

The assignment to group 1 and 2 could not be done randomly. The children in group 2 had to live in the accommodation of the Rehabilitation Centre for the two weeks of intensive physical therapy. Thus, the allocation to groups was done by the social and domestic factors influencing their families. This results in group 1 containing 18 children and group 2 containing 28 children. The characteristics of the two groups were reasonably balanced for gender and body weight and baseline GMFM scores. These data are reported in section 2.3. Measurements were made one week before the first injections and at 4, 6 and 52 weeks later. See figure 2.1.

2.2 Ethical Approval

The design of the experiment was reviewed and approved by Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre in Saudi Arabia. Inspection of the clinical records identified 47 children as potential subjects. Since the children were too young to give consent, each patients' parents were informed of the purpose of the study. Their parents gave informed written consent before treatment started. At least one parent was present throughout the four scheduled visits. The consent forms are shown in appendix 2. These are translations of the original Arabic documents.

One child dropped out of the study after second assessment because of severe allergy. This was not associated with the experiment. Four children from group 2 did not attended at final assessment for GMFM at 52 weeks.

2.3. Subjects

46 children, 25 boys and 21 girls were recruited for the study. They all had spastic diplegia and dynamic equinus foot deformity. They were between 25-154 months at the start of the study. Details of anthropometric data of patients, their height, weight, and age are shown in tables 2.1. and 2.2.

2.3.1. Inclusion criteria for the study

Parental consent was obtained.

The patients had cerebral palsy, diplegia and spasticity of the ankle plantar flexors, significant gait abnormalities due to dynamic equinus with an inability to achieve heel strike because of lower limb spasticity predominantly affecting the calf muscles. The patient should be ambulatory. This includes children using walkers.

2.3.2. Exclusion criteria for the study:

1. Evidence of contracture of gastrocnemius/soleus defined as significantly reduced range of motion at the ankle during passive stretches.

2. Severe athetoid movement in the target leg.

3. A significant difference between the length of the right and left legs causing a gait asymmetry.

4. Obvious atrophy of the calf muscles of the leg to be treated in the study.

5. Child is waiting for surgery or has had previous surgery of the foot, leg, or ankle.

6. Other conflicting concurrent treatment, such as plaster casts, orthoses.

ID. No.	Gender	Treatment	Weight (Kg)	Height (cm)	Age (month)
35	F	BTX-A	15	107	74
23	F	BTX-A	11	84	29
44	M	BTX-A	16	105	70
40	M	BTX-A	16	109	74
37	M	BTX-A	17	107	77
30	M	BTX-A	16	108	78
28	F	BTX-A	17	107	80
41	M	BTX-A	15	98	86
17	M	BTX-A	18	110	80
32	F	BTX-A	15	99	97
9	F	BTX-A	30	104	109
20	F	BTX-A	44	139	129
5	F	BTX-A	46	145	154
25	M	BTX-A	13	88	45
36	M	BTX-A	13	106	74
45	M	BTX-A	13	107	79
46	F	BTX-A-	15	108	96
10	M	BTX-A-	38	111	104

Table 2.1.

The characteristic of children in group 1. The table shows the anthropometric details of patients: their ages, (in months) heights in cm, and weights in kg. The middle column shows the type of treatment Botulinum toxin type A only.

ID. No.	Gender	Treatment	Weight (Kg)	Height (cm)	Age (month)
31	M	BTX-A+PT	16	105	69
27	M	BTX-A+PT	12	86	28
4	F	BTX-A+PT	16	98	84
7	F	BTX-A+PT	27	105	82
21	M	BTX-A+PT	11	84	25
42	M	BTX-A+PT	11	86	27
33	M	BTX-A+PT	11	84	28
11	F	BTX-A+PT	11	85	32
26	F	BTX-A+PT	12	87	25
43	F	BTX-A+PT	13	84	36
38	F	BTX-A+PT	12	85	37
39	M	BTX-A+PT	12	86	43
29	M	BTX-A+PT	12	85	45
3	F	BTX-A+PT	17	85	45
6	F	BTX-A+PT	12	84	46
15	F	BTX-A+PT	13	85	48
34	F	BTX-A+PT	13	85	33
18	F	BTX-A+PT	14	95	56
1	M	BTX-A+PT	13	84	59
8	F	BTX-A+PT	14	85	60
2	M	BTX-A+PT	16	86	66
14	F	BTX-A+PT	17	85	67
19	M	BTX-A+PT	15	93	72
22	M	BTX-A+PT	18	106	73
12	M	BTX-A+PT	20	110	91
13	M	BTX-A+PT	17	109	94
24	F	BTX-A+PT	43	144	106
16	F	BTX-A+PT	40	135	132

Table 2.2.

The characteristic of children in group 2. The table shows the anthropometric details of patients: their ages (in months) heights in cm, and weights. The middle column shows the type of treatment Botulinum toxin type A + Physical therapy.

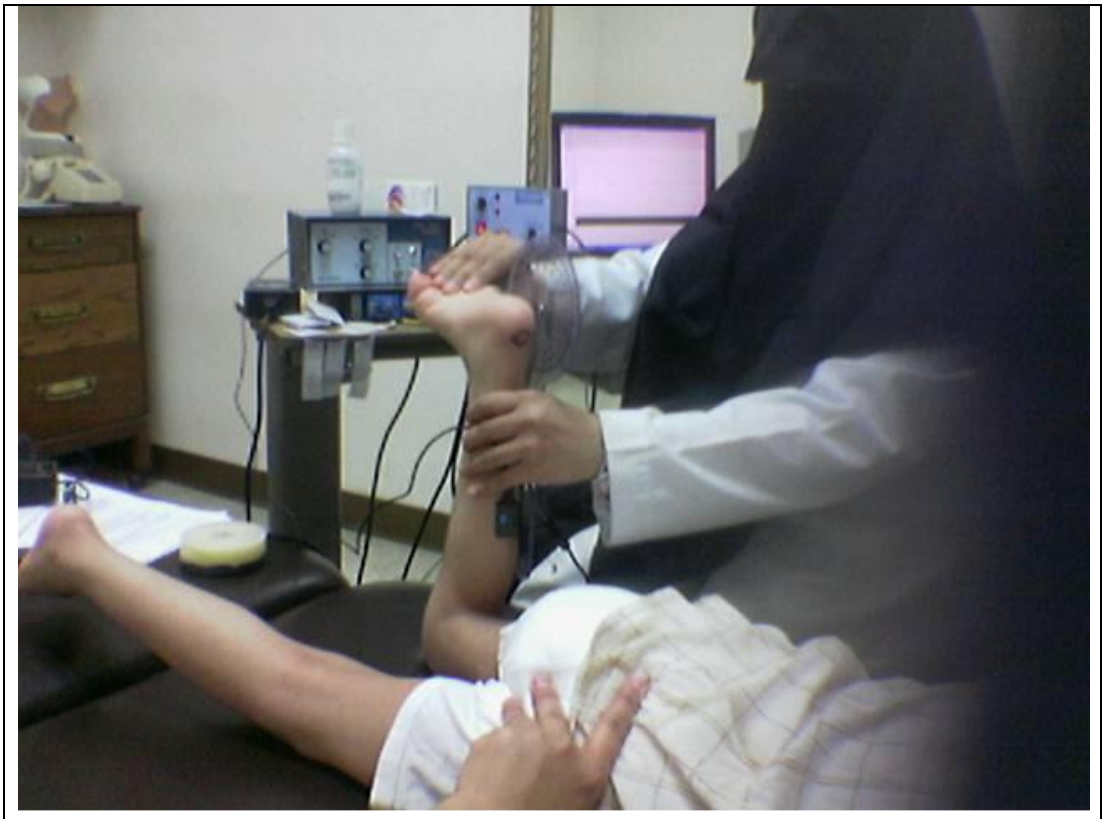


Figure 2.2.

The picture shows the investigator working with one of the children.

The child is lying on a bed in a prone position. The knee of the target leg is flexed to 90 degrees. The skin mounted EMG electrode-amplifier can be seen fixed over the soleus muscle. A manual and an electrogoniometer measurement of the range of motion of the ankle are taken simultaneously.

2.4 Physical Examination

The week before the Botulinum toxin type A injects were made, each child was examined by an orthopaedic surgeon and a physical therapist. This was done to define a treatment plan to identify which muscles will receive Botulinum toxin type A injections and to calculate the appropriate doses. In addition, the passive range of motion of the hip, knee, and ankle joints of both limbs were measured.

2.5. Dosing and injection procedure

All the Botulinum toxin type A injections were made by Dr Shakfa, the head of the Orthopaedic Surgery Department of the Prince Sultan and Al-Hada Armed Forces Hospital and Rehabilitation Centre at Saudi Arabia. Botulinum toxin type A product used in this study was Botulinum toxin type A (Allergan, USA).

All injections were prepared by following a standard procedure. Each vial of contains a powder containing 100 units. This was reconstituted by dissolving it in 1 ml of normal saline. The powder dissolves readily and it is not necessary to shake the vial (Bakheit, 2001). The dose administered was 6 units/kg of body weight per injection site.

Where a child receives multiple injections, the dosage of Botulinum toxin type A per muscle or the number of sites targeted was restricted by a total permissible dose. The dose calculation takes into account the mass of the child and the number of muscles targeted (Preiss, Condie, Rowley and Graham, 2003). In this study, the maximum allowed dose was 200 units per treatment session.

The orthopaedic surgeon identified the target muscles using anatomical land marks without electromyography guidance. The soleus and gastrocnemius muscle were palpated whilst being stretched passively. The choice of muscles selected for injection depended on the degree of spasticity. The injections were performed using appropriately sized syringe under antiseptic conditions. The needle was inserted through the fascia into the proximal third of the muscle and the drug was injected. Local anaesthetics were not used before administering the Botulinum toxin type Ainjections in this study. Koman et al, (1993) found that unbuffered lidocaine was more painful than a toxin injection alone.

Figure 2.3.

The picture shows the investigator and the orthopaedic surgeon. The child during injection of Botulinum toxin type A. One of the parents was present throughout the injection and injection was performed under antiseptic condition, without local anaesthesia.

ID. No.	R Hip Adductor	L Hip Adductor	R Knee Flexor	L Knee Flexor	R. Gastro	L. Gastro	R. Soleus	L. Soleus
2	.	.	.	.	50	50	10	10
3	.	.	.	.	40	40	10	10
4	.	.	20	20	20	20	10	10
6	20	20	.	.	30	30	.	.
7	.	.	25	25	50	50	25	25
8	.	.	.	.	40	40	10	10
11	.	.	.	.	30	30	20	20
12	25	25	20	20	20	20	10	10
13	.	.	25	25	30	30	20	20
14	.	.	.	.	30	30	20	20
15	.	.	.	.	40	40	10	10
16	20	20	50	50	20	20	10	10
18	.	.	.	.	30	30	20	20
19	.	.	.	.	40	40	10	10
21	20	20	.	.	30	30	10	10
22	.	.	.	.	30	30	20	20
24	.	.	.	.	50	50	10	10
26	20	20	.	.	20	20	10	10
27	25	25	15	15	30	30	.	.
29	.	.	15	15	30	30	10	10
31	.	.	.	.	35	35	15	15
33	20	20	.	.	20	20	10	10
34	25	25	25	25	20	20	10	10
38	15	15	.	.	30	30	.	.
39	.	.	20	20	30	30	10	10
42	20	20	.	.	20	20	10	10
43	25	25	25	25	30	30	.	.

Table 2.3.

Botulinum toxin type A dose according to treatment Botulinum toxin type A + Physical therapy, group 2. The choice of muscles selected for injection depends on the degree of spasticity and the expected short-term goal of the physiotherapist. The used dose for each child was at 6-unit/Kg--body weight but not more than 200 units.

ID. No.	R Hip Adductor	L Hip Adductor	R Knee Flexor	L Knee Flexor	R Gastro	L. Gastro	R. Soleus	L. Soleus
5	.	.	.	.	50	50	10	10
9	35	35	25	25	30	30	10	10
10	.	.	40	40	40	40	20	20
17	.	.	.	.	35	35	15	15
20	.	.	.	.	50	50	.	
23	.	.	.	.	40	20	25	15
25	.	.	.	.	30	30	20	20
28	.	.	.	.	30	30	10	10
30	35	35	25	25	30	30	10	10
32	35	35	25	25	30	30	20	
35	.	.	.	.	40	40	10	10
36	30	30	15	15	25	25	15	15
37	.	.	30	30	30	30	10	10
40	35	35	25	25	30	30	10	10
41	35	35	25	25	30	30	10	10
44	.	.	.	.	40	40	10	10
45	30	30	15	15	25	25	15	15
46	.	.	25	25	30	30	10	10

Table 2.4.

Botulinum Toxin-A dose according to treatment Botulinum Toxin-A only, group 1. The choice of muscles selected for injection depends on the degree of spasticity and the expected short-term goal of the physiotherapist. The used dose for each child was at 6-unit/Kg- body weight but not more than 200 units.

Figure 2.4.

This picture shows an example of the medical shoes fitted to all the children in the study 4 weeks after the Botulinum toxin –A injection.

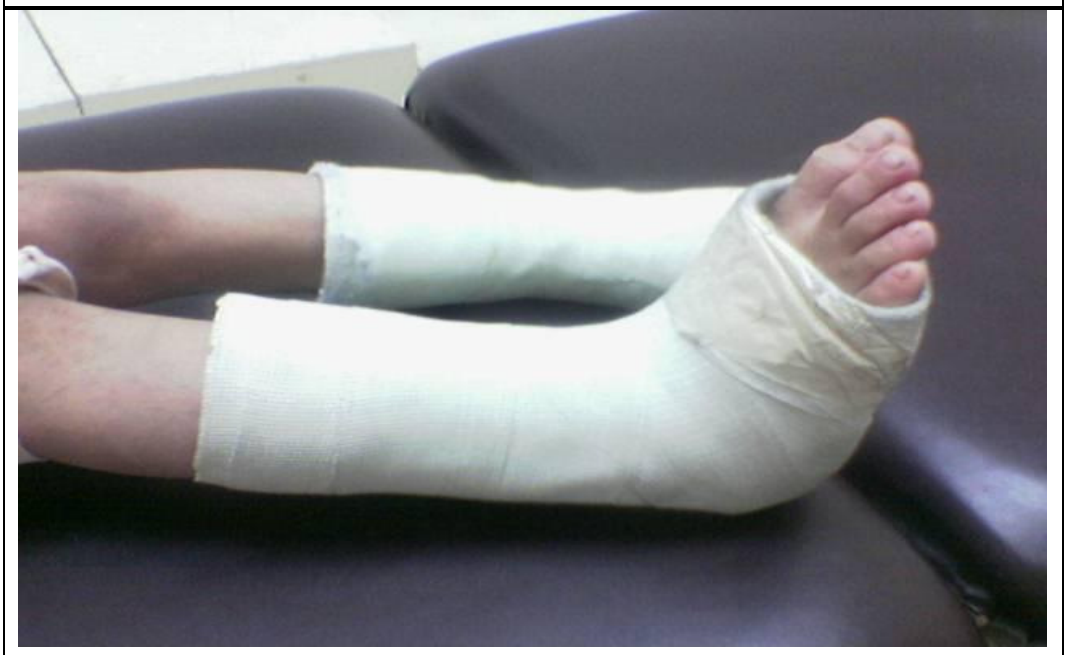


Figure 2.5.

This picture shows an example of the casts fitted to all the children in the study 2 weeks after the Botulinum toxin –A injection.

2.6. The outcome measures

The primary outcome measure was the gross motor function measurement (GMFM). The secondary outcome measures were range of motion at the left ankle joint as assessed by electrogoniometers and stretch reflex changes as assessed by electromyography during stretches of the ankle extensor muscles.

Each of these will be described in turn.

2.6.1. Gross Motor Function Measurement

The GMFM questionnaire is a standardised observational instrument designed and validated to measure the change in gross motor function over time in children with cerebral palsy (Russell, 2002).

The GMFM test includes 88 items grouped in five dimensions:

(A) Lying and Rolling

(B) Sitting

(C) Crawling and Kneeling

(D) Standing

(E) Walking, Running and Jumping

Each item of the test is scored on a 4-point scale and percentage score is calculated for each dimension. The total score is obtained by calculating the mean of the five dimension scores. The full GMFM scale is shown in Appendix 2 at the end of thesis.

The guidelines contained in the GMFM manual used for scoring of each item were followed. These were:

0 = does not initiate

1 = initiates

2 = partially completes

3 = completes

NT = not tested

Each of these scores is defined as:

(0) “Does not initiate” applies to the child who is requested to attempt an item and he/she is unable to commence any part of the activity.

(1) “Initiates” refers to less than 10% task completion.

(2) “Partially completes activity “ >10% but <100% of the task completed.

(3) “Completes” describes 100% task completion.

“Not tested” was used when an item had not been administrated or when a child refused to attempt an item which he/she was expected to complete partially (Russell et al, 1994).

The total GMFM score and dimension scores collected at each evaluation.

2.6.2. Electronic Goniometer

A twin axis electrogoniometer (SG 110 Ankle dorsiflexion/plantarflexion Biometrics Ltd, Nine Mile Point Ind. Est., Gwent, NP11 7HZ, UK) was used to detect the movement of the ankle joint during tests. The goniometers were sensitive to the movement in the dorsiflexion –plantarflexion plane. Any relative movement between the arms of the goniometer changes its output voltage proportional to the movement applied. The output voltage was amplified, digitised by a CED micro 1401 (Cambridge Electronic Design, Cambridge, UK) interface and recorded in the computer during the test.

The goniometer was fixed on the lateral side of the patient's ankle joint. The proximal end-block was placed parallel to a line between the lateral malleolus and the fibula head. The distal ankle end-block was aligned with the plantar surface.

2.6.3. Calibration of Electrogoniometers

A calibration was performed on the electrogoniometer during the assessment session. The electrogoniometer was attached to the limb as described above. Patients were barefoot and dressed in shorts to facilitate the correct positioning of the goniometer. The ankle joint was held at five positions at 10-degree steps between 60 and 120 degrees of dorsiflexion. The positions were determined with reference to a manual goniometer (See figure 2.5 and 2.6.).

The electrogoniometer signals were filtered to remove 50 Hz components before being digitised at 100Hz by CED 1401 micro A-D converter. The output was recorded with Spike 2. Data were saved for analysis.

The graph in figure 2.7. shows typical calibration data. The electrogoniometer has linear relationship with the ankle joint position. Therefore the equation can be used to translate output voltages values into ankle angles.

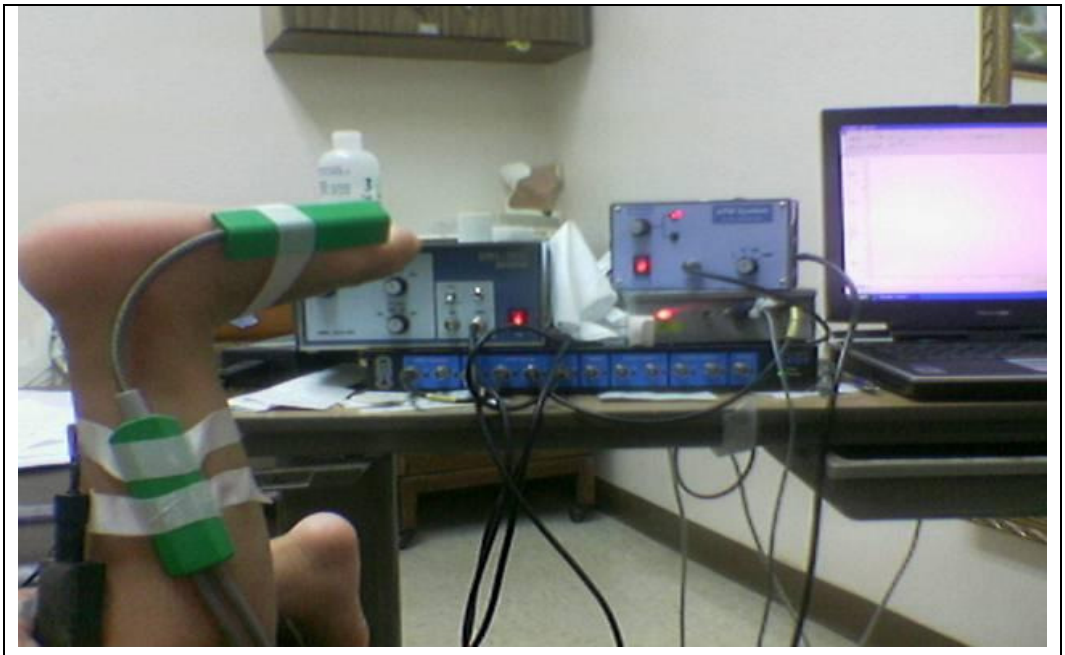


Figure 2.6.

The child lay on bed in prone position, with the target leg flexed at 90 degrees. EMG electrode fixed on the soleus muscle, and the skin was cleaned with an alcohol wipe. Range of motion measured by Electronic Goniometer fixed on the lateral side of the left ankle. Data were analysis using the spike 2 software systems.

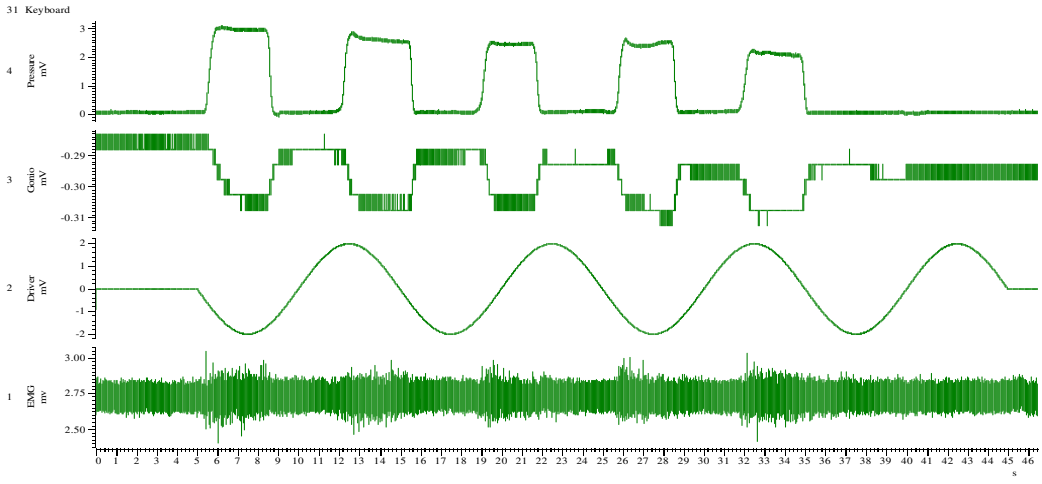


Figure 2:7.

A raw data of EMG. The channels show: 1) EMG activity of the soleus muscle. 2) Driver 3) Ankle joint movement recorded by electrogoniometer 4) Pressure to stretch ankle joint from neutral position to dorsiflexion position 5 times

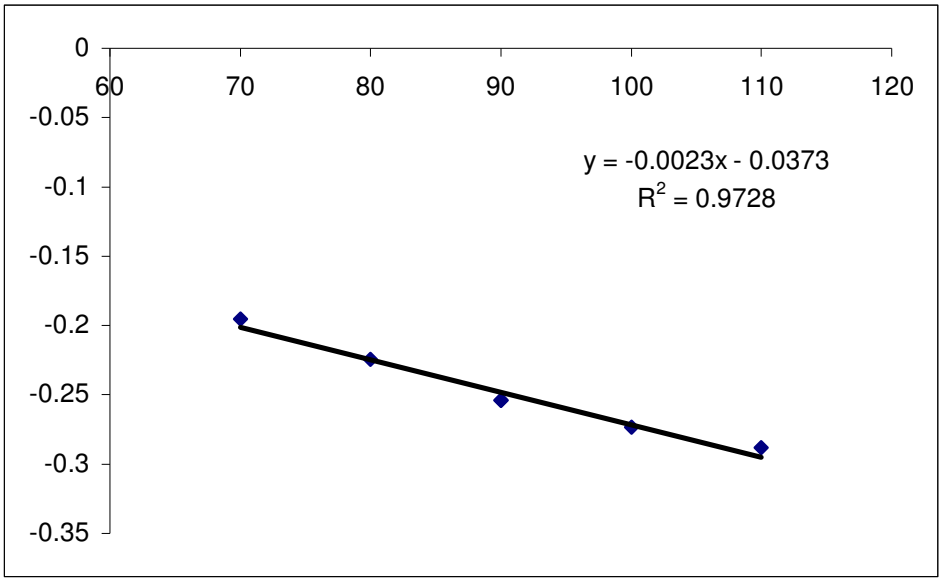


Figure 2.8.

The calibration of the electrogoniometer used to measure ankle joint position

2.6.4 Electromyography Recording

Electromyography (EMG) is widely used to evaluate muscle activity (Basmaijan, 1985). In this project surface electromyography was used to record activation of the muscles under investigation. This was preferred to needle electromyography in the hope that it would be better tolerated by the children. Needle EMG can work well when movement is restricted and forces are low. This could not be guaranteed in this study and the experimenters wanted to minimise discomfort in the children. Needle EMG allows more restricted spatial sampling of motor unit needle the needle tip and this can give clearer records of single motor unit activity. However, the surface EMG gives a broader sample of many motor units in the muscle and this wider sample will allow a better representation of whole muscle activity.

A small skin mounted pre-amplifier with integrated electrodes, measuring 7mm in diameter, was used for recording the electromyography (EMG). This recording configuration eliminated connecting wire and so movement artefacts were kept to a minimum. The EMG electrode with its integrated preamplifier can be seen in figure 2.8. The skin at the recording sites was prepared very carefully before attaching the electrodes. It was cleaned with alcohol to decrease the impedance and to improve the EMG recording. When the skin dried, the electrodes were coated with conductive gel and attached by tapes. This ensured good signal/noise characteristics. The electrodes were placed over the belly of the soleus muscles, longitudinal to the predicted path of the muscle fibres as shown in figure 2.9.

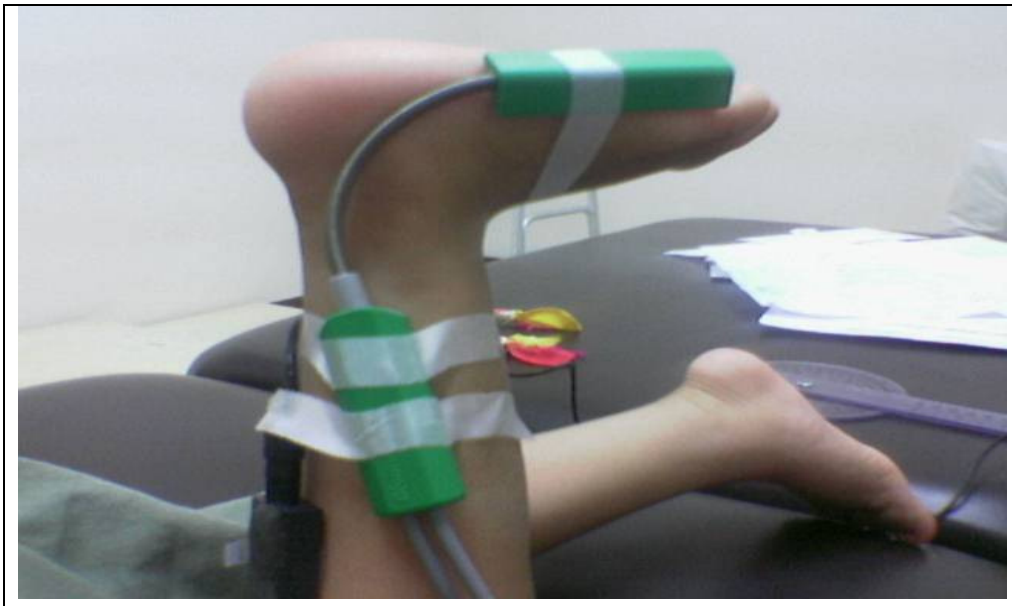


Figure 2:9.

The patient lay on bed in prone position, with the target leg flexed at 90 degrees. EMG electrode fixed on the soleus muscle, and the skin was cleaned with an alcohol wipe. ROM measured by manual goniometer and electrogoniometer. Both of them were fixed on the lateral side of the left ankle.

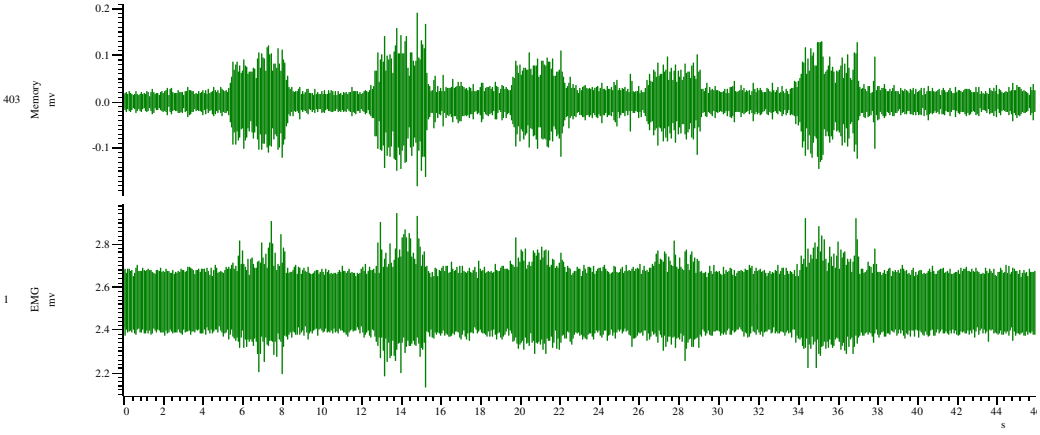


Figure 2:10.

The EMG pattern after high pass filter band stop filter.

2.6.5 General EMG Processing Procedures

The raw EMG data were not always clear. There were frequent movement artefacts because the children did not always lie still during tests. In addition, sometimes there was low EMG activity. This was always likely after Botulinum Toxin-A injections had paralysed muscles.

The Spike2 software (version 3.15) has a number of digital filters and these were used to remove artefacts and to enhance the EMG signal. EMG was filtered by using high pass digital filter and then by band stop filter.
The filtered EMG could then be rectified and smoothed. Typically, a smooth function with a 0.05 time constant was used. In addition, full wave rectification helped the analysis (see figure 2.10.).

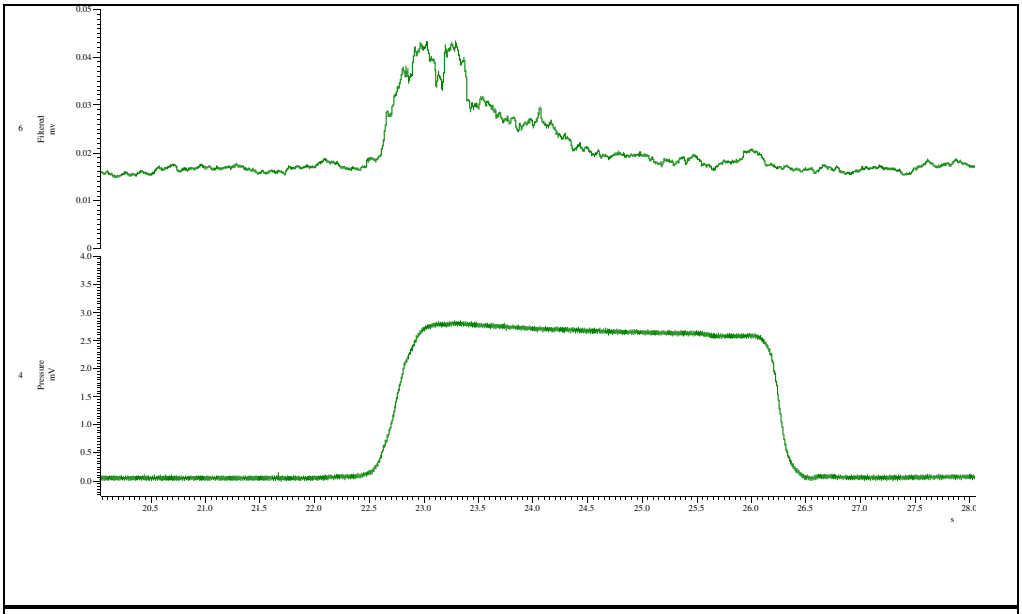


Figure 2.11.

The figure shows the EMG pattern after high pass filtering and after subsequent rectification.

The onset of EMG activity was determined by setting a notional threshold five times larger than the mean value of the background EMG. Horizontal cursors were used.

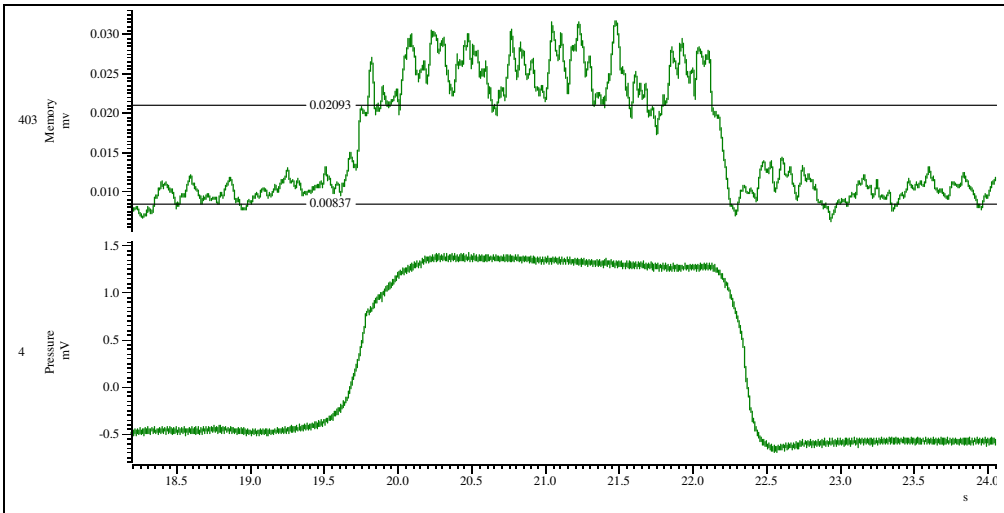


Figure 2.11.

The figure shows the EMG pattern after high pass filtering and after subsequent rectification.

2.6.6. Dynamometer (Pressure gauge)

The pressure applied was monitored with a pressure transducer. The pressure needed to stretch the calf muscles from the rest position in flexion to the maximum in dorsiflexion was applied at a constant rate. The change in angle from the initial position to the angle at peak pressure will be estimated for each of the five stretches.

2.7. Statistical Analysis

A computer program was used to interpret scores for the GMFM-66. This scoring program is called the Gross Motor Ability Estimator (GMAE), the GMAE program has a self-contained tutorial. GMFM-66 scores are obtained by entering the GMFM item scores into the program individually for each child. The option to enter the GMFM scores individually into the program was designed for clinical evaluation of children and to track their progress over time (Russell, 2002).

During experiments, all values were collected as numerical outputs by GMFM, or angle of motion. Data were saved as Excel files in the first instance. Following this, data were transferred to the Minitab version 14 for further statistical analysis. The data were analysed using a one-way analysis of variance (unstacked). Results were considered to be significant at $P < 0.05$.

Chapter 3

Results

3.1. Introduction

This chapter contains results from experiments performed in The Rehabilitation Centre of The Prince Sultan Military Hospital in Al Hada and in the centres of The Disabled Children' Association in Mecca and Jeddah. These centres treat children who live in the eastern area of Saudi Arabia in the cities of Jeddah, Taif and Makkah.

The results are divided into four main sections:

1. Characteristic features of children with cerebral palsy in institutionalised care.
2. GMFM measurements in children included in the study.
3. Measurements of the range of motion at the ankle joint in these children.
4. Measurements of stretch reflex characteristics in a sample of these children.

3.2 Characteristic features of children with Cerebral Palsy.

The experimental procedures were reviewed and approved by The Rehabilitation Centre of The Prince Sultan Military Hospital in Al Hada and in the centres of The Disabled Children' Association in Mecca and Jeddah. Proxy consent was obtained from the parents, who attended all sessions.

The author comprehensively assessed 163 children. In addition, all the selected children were evaluated in physical therapy department at The Rehabilitation Centre of The Prince Sultan Military Hospital in Al Hada. The physical therapy assessment forms used in this study are provided in Appendix 3.

Children were recruited from Prince Sultan Hospital and Al-Hada Armed Forces Hospital, Disabled Children Association Jeddah and Makkah Centre and Rehabilitation Centre. The Ministry of Labour and Social Affairs of the Kingdom of Saudi Arabia supervises these centres.

Recruiting children from several sites increased the number of suitable subjects for inclusion in the study. However, it also posed logistical problems. In an attempt to standardise treatments, Dr Shakfa and the investigator referred children to Prince Sultan Hospital and Al-Hada Armed Forces Hospital where they were all assessed before receiving Botulinum Toxin-A injections. In addition, all the children who received intensive physical therapy were treated by a single team of physiotherapists at The Disabled Children' Association Centre in Makkah. This ensured consistent treatment but it meant that the assignment of children to the two experimental groups was not fully randomized. The details of the assignment were given in chapter 2 section 2.1. The effects of this process are analysed in section 3.3. Briefly, there were no significant statistical differences caused by the assignment process.

The costs of the treatment were divided between the Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre and the Ministry of Labour and Social Affairs. The Botulinum Toxin-A injections for each child cost approximately £300, a total of £14100 for the 47 children. The costs of the additional physiotherapy sessions were borne by the Ministry.

One hundred and sixty three children were comprehensively assessed by a physical therapy examination in each centre and hospital. The characteristics of these children are summarised in table 3.1.

Approximately equal numbers of male and female children were assessed. None of the children were assessed as spastic monoplegic. However, the other five types of cerebral palsy were observed.

The largest group of children was classified as spastic diplegic. This group accounted for 60% of children assessed. There were significant numbers of hemiplegic and paraplegic children, 19% and 15% respectively in the group. There were smaller numbers of dyskinetic, hyperkinetic, triplegic and ataxic cases. This pattern reflects the expected frequencies of these types of cerebral palsy. The data on the aetiology of the cases shows the expected pattern, where prenatal problems predominate. Figure 3.1 and 3.2

The assessment of ambulatory status was done by visual inspection in the clinic and with reference to their clinical records. The ambulatory status was very varied. 34% of the children were capable of walking independently. 25% of the children used a walker. Children who walked supported by their parent or with crutches represented 6% and 5% respectively. 27% of the children could not walk and relied on a wheelchair. Only 3% of the children depended on baby wheelchairs.

A	Sex	Number	%
	Male	85	52%
	Female	78	48%
B	**Cerebral Palsy Classification**		
	Spastic diplegia	98	60%
	Spastic hemiplegia	31	19%
	Spastic quadriplegia	24	15%
	Dyskinetic hyperkinetic	7	4%
	Spastic triplegia	2	1%
	Ataxia	1	1%
C	**Aetiology**		
	Prenatal	75	46%
	Postnatal	55	34%
	Perinatal	33	20%
D	**Ambulation Status**		
	Independent	55	34%
	Wheelchair	44	27%
	Walker	41	25%
	Holding by parents	10	6%
	Crutches	8	5%
	Baby wheelchair	5	3%
E	**Gait Characteristics**		
	Toe-to-toe	65	40%
	Unable to walk	58	36%
	Occasional heel-to-toe	31	18%
	Toe-to-Heel	8	5%
	Ataxic Gait	1	1%
F	**Included**		
	No	116	71%
	Yes	47	29%

Table 3.1.

Characteristic features of the 163 children assessed for this study. The assessment of the children status was done by visual inspection in the clinic and with reference to their clinical records

Figures 3.1 to 3.3 show the data tabulated above.

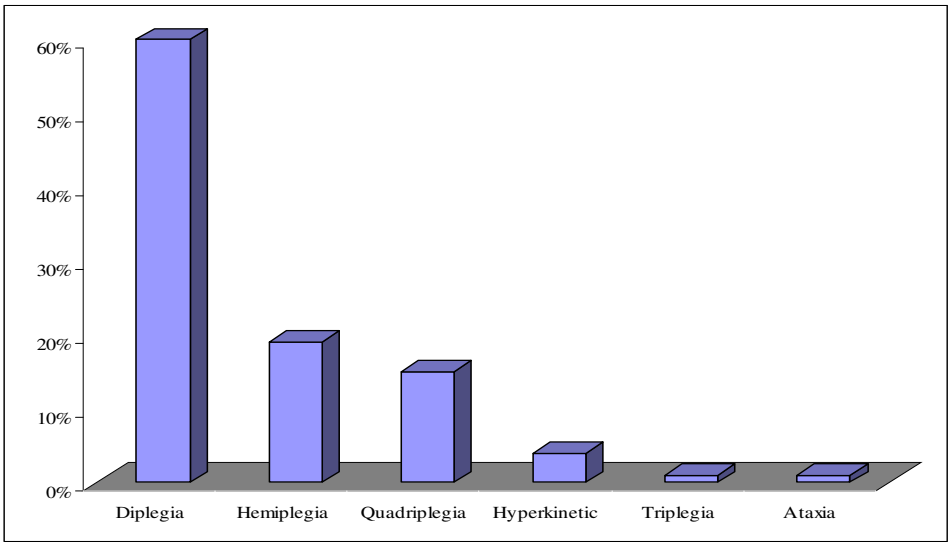


Figure 3.1.

Classification of Cerebral Palsy replotted from the data in table 3.1. 60% of children were classified as spastic diplegic. There were 19% and 15% hemiplegic and paraplegic. There were smaller numbers of dyskinetic, hyperkinetic, triplegic and ataxic cases

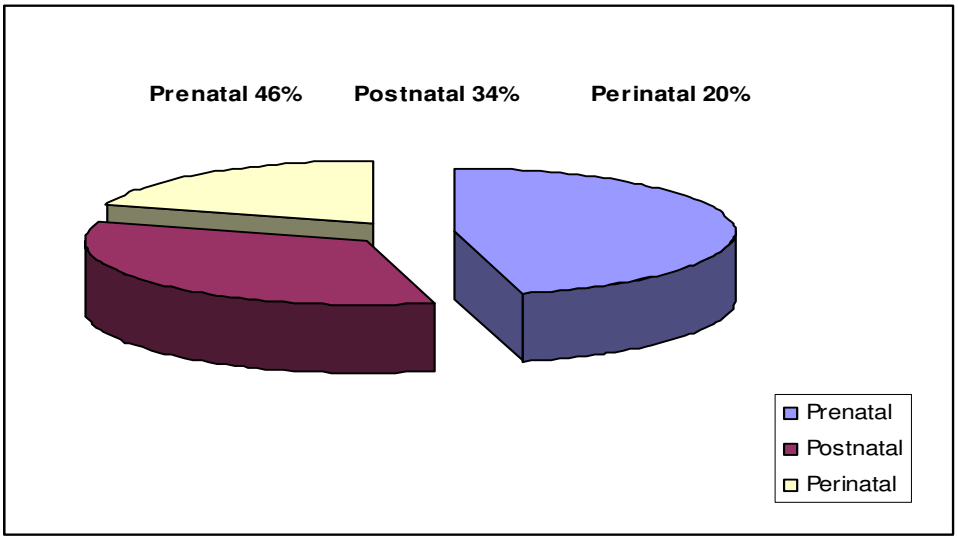


Figure 3.2.

Aetiology of 163 Cerebral Palsy children, 75 prenatal, 55 postnatal and 33 perinatal. Replotted from the data in table 3.1.

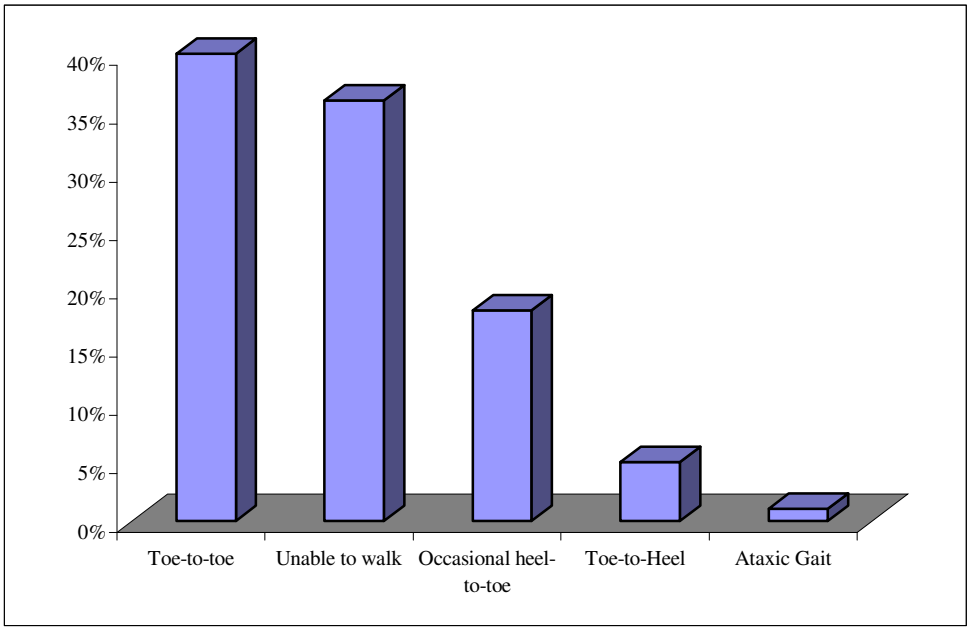


Figure 3.3.

Descriptions of the gait in the children reviewed. Replotted from Table 3.1

Further classification of the children who were able to walk showed that the most frequent pattern used was toe-to-toe walking. The next largest group was those who occasionally manage heel to toe walking.

Using the inclusion and exclusion criteria listed in tables 3.2.and 3.3, only 46 children satisfied the inclusion criteria and entered the study. This was 29% of the children initially assessed. A list of reasons for exclusion is summarized in Table 3.3. The main reasons excluding children was they were unable to walk, 42% of those excluded and children have history of surgery of the left leg, foot, or ankle, 29% of those excluded.

	Number	Percentage
Fixed contracture	25	22%
Surgery	17	5%
Unable to walk	14	12%
Quadriplegia	10	9%
Sever mental retardation	8	7%
Previous BTX-A injection	8	7%
Hemiplegia	8	7%
Athetosis	8	7%
Hypotonic	5	4%
Parents refused due to physician advice	5	4%
Younger than 2 years	3	3%
Parents refused	3	3%
Older than 13 years	2	2%
Total	116	

Table 3.2.

A list of reasons why children were excluded from the study. The main reasons excluding children was they were unable to walk, 42% of those excluded and children have history of surgery of the left leg, foot, or ankle, 29% of those excluded.

3.2.1 Lower limb surgery

Forty-six children were excluded from the study because they had had surgery to correct deformities in their lower limbs. These deformities usually resulted from contractures of the calf muscles. Table 3.3 shows the details of the surgeries. Bilateral calf surgery was the most frequent followed by unilateral calf surgery.

	Frequency	**%**
Bilateral Calf Muscle	12	26%
Unilateral Calf Muscle	8	17%
Bilateral Hamstrings	7	15%
Bilateral Adductor	4	9%
Unilateral Calf &Hamstrings	4	9%
Bilateral Calf & Hamstrings	3	7%
Bilateral Calf & Adductor	2	4%
Bilateral Hamstrings & Adductor	2	4%
All	1	2%
Back	1	2%
Left tibialis anterior	1	2%
Neurotomy	1	2%

Table 3.3.
The numbers of children who had previous surgery to their lower limbs to correct deformities in their lower limbs. These deformities usually resulted from contractures of the calf muscles

3.2.2. Visual and auditory impairments.

The sensory impairments of the children were also recorded. These data came from the children' clinical records. Their vision was usually normal, and only 14.7 % of the children had some vision abnormality. These problems included poor vision, nystagmus and strabismus. There was a similar pattern with auditory impairments with 6% having some auditory problem. Only 2 children used hearing aids.

3.2.3 Speech disorders

Speech disorders were more frequent than visual or auditory problems. 30.4 % of the children had delayed development of language skills due to mental retardation. 12.7 % had dysartheria. This is a neurogenic speech disorder.

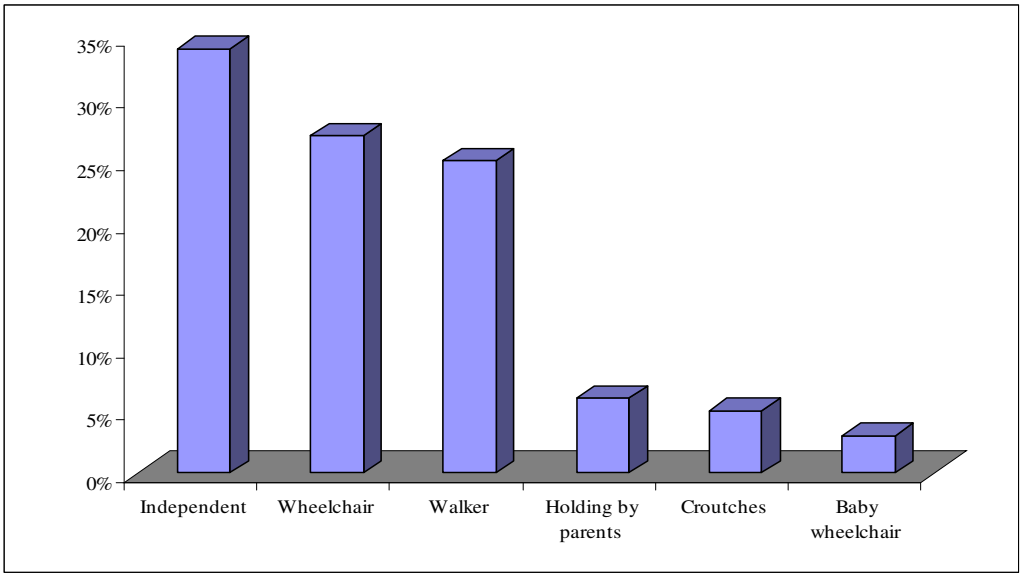


Figure 3.4.
Ambulation status of the 163 children reviewed. The assessment of ambulatory status was done by visual inspection in the clinic and with reference to their clinical records. 34% of the children were capable of walking independently. 25% of the children used a walker. Children who walked supported by their parent or with crutches represented 6% and 5% respectively. 27% of the children could not walk. Only 3% of the children depended on baby wheelchairs Replotted from Table 3.1

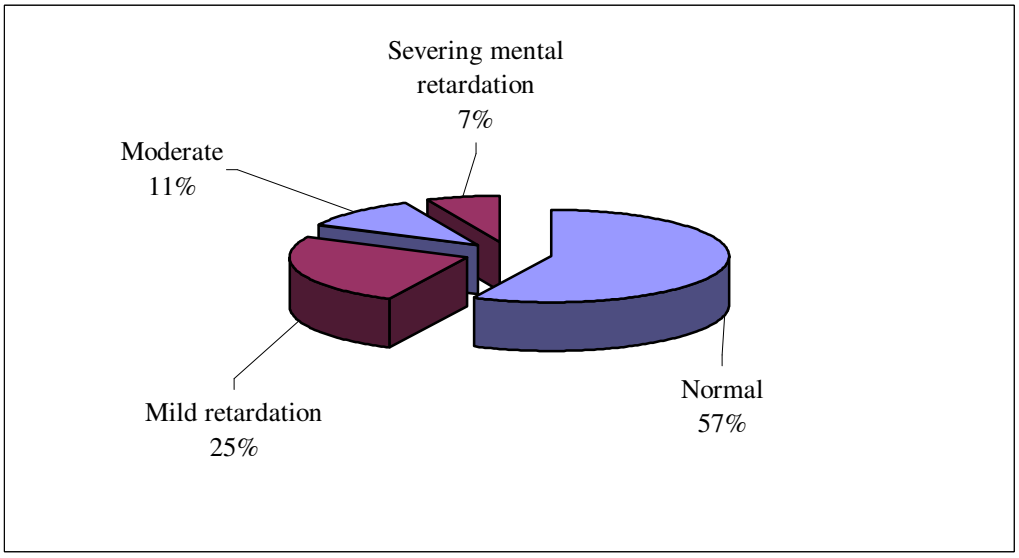


Figure 3.5.
Mental states of the 163 children reviewed. Replotted from Table 3.1.

In summary, 47 children (26 boys and 21 girls) with cerebral palsy were recruited for the study. This represents 29% of the children screened. The total number of children treated in these centres is about 325. Thus the study includes a significant proportion of the total clinical population.

The characteristics of 47 children who participated in the project are shown in tables 3.4 and 3.5. Table 3.4 shows the details of children who received the Botulinum Toxin-A treatment (Group 1). Table 3.5 shows the details of children who received the Botulinum Toxin-A treatment and physical therapy (Group 2).

Approximately 10% of the physical therapy and measurement sessions were stopped because the child involved did not cooperate or became distressed. These instances are reported in the relevant data tables, where it is recorded as ‘data missing’. In a small number of cases the parent terminated the session.

Group 1: Botulinum Toxin-A Treatment

ID. No.	Gender	Age (month)	Weight kg	Height	Ambulation	Mental Status
5	F	168	26	135	Independent	Normal
20	F	131	23	109	Independent	Normal
30	M	80	16	85	Independent	Mild retarded
35	M	76	15	85	Independent	Normal
40	M	76	16	86	Independent	Mild retarded
44	M	70	16	85	Independent	Normal
9	F	108	18	110	Walker	Mild retarded
23	F	31	12	109	Walker	Normal
28	F	81	17	85	Walker	Mild retarded
32	F	96	17	106	Walker	Mild retarded
41	F	88	20	85	Walker	Mild retarded
10	M	106	30	106	Walker	Mild retarded
17	M	96	20	85	Walker	Mild retarded
25	M	46	28	98	Walker	Normal
36	M	76	13	88	Walker	Normal
37	M	78	17	85	Walker	Normal
45	M	79	14	84	Walker	Normal
46	M	96	18	93	Walker	Normal

Table 3.4.

Demographic data of children in Group 1. The table shows the details their heights, weights and gender. The columns on the right show their ambulation status. The children either walked independently or with the help of a walker. Their mental status is also shown.

Group 2: Botulinum Toxin-A and physical therapy treatment

ID. No.	Gender	Age (month)	Weight kg	Height	Ambulation	Mental Status
1	M	60	18	139	Independent	Normal
2	M	68	15	84	Independent	Mild retarded
3	F	47	17	99	Independent	Mild retarded
8	M	60	15	145	Independent	Normal
15	F	48	18	111	Independent	Normal
16	F	132	19	144	Independent	Normal
18	F	58	13	104	Independent	Normal
19	M	72	12	87	Independent	Normal
22	M	72	18	84	Independent	Mild retarded
24	F	108	43	107	Independent	Normal
27	M	30	30	105	Independent	Normal
29	M	46	11	110	Independent	Normal
31	M	70	17	84	Independent	Mild retarded
39	M	45	12	105	Independent	Normal
4	F	84	18	84	Walker	Normal
6	F	48	11	108	Walker	Mild retarded
7	F	84	27	95	Walker	Normal
11	F	34	11	107	Walker	Mild retarded
12	M	94	20	86	Walker	Mild retarded
13	M	96	18	85	Walker	Normal
14	F	69	17	86	Walker	Mild retarded
21	M	24	13	107	Walker	Normal
26	F	36	29	84	Walker	Normal
33	M	30	10	86	Walker	Normal
34	F	48	13	108	Walker	Mild retarded
38	F	39	16	98	Walker	Normal
42	M	29	11	105	Walker	Normal
43	F	36	14	107	Walker	Normal

Table 3.5.

Demographic data of children in Group 2. The table shows details of their heights, weights and gender. The columns on the right show their ambulation status. Their mental status is also shown.

The allocation to the two groups was not fully randomized since it depended on the decisions of the parents about where their child should be treated. However, the two groups are well matched in terms of body sizes. There is no significant difference in the mean body weight and height of the children in the two groups. The mean weight of group 1 was 20 kg and the mean weight of group 2 was 16 kg. The mean height Group 1 was 108 cm and the mean height of group 2 was 94 cm. When compared with T tests the P-values were 0.253 for body weight and 0.100 for height.

The issue of the effect of the allocation on GMFM is addressed more fully later in figures 3.6. 3.7. and 3.8. section 3.3. The advice of Dr Aitchison of the Statistics Department of Glasgow University was sought and followed throughout this section.

3.3 The effect of botulinum toxin- A in spastic cerebral palsy children

Forty-six children were screened over a 52 -week period. 26 males and 21 females were recruited into the trial. The variables that were ROM at the ankle recorded via electrogoniometry, electromyography (EMG) of soleus, and gross motor function measurement (GMFM).

3.3.1 Group 1

These children came from a clinical centre in a village in western area Saudi Arabia in the Al- Taif region. Their families refused to stay at the Disabled Children' Association in Makkah or in Jeddah. They were given Botulinum Toxin-A injections, their ankles were fixed with casts and they were fitted with medical shoes.

3.3.2 Group 2

These children also came from the western part of Saudi Arabia. Their families chose residential care in Makkah and Jeddah. These children received the same treatment as Group 1 and intensive physical therapy. Tables 3.6 and 3.7 show details of the children in both groups and their GMFM scores before treatment started and at intervals of 4, 6 and 52 weeks later.

ID. No.	Gender	Weight kg	Height cm	Age (Month)	1 GMFM	2 GMFM	3 GMFM	4 GMFM
46	F	15	108	96	61	61	62	63
10	M	38	111	104	45	47	48	50
36	M	15	107	74	72	75	76	78
35	F	11	84	74	67	70	72	n/a
5	F	16	105	154	74	75	77	78
37	M	16	109	77	62	64	66	68
45	M	17	107	79	59	60	61	62
25	M	16	108	45	60	63	65	72
30	M	17	107	78	48	49	52	n/a
9	F	15	98	109	50	51	52	52
32	F	18	110	97	52	53	54	54
28	F	15	99	80	50	51	51	53
23	F	30	104	29	53	54	54	55
41	M	44	139	86	72	73	76	n/a
44	M	46	145	70	70	71	73	76
20	F	13	88	129	50	51	52	52
40	M	13	106	74	51	52	52	52
17	M	13	107	80	54	56	56	58
Mean					58.3	59.8	61.1	61.6
Max					74.0	75.0	77.0	78.0
Min					45.0	47.0	48.0	50.0
SD					9.1	9.3	9.8	10.0

Table 3.6.

The characteristic of children in Group 1. The table shows the details of children, their heights, weights and gender.

The columns on the right show the GMFM Scores at 1 before treatment, 2 after 4 weeks, 3 after 6 weeks and 4 after 52 weeks. n/a: data not available.

ID. No.	Gender	Weight kg	Height cm	Age (Month)	1 GMFM	2 GMFM	3 GMFM	4 GMFM
15	F	16	105	48	57	58	62	76
21	M	12	86	25	70	71	74	85
2	M	16	98	66	55	57	58	59
1	M	27	105	59	54	56	58	60
11	F	11	84	32	48	53	57	n/a
22	M	11	86	73	40	43	45	51
27	M	11	84	28	37	44	46	49
12	M	11	85	91	55	57	61	65
14	F	12	87	67	56	60	65	68
8	F	13	84	60	48	54	55	56
29	M	12	85	45	57	57	63	66
24	F	12	86	106	62	64	69	76
6	F	12	85	46	60	65	70	76
29	M	17	85	43	67	68	70	72
13	M	12	84	94	46	49	53	54
19	M	13	85	72	63	73	76	81
31	M	13	85	69	46	49	51	53
26	F	14	95	25	70	77	79	81
18	F	13	84	56	65	72	75	79
4	F	14	85	84	71	76	77	81
38	F	16	86	37	71	73	76	80
3	F	17	85	45	46	46	55	48
43	F	15	93	36	73	76	79	81
34	F	18	106	33	69	70	78	90
42	M	20	110	27	42	47	49	50
33	M	17	109	28	57	66	71	74
7	F	43	144	82	74	77	79	83
16	F	40	135	132	69	72	75	81
Mean					60.1	64.2	67.9	70.9
Max					74.2	77.5	79.1	89.7
Min					41.6	46.3	48.7	47.9
SD					10.5	10.9	10.6	12.8

Table 3.7.
The characteristic of children in Group 2. The table shows the details of children, their heights, weights and gender. The columns on the right show the GMFM Scores at 1 before treatment, 2 after 4 weeks, 3 after 6 weeks and 4 after 52 weeks. n/a: data not available.

The data in tables 3.6 and 3.7 is replotted in subsequent figures. Figure 3.6 is a box plot of the GMFM scores of both groups one week before treatment. The distribution of scores is similar in both groups. There seems to be more variability in group 2 than group 1. This may be due to group 2 having a larger sample size. The box plots are fairly symmetrical and this supports the suggestion that the data are normally distributed. A two sample t-test showed that there was no significant difference in GMFM score before the treatment began (P=0.950). In addition, the 95% CI for the difference contains zero. The results are shown below in table 3.8.

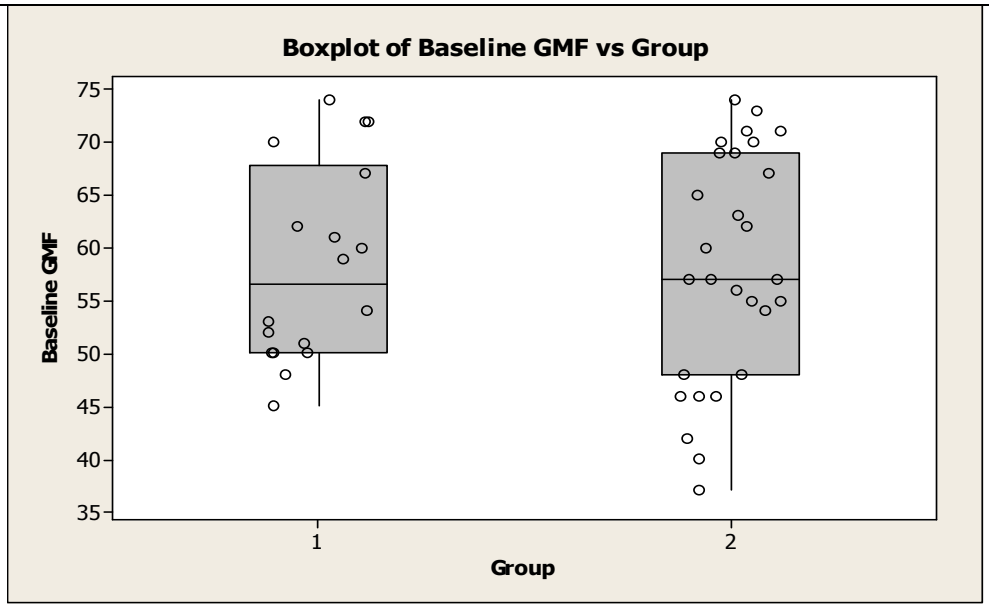


Figure 3.6.
Box plot of baseline GMFM scores in Group 1 and Group 2 one week before treatment. The distribution of scores is similar in both groups. There seems to be more variability in group 2 than group 1. This may be due to group 2 having a larger sample size.

Two-sample T for Baseline GMF

Group	No.	Mean	StDev	SE Mean
1	18	58.33	9.36	2.2
2	28	58.1	10.9	2.1

Difference = mu (1) - mu (2)

Estimate for difference: 0.190476

95% CI for difference: (-5.912570, 6.293523)

T-Test of difference = 0 (vs not =): T-Value = 0.06

P-Value = 0.950 DF = 40

Table 3.8.

Output for two sample t-test comparing GMFM in groups 1 and 2 scores before treatment begins

The box plot in figure 3.6 does not correct for other variables such as the sex of the child, their height, weight and age. Further analysis was done to discover if the data should be corrected for these variables. Box plots of the ages, weights and heights for both groups are shown in figure 3.7.

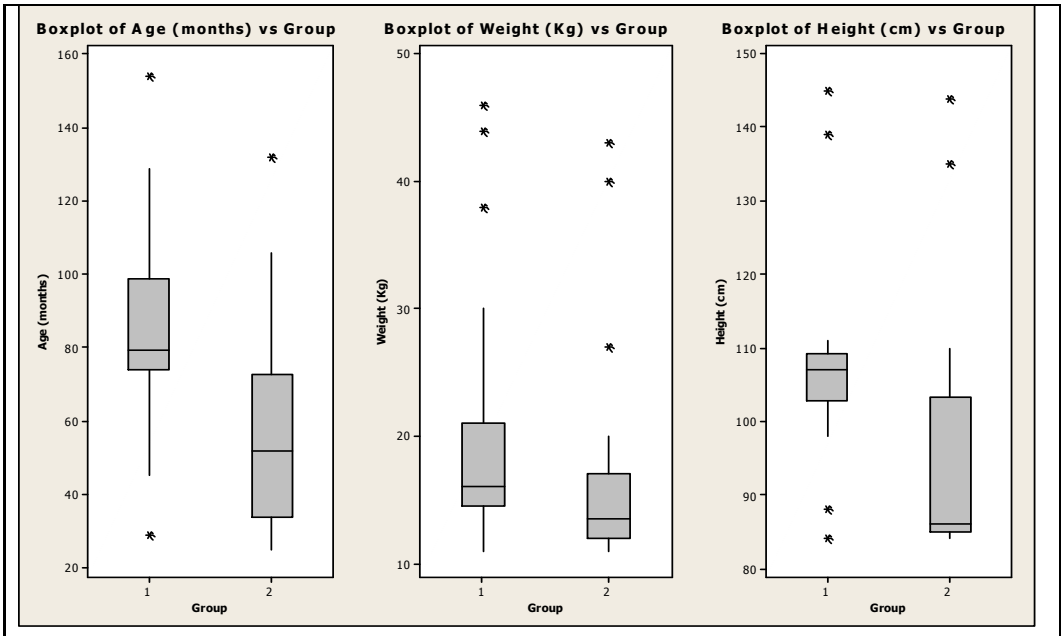


Figure 3.7.

Box plots of the age, weight and height of the children in Groups 1 and 2.

The two groups seem well matched for weight but less so for age and height.

Scatter plots were produced to investigate if any of these variables had an effect on the baseline gross motor function. These are shown in figure 3.8.

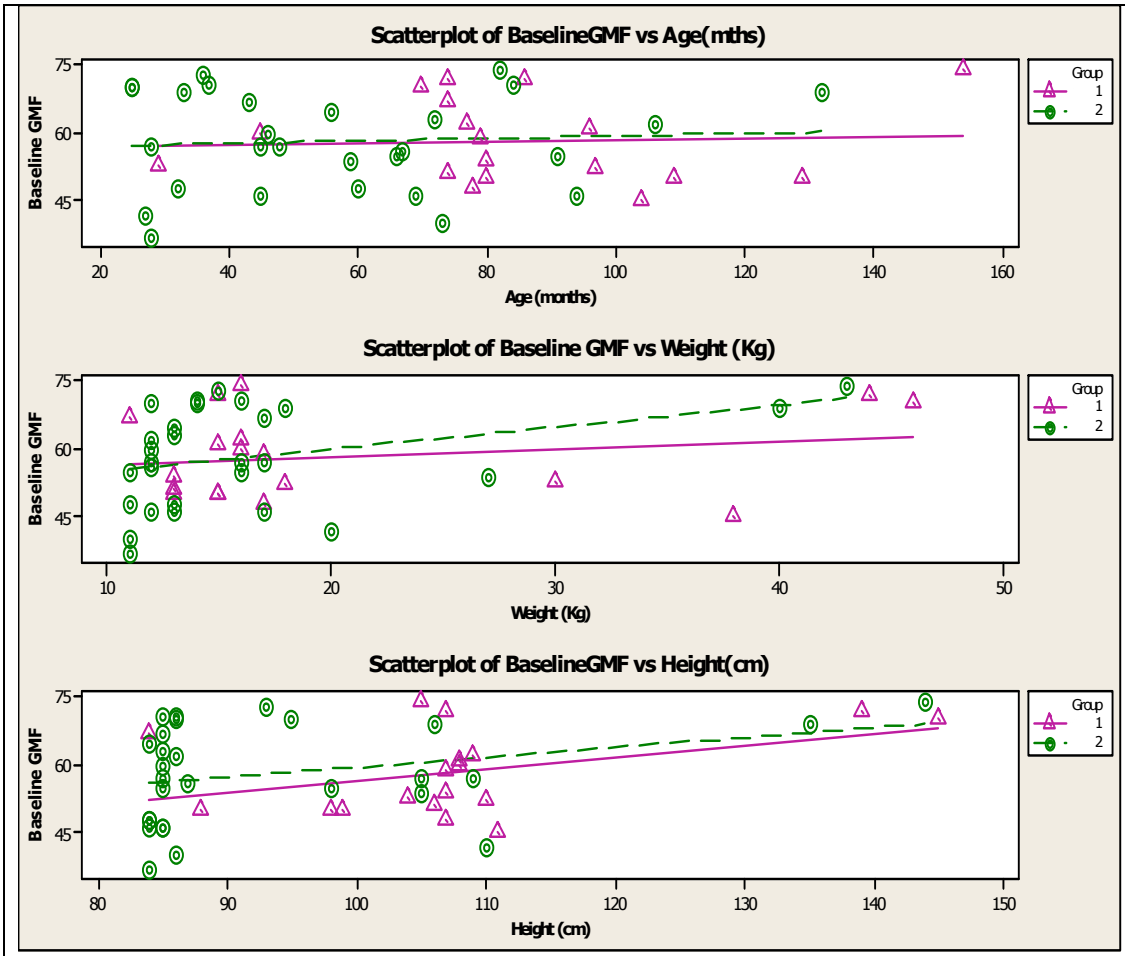


Figure 3.8.

Scatter plots of GMFM scores before treatment starts plotted against the age, weight and height of the children in both group 1 and 2. Regression lines are plotted for each group.

The plots in figure 3.8 show considerable overlap of the data points for group1 and 2. The regression lines are very similar in slope and intercept. This indicates that no correction is required and that two-sample t-test are appropriate. The result of these tests is shown in table 3.9. No significant effects were detected and this confirms that there is no real evidence of any significant difference in baseline GMFM between the 2 groups. Thus, retrospectively, it is good to note that the 'treatment allocation' was fair even if it was non-random.

3.4 Gross Motor Function Measurements after Intervention

3.4.1 Group 1

The GMFM scores of the 18 children in group 1 were measured before Botulinum Toxin-A injections and at four, six and 52 week later. The GMFM scores are shown in table 3.6. All the children were assessed before the injections and again at weeks 4, 6 and 52. Three children could be not assessed at the one-year follow up. This was due to their parent's reluctance to return to the clinic rather than to any adverse event.

It is clear from the data in the table 3.6 and figure 3.9 A and B that these children show an improvement in GMFM scores over the period of the study. The mean GMFM score one week before Botulinum Toxin-A injection was 58.3 ± 9.4. By 4 weeks after the injection it was 59.8 ± 9.6. By 6 weeks after the injection it was 61.1 ± 10.9 and at 52 weeks after injection it was 61.5 ± 10.3

However, the differences are not significant when tested statistically using an ANOVA. When the mean scores before treatment are compared with those at 4 week, the P Value is 0.650. When compared with the scores at 6 weeks, the P Value is 0.407. After 52 weeks the P Value is 0.358. These data are recorded in table 3.10.

Clinically, there is an improvement in some children in-group 1. Figure 3.9 B shows the data for each child at the four points of measurement. There is a clear trend upwards in the data. 15 children had increased GMFM scores after Botulinum Toxin-A injection. It is also clear that in this figure and from the data in the table there is a big range of GMFM scores.

A		GMFM before	GMFM at 4 weeks
	Mean	58.3	59.778
	St.Dev	9.4	9.589
	P Value	0.650	
B		**GMFM before**	**GMFM at 6 weeks**
	Mean	58.3	61.1
	St.Dev	9.4	10.1
	P Value	0.407	
C		**GMFM before**	**GMFM at 52weeks**
	Mean	58.3	61.5
	St.Dev	9.4	10.3
	P Value	0.358	

Table 3.9.

A summary of the results of ANOVA test comparing the magnitude of the GMFM scores pre and post Botulinum Toxin-A injection in group 1

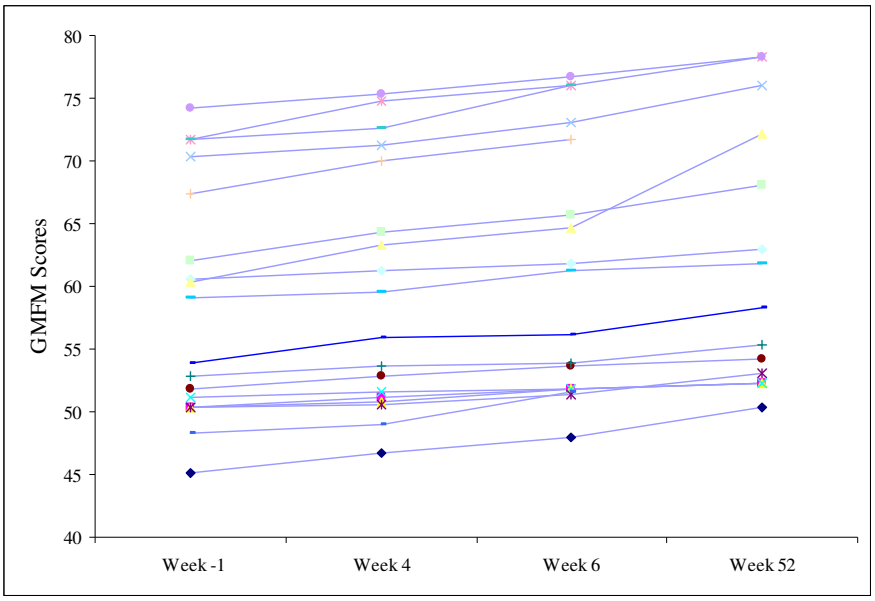
The results of ANOVA tests of GMFM scores in group 1 comparing GMFM scores before treatment with A 4 weeks after injection.

B 6 weeks after injection.

C 52 weeks after injection

The results show that the mean GMFM scores were not significantly improved after Botulinum Toxin-A injection.

A



B

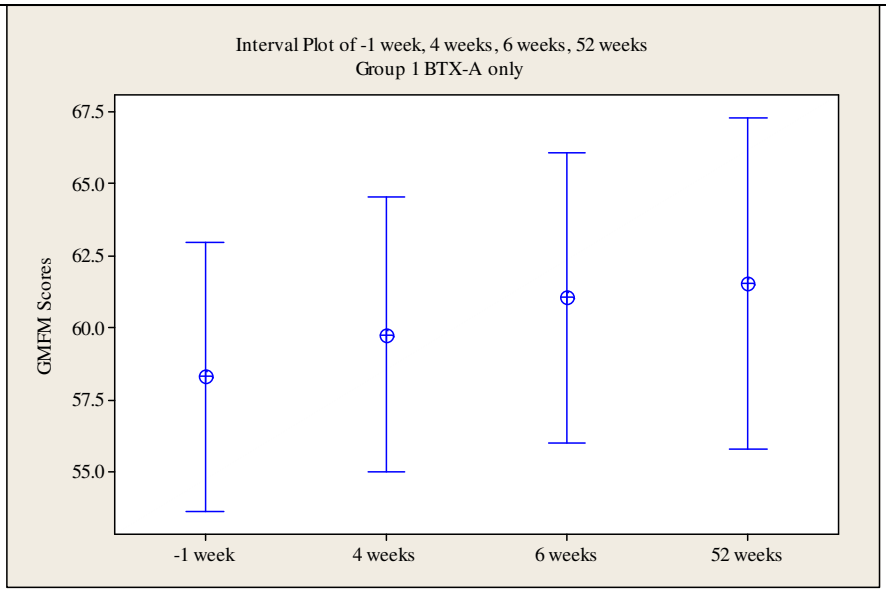


Figure 3.9.

Panel A shows the GMFM scores for all the children in group1.

Panel B shows the interval plot of the mean GMFM ± SD scores one week before, 4 weeks, 6 weeks and 52 weeks after Botulinum Toxin-A injection for the 18 diplegic children in group 1.

3.4.2 Group 2

The GMFM scores of the 28 children in group 2 were measured before Botulinum Toxin-A injections and at four, six and 52 weeks later. The GMFM scores are shown in table 3.7. 26 children of the 28 children increased their score after Botulinum Toxin-A injection. However, one child's score decreased at 52 weeks. This was probably a consequence of a fracture in the head of femur. This injury was unrelated to the study. In addition, one other child did not return to the clinic for the final assessment at 52 weeks. This was due to the parent's reluctance to return to the clinic rather than to any adverse event.

Clinically, there is an improvement in most of the children in group 2. Their GMFM scores are plotted in figure 3.10 A and B. It is clear from the data in the table 3.7 and figures 3.10 A and B that these children show an improvement in GMFM scores over the period of the study. The mean GMFM score one week before Botulinum Toxin-A injection was 58.1 ± 10.9. Four weeks after the injection it was 61.8 ± 11.0 and by 6 weeks after the injection it was 65.1 ± 11.0. By 52 weeks after injection it was 69.4 ± 13.00.

The results of ANOVA tests of GMFM scores are shown in table 3.14. The improvement in mean GMFM between the initial assessments and 4 weeks after Botulinum Toxin-A injection is not statistically significant (P =0.219). However, the improvements in mean GMFM were statistically significant at 6 weeks (P =0.019) and at 52 weeks (P=0.001). This improvement contrasts sharply with the lack of significant change for group 1 which was reported in the previous section.

A		**GMFM before**	**GMFM at 4 weeks**
	Mean	58.14	61.79
	St.Dev	10.92	11.01
	P Value	0.219	
B		**GMFM before**	**GMFM at 6 weeks**
	Mean	58.14	65.21
	St.Dev	10.92	13.00
	P Value	0.019	
C		**GMFM before**	**GMFM at 52 weeks**
	Mean	58.14	69.44
	St.Dev	10.92	13.00
	P Value	0.001	

Table 3.10.

A summary of the results of ANOVA test comparing the magnitude of the GMFM scores pre and post Botulinum Toxin-A injection in group 2

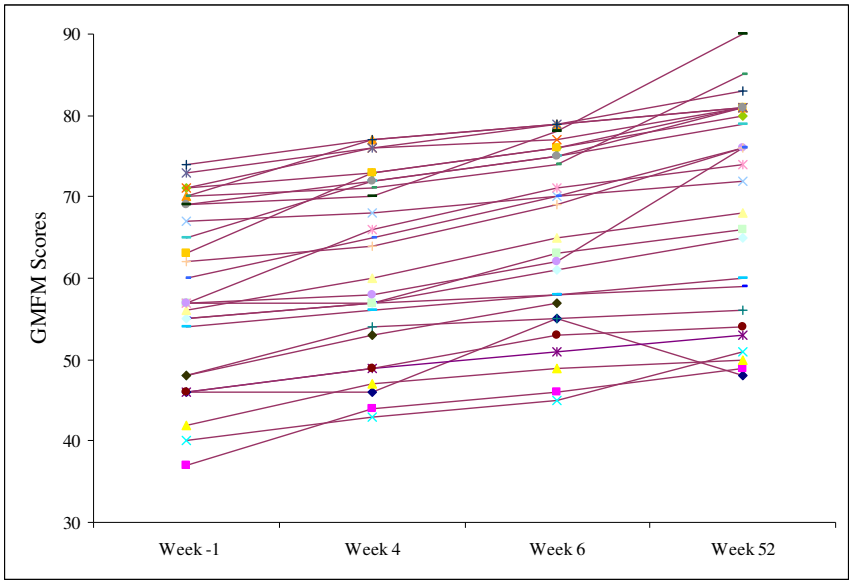
The results of ANOVA tests of GMFM scores in group 2 comparing GMFM scores before treatment with A 4 weeks after injection.

B 6 weeks after injection.

C 52 weeks after injection

The results show that the mean GMFM scores were significantly improved at 6 and 52 weeks after Botulinum Toxin-A injection in this group of children

A



B

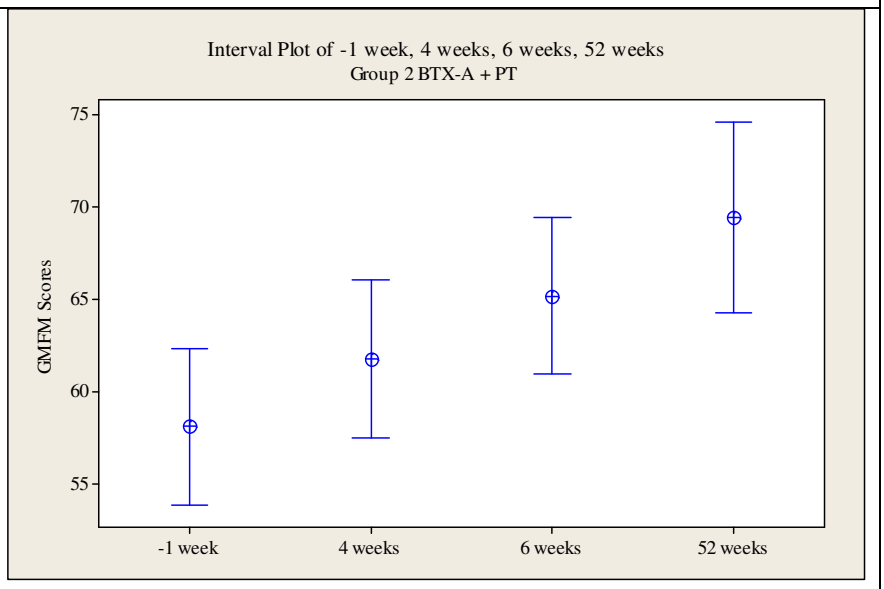


Figure 3.10.

Panel A shows the GMFM scores for all the children in Group 2.

Panel B shows the interval plot of the mean GMFM ± SD scores one week before, 4 weeks, 6 weeks and 52 weeks after Botulinum Toxin-A injection for 28 diplegic children.
The increase in mean scores is statistically significant after 6 and 52 weeks.

3.4.3 Comparison of GMFM in Group1 and Group 2

The previous sections have described the changes in GMFM in the two groups of children over the year after the injection of Botulinum Toxin-A. In summary, Group 1 showed no significant changes in GMFM over the year whilst group 2 showed a significant improvement in mean GMFM at 6 and 52 weeks. This section will compare the performance of the two groups.

The GMFM scores of the 46 children in the both groups were measured before Botulinum Toxin-A injections and at 4, 6 and 52 week later. The GMFM scores are shown in table 3.5.and 3.6. The raw GMFM scores for each child are re-plotted in figure 3.11.

One week before Botulinum Toxin-A injection the mean GMFM scores were 58.3 ± 9.4 in group 1 and 58.1 ± 10.9 in group 2. At 4 weeks after the injection the mean scores were 59.8 ± 9.6 in-group 1 and 61.8 ± 11 in group 2. By 6 weeks the mean score for group 1 was 61.1± 10.1 and 65.2 ± 1 in group 2. Finally after 52 weeks it was 61.5 ± 10.3 in group 1 and 69.4 ± 13 in group 2. These data are plotted in figure 3.12. It is clear by eye that the mean values are almost identical before the Botulinum Toxin-A injections. Data shown in table 3.8 confirms that the means scores are not significantly different. The mean scores do not change significantly over the 52 weeks in Group 1. However, the improvement in mean GMFM increases significantly in group 2.

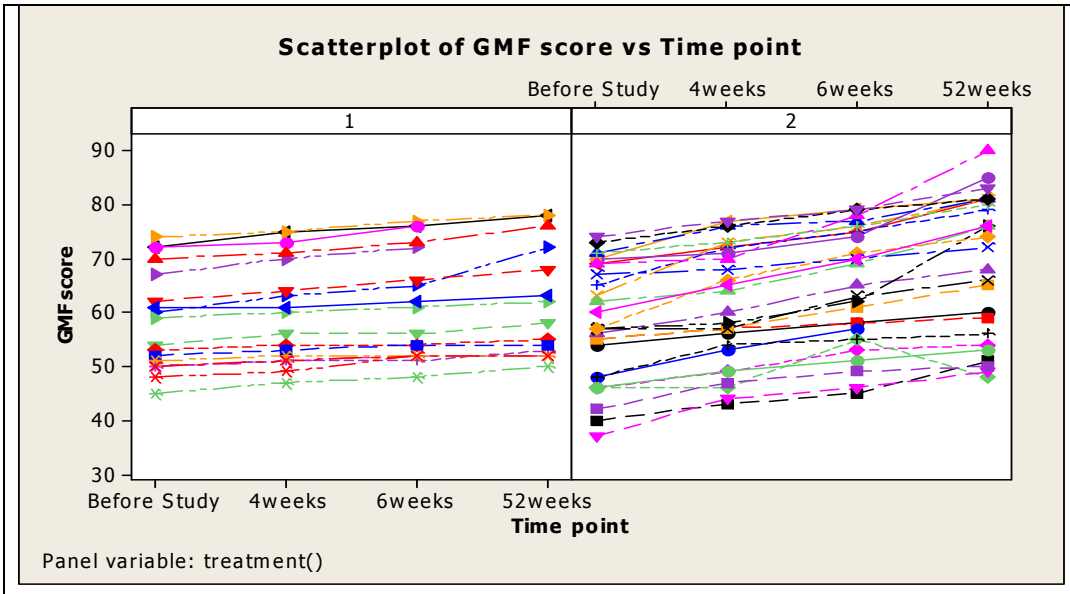


Figure 3.11.

Individual profile plot showing GMF score from baseline to the 52nd week of the study. Group 1 is plotted on the left and group 2 is plotted on the right.

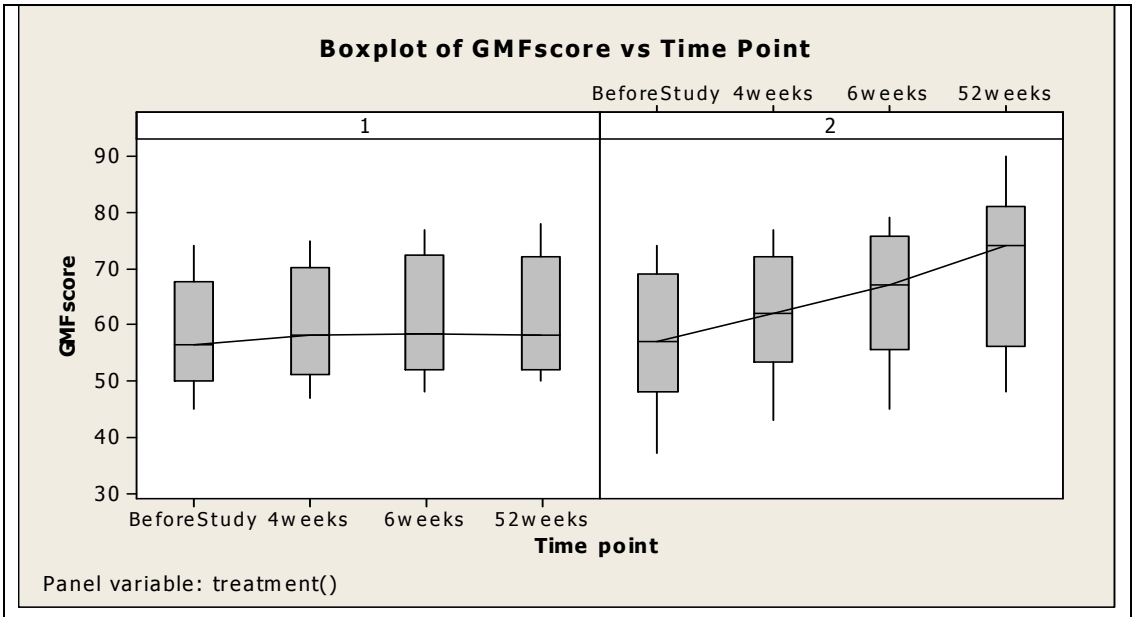


Figure 3.12.

Box plots of GMFM scores from baseline to the 52nd week of the study. Group 1 is plotted on the left and group 2 is plotted on the right.

The difference in GMFM scores in the two groups were analysed using analysis of covariance (ANCOVA). This approach was recommended by Dr Aitchison of the Statistics Department. The results are shown below in tables 3.11. to 3.13.

Analysis of Variance for GMF 4 weeks, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	**P**
Baseline GMF	1	4628.5	4637.2	4637.2	1003.91	0.000
Group	1	52.9	52.9	52.9	11.45	**0.002**
Error	43	198.6	198.6	4.6		
Total	45	4880.0				

S = 2.14922 R-Sq = 95.93% R-Sq(adj) = 95.74%

Term	Coef	SE Coef	T	P
Constant	2.967	1.853	1.60	0.117
Baseline GMF	0.99272	0.03133	31.68	0.000

Bonferroni 95.0% Simultaneous Confidence Intervals
Response Variable GMF 4 weeks
All Pairwise Comparisons among Levels of Group
Group = 1 subtracted from:

Group	Lower	Center	Upper	---------+---------+---------+-------
2	0.8875	2.197	3.507	(----------*----------)

---------+---------+---------+-------
1.60 2.40 3.20

Table 3.11.
Results of a comparison of mean GMFM scores in groups 1 and 2 at 4 weeks after injection. The results of the ANCOVA show that the difference is significant ($p < 0.001$).

Analysis of Variance for GMF 6 weeks, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	**P**
Baseline GMF	1	4750.5	4768.4	4768.4	879.03	0.000
Group	1	207.4	207.4	207.4	38.22	**P<0.001**
Error	43	233.3	233.3	5.4		
Total	45	5191.2				

S = 2.32908 R-Sq = 95.51% R-Sq(adj) = 95.30%

Term	Coef	SE Coef	T	P
Constant	4.508	2.008	2.24	0.030
Baseline GMF	1.00667	0.03395	29.65	0.000

Bonferroni 95.0% Simultaneous Confidence Intervals
Response Variable GMF 6 weeks
All Pairwise Comparisons among Levels of Group
Group = 1 subtracted from:

Group	Lower	Center	Upper	---+---------+---------+---------+---
2	2.931	4.350	5.770	(----------*----------)
				---+---------+---------+---------+---
				3.20 4.00 4.80 5.60

Table 3.12.
Results of a comparison of mean GMFM scores in groups 1 and 2 at 6 weeks after injection. The results of the ANCOVA show that the difference is significant (p< 0.001).

Analysis of Variance for GMF 52weeks, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	**P**
Baseline GMF	1	5428.1	5270.8	5270.8	332.87	0.000
Group	1	446.2	446.2	446.2	28.18	**P<0.001**
Error	39	617.6	617.6	15.8		
Total	41	6491.9				

S = 3.97928 R-Sq = 90.49% R-Sq(adj) = 90.00%

Term	Coef	SE Coef	T	P
Constant	0.643	3.612	0.18	0.860
Baseline GMF	1.11753	0.06125	18.24	0.000

Bonferroni 95.0% Simultaneous Confidence Intervals
Response Variable GMF 52weeks
All Pairwise Comparisons among Levels of Group
Group = 1 subtracted from:

Group	Lower	Center	Upper	--+---------+---------+---------+----
2	4.215	6.810	9.405	(----------*----------)
				--+---------+---------+---------+----
				4.5 6.0 7.5 9.0

Table 3.13.
Results of a comparison of mean GMFM scores in groups 1 and 2 at 52 weeks after injection. The results of the ANCOVA show that the difference is significant (p< 0.001).

Thus there was no significant difference in the mean GMFM scores before treatment started. The scores in group 1 (Botulinum Toxin-A alone) did not change significantly over the 52 week. The scores in Group 2 (Botulinum Toxin-A and intensive physical therapy) did increase significantly at 4, 6 and 52 weeks. The children in Group 2 had significantly higher GMFM score at 4, 6 and 52 weeks.

Figure 3.12 shows clearly that the data from group 1 shows an initial rise in GMFM scores from before the study. It is small and does not change further over the 52 weeks after first treatment. In group 2 however, the initial rise continues throughout the study. The individual data plotted in figure 3.11. show that the improvement is not constant for each child throughout the study.

The causes of the different improvements in group 1 and 2 were investigated further. The ultimate aim was investigate if the improvement was larger in children with low GMFM scores at baseline. Plots of the starting GMFM scores at the scores at later times are given in figures 3.13, 3.14 and 3.15. These also show a line of equality line indicating ‘no change’ in GMFM.

Figure 3.13 shows a scatter plot of baseline GMFM score against GMFM score at 4 weeks for groups 1 and 2. Firstly, it is easy to see that all the points lie on or above the line of equality i.e. all children are unaffected or improve.

The points representing group 2 lie further above the line of equality i.e. group makes a greater improvement. This repeats graphically the results of the ANCOVA tests reported above showing that group 2 scores were significantly greater at week 4. Regression lines are fitted to each set of data and all points lie close to this indicating that children with low initial scores improve by a similar amount to those with higher initial scores. The

regression line for group 2 lies above that for group 1 and this shows a slightly greater improvement in group 2 across the range of baseline GMFM.

Figure 3.14 shows a similar plot for data at 6 weeks. Group 2 points lie further away from group 1 as indicated by the plots of means scores shown above in figure 3.12. The children with higher initial scores in group 1 now appear to make a greater improvement than lower scoring member of group 1.

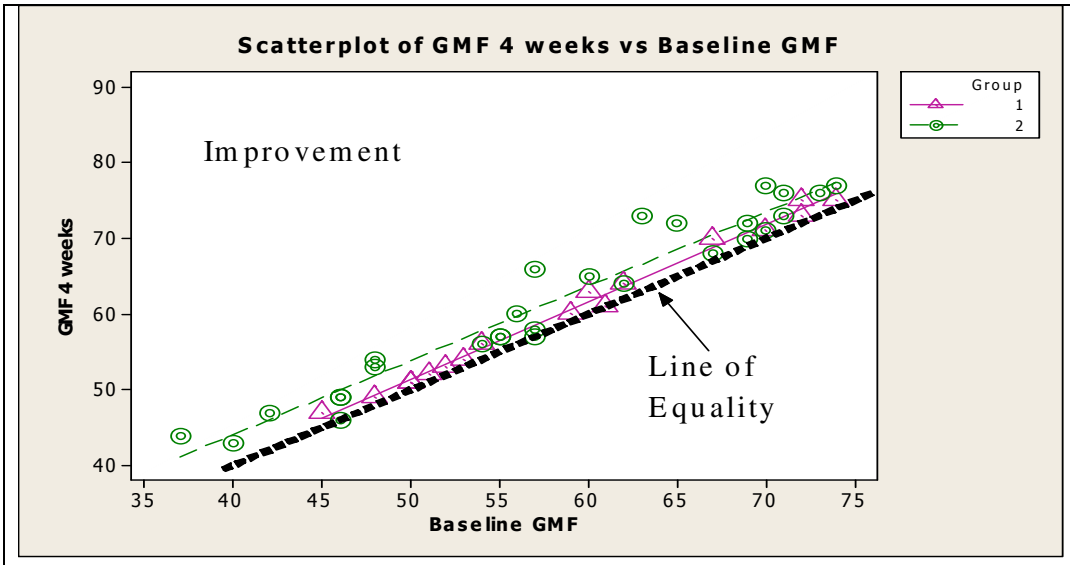


Figure 3.13.

Scatter plot of baseline GMFM score vs. GMFM score at 4 weeks. Children in group 1 are shown as triangles and those in group 2 are shown as circles.

All points lie on or above the line of equality i.e. all children are unaffected or improve. The points representing Group 2 lie further above the line of equality i.e. group makes a greater improvement.

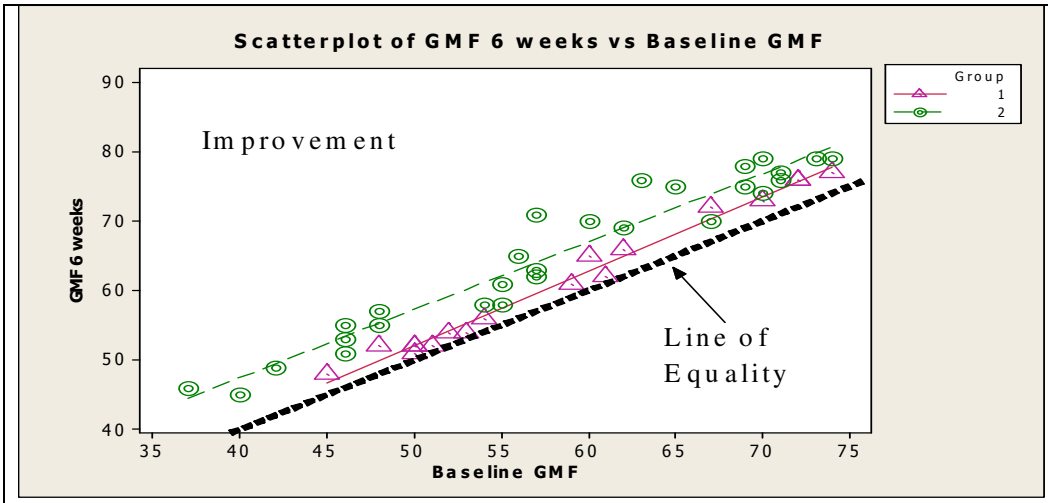


Figure 3.14.

Scatter plot of baseline GMF score vs. GMF score at 6 weeks. Children in group 1 are shown as triangles and those in group 2 are shown as circles.

The points representing Group 2 lie further away from group 1. The children with higher initial scores in group 1 now appear to make a greater improvement than lower scoring member of group 1

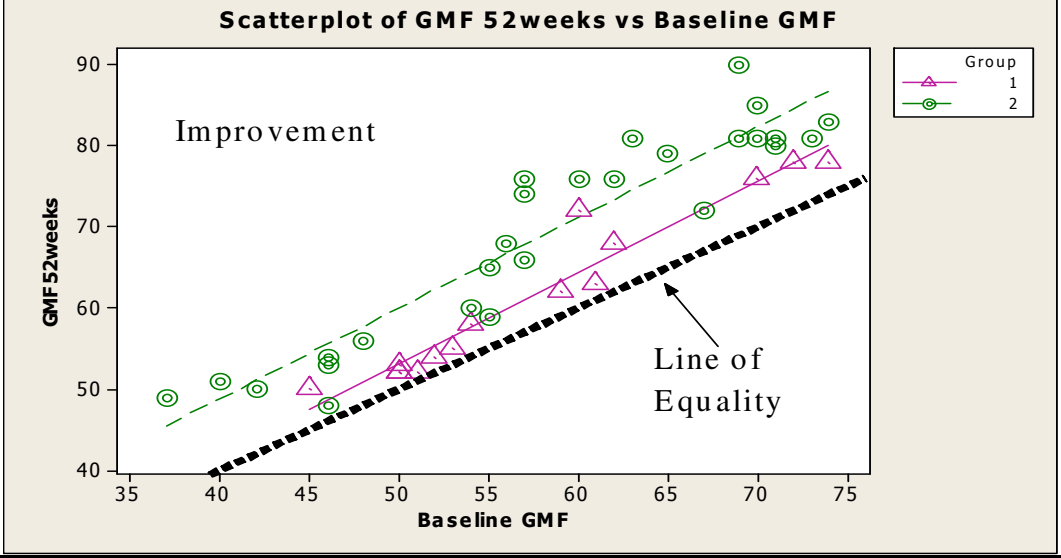


Figure 3.15.

Scatter plot of baseline GMF score vs. GMF score at 52 weeks. Children in group 1 are shown as triangles and those in group 2 are shown as circles.

The points representing Group 2 lie further away from group 1. The children with higher initial scores in group 1 now appear to make a greater improvement than lower scoring member of group 1

Figure 3.15 is a similar plot again for data at 52 weeks. It can be seen that the children in group 2 have improved much more than those in group 1. This reflects the earlier results in mean data. However it is now clear that those with the highest initial scores made the biggest improvements. No child in group 1 finished with a lower GMFM score. However, the children with the lowest initial score often lie very close to the line of equality i.e. they did not improve much. The biggest improvements in group 1 lie in the children with the higher initial scores though their gains are smaller than high scoring children in group 2.

The GMFM scores in groups 1 and 2 do not appear to improve in a uniform manner with respect to the initial GMFM score i.e. the children who started with 'higher' baseline GMFM scores show more of an increase at each time point than those with 'lower' baseline GMFM scores. This complicates any formal statistical analysis. It is important to allow for this when choosing a statistical model. However, whilst this problem remains for statisticians, it may be relevant in considering which treatments to recommend for individual children. Those with low baseline scores will probably benefit least from either intervention.

3.5 Range Of Motion Measurements after Intervention

In addition to the GMFM measurements described before, the range of motion at the ankle of each child was measured before Botulinum Toxin-A injections and at 4 and 6 weeks after injection. Electro-goniometers were used to measure the range of motion (ROM). The author used traditional manual goniometers to calibrate the electro-goniometers. Details are given in chapter 2.

3.5.1 Range of Motion in Group 1

These children were treated with Botulinum Toxin-A only. Their ROMs are shown in table 3.14. Figure 3.16. A shows a plot of the data for each child at the three points of measurement.

The means of the ROM are shown in figure 3.16 B. There is a clear trend upwards in the data. The children had an increased ROM after Botulinum Toxin-A injection. It is also clear that in this figure and from the data in the table there is a big range of ROM degrees. The mean ROM degrees one week before Botulinum Toxin-A injection was 17.4 ± 5.7 degrees, 4 weeks after the injection it was 21.2 ± 8.0 degrees. At 6 weeks after the injection it was 23.9 ± 5.6 degrees

The data were analyzed using a one-way analysis of variance (Unstacked) ANOVA. The differences in mean ROM before the injections and at 4 week after the injection were found to be not significant (P = 0.127). However, when the initial values are compared with those at 6 weeks, the differences were found to be significant (P = 0.003).The summary of these results is given in table 3.16.

ID. No.	Gender	Weight kg	Height cm	Age (month)	ROM Week -1	ROM Week 4	ROM Week 6
25	M	13	88	45	12	15	25
33	M	11	84	28	14	17	20
10	M	38	111	104	26	34	31
37	M	17	107	77	25	14	27
12	F	20	110	91	17	29	26
23	F	16	105	29	13	8	15
32	F	15	99	97	22	20	22
9	M	30	104	109	16	33	27
17	M	18	110	80	23	35	27
28	F	17	107	80	8	14	14
5	F	46	145	154	17	21	22
30	M	16	108	78	19	19	30
34	F	13	85	33	7	14	14
42	M	11	86	27	17	22	27
20	F	44	139	129	23	26	26
Mean					17	21	24
Max					26	35	31
Min					7	8	14
SD					6	8	6

Table 3.14.

The range of motion at the ankle joint of the children in Group 1. The table shows the details of children, their heights, weights and gender. The columns on the right show the ranges of motion.

A

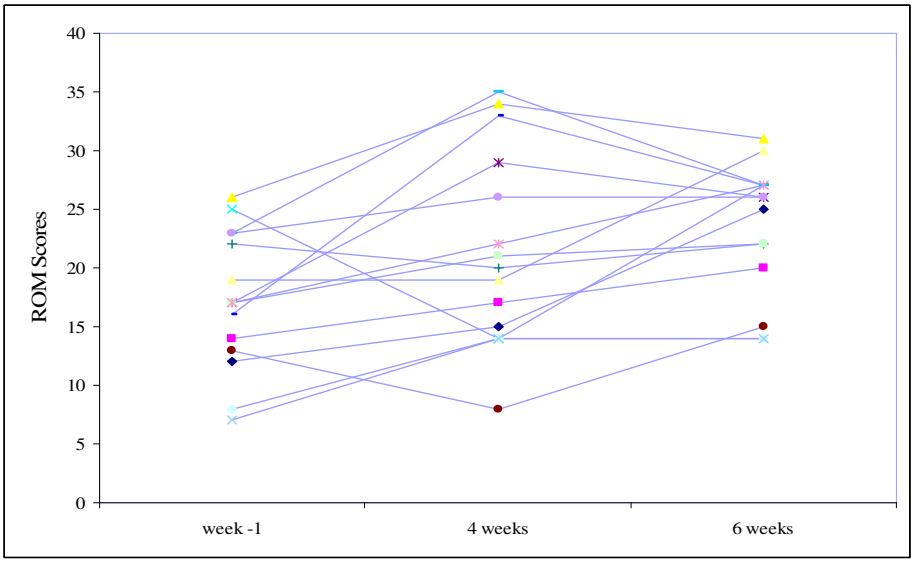


Figure 3.16.

Panel A shows the range of motion at the ankle the children in Group 1 week before, 4 weeks and 6 weeks after Botulinum Toxin-A injection. Data for 18 diplegic children.

	Group 1	**-1 week vs 4 weeks**	**-1 week vs 6 weeks**
Mean	17.4°	21.2°	23.9°
St.Dev	5.7°	8.0°	5.6°
P Value		0.127	0.003

Table 3.15.

A summary of the results of ANOVA tests comparing the mean ROM pre and post Botulinum Toxin-A injection in group1. The results show that the mean ROM was statistically significant in group1 after Botulinum Toxin-A injection 6 weeks.

3.5.2 Group 2

A similar analysis was done for the ROM in the children in group 2. Their data are shown in table 3.16. Figure 3.17. A shows a plot of the data for each child at the three points of measurement all goes up.

The means of the ROM data are shown in figure 3.17. B. In this case there is a very clear trend upwards in the data. The mean ROM degrees one week before Botulinum toxin type A injection was 15.5 ± 5.0 degrees, 4 weeks after the injection it was 25.6 ± 7.2 degrees. At 6 weeks after the injection it was 27.9 ± 10.4 degrees

The data were again analyzed using a one-way analysis ANOVA. The difference in mean ROM before the injections and at 4 week after the injection was found to be significant ($P<0.001$). The result was still significant at 6 weeks ($P<0.001$). The data are summarised in table 3.18.

ID. No.	Gender	Weight kg	Height cm	Age (Month)	ROM Week -1	ROM Week 4	ROM Week 6
22	M	18	106	73	7	18	14
19	M	15	93	72	22	27	34
15	F	13	85	48	9	32	33
21	M	11	84	25	9	22	33
13	M	17	109	94	18	24	14
27	M	12	86	28	17	4	26
2	M	16	86	66	18	22	28
1	M	13	84	59	17	21	11
11	F	11	85	32	10	15	23
14	F	17	85	67	15	27	24
29	M	12	85	45	27	9	27
8	M	14	85	60	6	21	24
16	F	40	135	132	19	49	58
7	F	27	105	82	20	34	35
3	F	17	85	45	18	29	33
31	M	16	105	69	15	25	25
18	F	14	95	56	19	32	39
26	F	12	87	25	17	22	18
38	F	12	85	37	14	18	22
4	F	16	98	84	16	22	34
6	M	12	84	46	12	30	21
11	F	11	85	32	16	22	38
Mean					16	24	28
Max					27	49	58
Min					6	4	11
SD					5	9	10

Table 3.16.

The range of motion at the ankle joint of the children in group 2 who had Botulinum toxin type A injection with additional physical therapy. The table shows the details of children, their heights, weights and gender. The columns on the right show the ROM Scores.

A

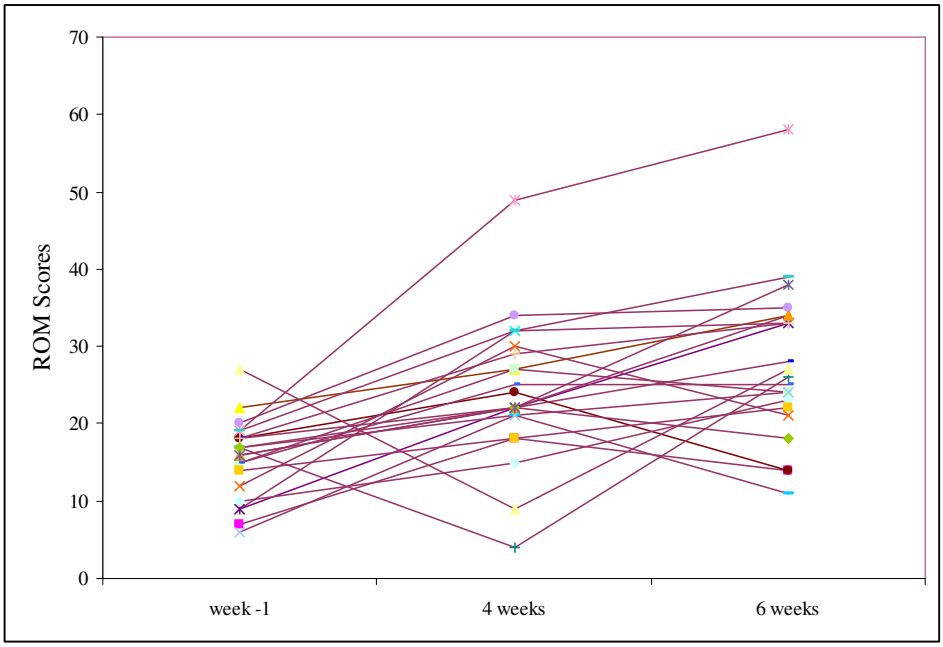


Figure 3.17.

Panel A shows the ROM scores for all the children in Group 2.

28 diplegic children. The improvement form baseline is significant at 4 and 6 weeks.

	Group2	**-1 week vs 4 weeks**	**-1 week vs 6 weeks**
Mean	15.5°	25.6°	27.9°
St.Dev	5.1°	7.1°	10.4°
P Value		<0.001	<0.001

Table 3.17.

A summary of the results of ANOVA test comparing the magnitude of the ROM pre and post Botulinum toxin type A injection in group 2. The results show that the mean ROM was statistically significant in group 2 4 and 6 weeks after the Botulinum toxin type A injection.

3.5.3 Comparison of ROM in Group 1 and Group 2.

The previous sections have described the changes in ROM in the two groups of children over the year after the injection of Botulinum toxin type A. In summary, group 1 showed no significant changes in mean ROM after 4 weeks but there was significant improvement after 6 weeks. Group 2 showed a significant improvement in mean ROM at 4 and 6 weeks. This section will compare the ROM of the two groups.

The results of testing these data with an ANOVA are shown in table 3.18. The mean ROMs in group 1 and group 2 were not significantly different before the Botulinum toxin type A injection (P-Value =0.290). Four weeks after Botulinum toxin type A the difference in means had increased but this difference was still not significant. (P =0.085). The same result was found after 6 weeks (P =0.173). These data are plotted in figure 3.19.

A good clinical response to Botulinum toxin type A injection in soleus and gastrocnemius muscle was shown by a decrease in toe walking in the children in both groups. This observation was noted by the parents and several clinicians, but not formally investigated.

		Group 1	Group 2
A	**Mean**	**17.4°**	**15.5°**
	St.Dev	5.7°	5.1°
	P Value	0.290	
B	Mean	21.2°	25.6°
	St.Dev	8.0°	7.2°
	P Value	0.085	
C	Mean	23.9°	27.9°
	St.Dev	5.6°	10.4°
	P Value	0.173	

Table 3.18.

A summary of the result of ANOVA tests comparing the magnitude of the ROM pre and post Botulinum toxin type A injections in group 1 and group 2.

A One week before Botulinum toxin type A injection

B Four weeks after Botulinum toxin type A injection

C Six weeks after Botulinum toxin type A injection

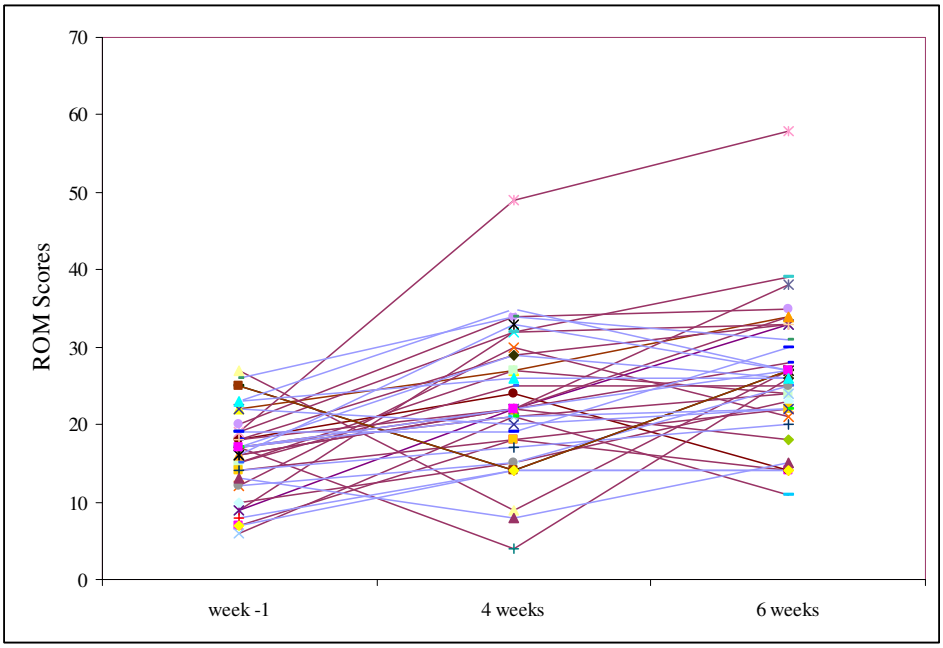


Figure 3.18.

This shows the mean ROM scores for Group 1 and group 2 one week before, 4weeks and 6weeks after BTX-A injection for 46 diplegic patients

3.6 Electromyography Data

The main aims in this section were to investigate how effective the Botulinum toxin type A injections were in paralysing the muscles and to investigate the effects on the stretch reflexes in soleus.

The surface EMG was recorded over soleus when the child was in a prone position with their knee flexed at 90º. The details of the EMG technique were described in section 2.8.4 of chapter 2. The EMG was recorded during ankle dorsiflexion, before the Botulinum toxin type A injection and at weeks 4 and 6 later.

There were remarkably few sessions where EMG could not be investigated. A typical set of recordings is shown in figure 3.19. The upper panel shows soleus EMG before during and after a dorsiflexion of the ankle joint. This recording was made before the Botulinum toxin type A injections. The lower panel shows similar recordings in the same child 4 weeks later. In this case, no surface EMG can be seen. The summary data showing the overall responses is shown in table 3.19.

One child in group 1 and three children in group 2 could not be investigated because of problems with hyperactivity. It was not possible to make EMG recordings in these cases. One child in group 2 withdrew because of an allergic skin reaction, which was not related to the conductive gel or tapes used. All other 17 children in group 1 and 25 child in group 2 were investigated.

	Group 1	Group 2
A	18 children treated with Botulinum toxin type A	28 children Botulinum toxin type A + intensive physical therapy
B	7 (38%) had EMG at -1, 4 and 6 weeks	17 (60%) had EMG at 1, 4 and 6 weeks.
C	6 had EMG at -1, 6 and not week 4	5 had EMG at 1, 6 and not week 4.
D	5 had EMG at -1 and not week 4, 6.	3 had EMG at -1 and not week 4, 6.

Table 3.19.

This shows the frequency of EMG activity 1-week before Botulinum toxin type A injection and at 4 and 6 weeks later. Group 1 received only Botulinum toxin type A whilst group 2 received Botulinum toxin type A and additional physical therapy.

There is no data for 3 children in group 2. There is no data for 1 child in group 1 at week 4.

Soleus EMG was recorded at the initial session in all 18 children in-group 1.

The individual EMG responses are shown in tables 3.20 and 3.21.

11 children of this group had no surface EMG activity at week 4 (61%) and 5 children still showed no EMG activity at week 6 (28%). In group 2, all the children showed surface EMG activity at the initial session. 8 children (28%) had no EMG at week 4 and 3 children had no EMG activity at week 6 (11%). Thus the doses of Botulinum toxin type A used appear to give abolition of EMG activity for 4 week in about half the children, (See Chapter 2, Section 2.5, tables 2.3 and 2.4.). The EMG activity was still absent in 8 children at six weeks after the injection.

ID. No.	Gender	Weight kg	Height cm	Age (month)	EMG week-1	EMG week 4	EMG week 6
35	F	15	107	74	EMG	EMG	EMG
44	M	16	105	70	EMG	EMG	EMG
37	M	17	107	77	EMG	EMG	EMG
28	F	17	107	80	EMG	EMG	EMG
17	M	18	110	80	EMG	EMG	EMG
20	F	44	139	129	EMG	EMG	EMG
46	F	15	108	96	EMG	EMG	EMG
9	F	30	104	109	EMG	No Data	EMG
23	F	11	84	29	EMG	No EMG	EMG
40	M	16	109	74	EMG	No EMG	EMG
30	M	16	108	78	EMG	No EMG	EMG
36	M	13	106	74	EMG	No EMG	EMG
45	M	13	107	79	EMG	No EMG	EMG
41	M	15	98	86	EMG	No EMG	No EMG
32	F	15	99	97	EMG	No EMG	No EMG
5	F	46	145	154	EMG	No EMG	No EMG
25	M	13	88	45	EMG	No EMG	No EMG
10	M	38	111	104	EMG	No EMG	No EMG

Table 3.20.

The EMG at the Soleus muscle of the ankle joint of the children in Group 1. The table shows the details of children, their heights, weights and gender. The columns on the right show the presence of absence of EMG.

ID. No.	Gender	Weight kg	Height cm	Age (month)	EMG week-1	EMG week 4	EMG week 6
27	M	12	86	28	EMG	EMG	EMG
4	F	16	98	84	EMG	EMG	EMG
21	M	11	84	25	EMG	EMG	EMG
33	M	11	84	28	EMG	EMG	EMG
43	F	13	84	36	EMG	EMG	EMG
39	M	12	86	43	EMG	EMG	EMG
29	M	12	85	45	EMG	EMG	EMG
3	F	17	85	45	EMG	EMG	EMG
6	F	12	84	46	EMG	EMG	EMG
15	F	13	85	48	EMG	EMG	EMG
34	F	13	85	33	EMG	EMG	EMG
18	F	14	95	56	EMG	EMG	EMG
1	M	13	84	59	EMG	EMG	EMG
19	M	15	93	72	EMG	EMG	EMG
22	M	18	106	73	EMG	EMG	EMG
13	M	17	109	94	EMG	EMG	EMG
16	F	40	135	132	EMG	EMG	EMG
42	M	11	86	27	EMG	No EMG	EMG
11	F	11	85	32	EMG	No EMG	EMG
26	F	12	87	25	EMG	No EMG	EMG
38	F	12	85	37	EMG	No EMG	EMG
2	M	16	86	66	EMG	No EMG	EMG
31	M	16	105	69	EMG	No EMG	No EMG
7	F	27	105	82	EMG	No EMG	No EMG
8	F	14	85	60	EMG	No EMG	No EMG
14	F	17	85	67	No Data	No EMG	No EMG
12	M	20	110	91	No Data	No Data	No Data
24	F	43	144	106	No EMG	No EMG	No EMG

Table 3.21.

The EMG at the Soleus muscle of the ankle joint of the children in group 2. The table shows the details of children, their heights, weights and gender. The columns on the right show the presence of absence of EMG.

3.7 The Stretch Reflex Responses

Stretch reflexes were elicited by manipulation of the ankle joint by the author. She followed a sine wave generated by the Spike 2 software to improve consistency in the amplitude and duration of stretch and relaxation phases. The amplitude of ankle movements was recorded using and electrogoniometer and the pressure applied was recorded (See chapter 2 sections 2.8.4 and 2.8.6.).

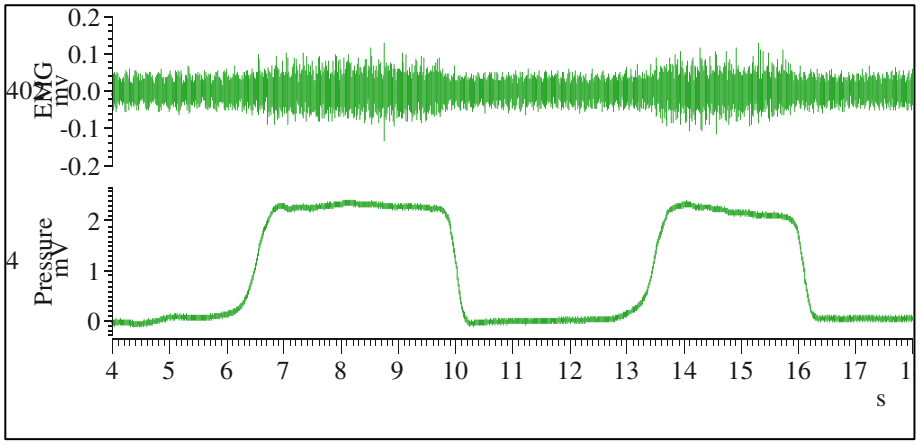
Figure 3.19. shows soleus EMG recorded during stretches of the muscle. The upper panel shows the pressure applied to the foot to dorsiflex the ankle. The upper trace shows the EMG recorded concurrently. The lower panel shows similar stretches applied to the same ankle of the same child 4 weeks after Botulinum toxin type A injections. There is no sign of EMG signal indicating the absence of stretch reflexes. In practice it was very difficult to produce consistent stretches over the three experimental days. This was a result of day-to-day variation in the author's technique and variable co-operation from the children.

In the present study, data from 6 children has been identified as suitable for analysis because they show consistent stretches of soleus over the 3 sessions.

The first level of analysis eliminated data from children where there was voluntary EMG before the stretch was applied or there were unwanted body movements. Effectively, these children did not co-operate with instructions to relax. A second level of analysis looked at the consistency of the amplitude and velocity of the five applied stretches. Figure 3.20 shows a recoding of EMG during five repeated dorsiflexions an example of good data the top panel shows the responses before Botulinum toxin type A injections. The two lower panels show recording from the same very

cooperative child 4 and 6 weeks later. Figure 3.21. shows a recoding of EMG during five repeated dorsiflexions an example of bad data recorded.

A



B

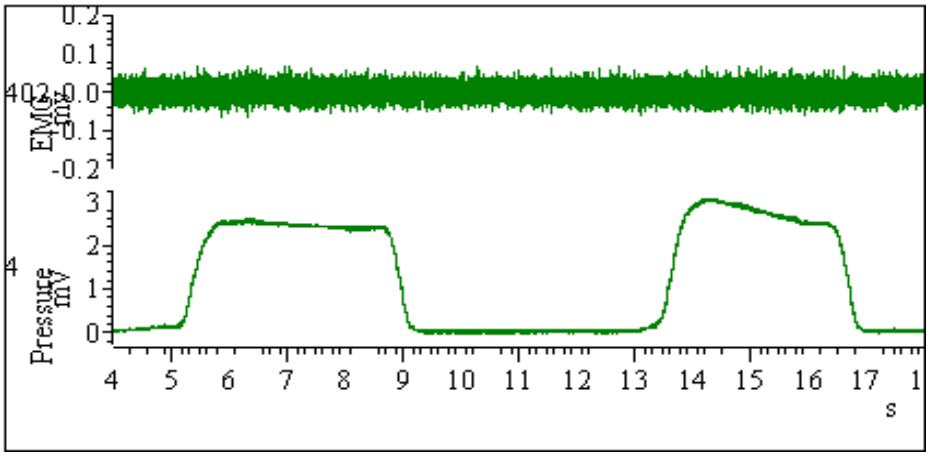
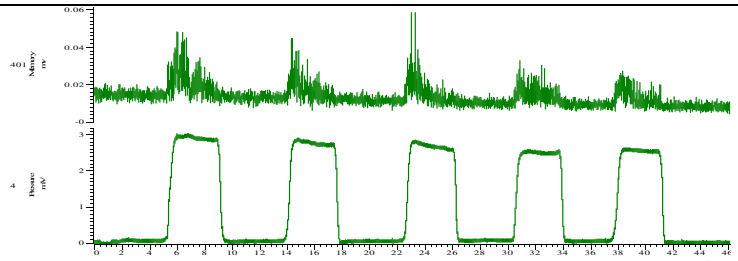
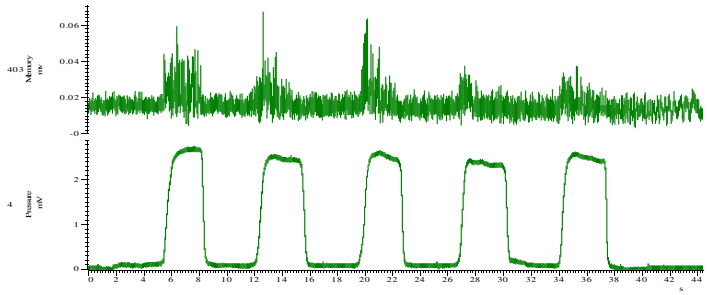
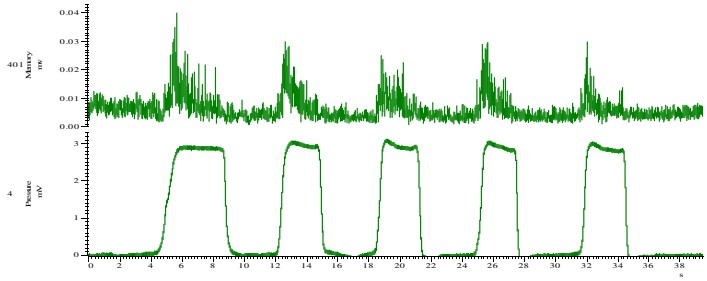


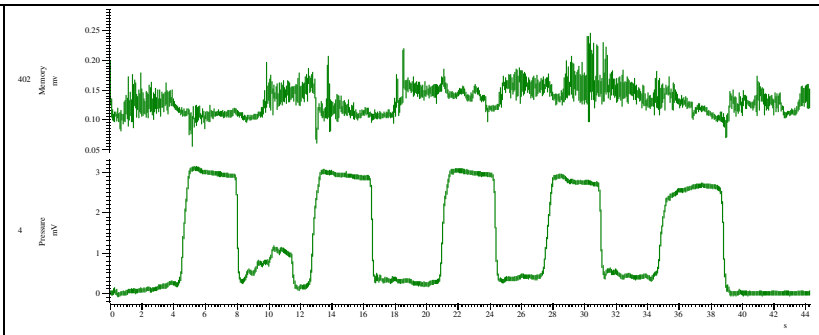
Figure 3.19.

Panel A shows the EMG activity in the soleus muscle during ankle dorsiflexion one week before Botulinum toxin type A injection.

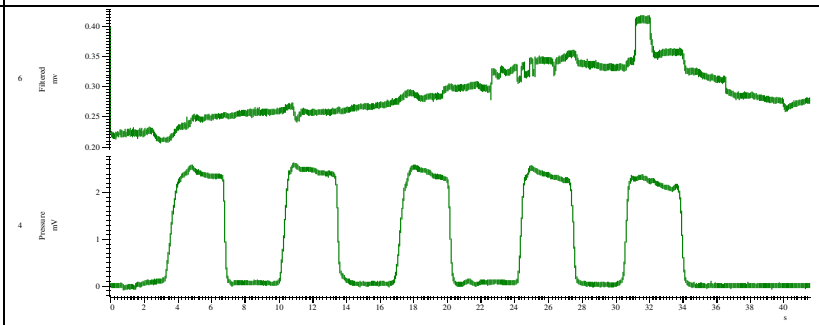
Panel B shows the EMG in the soleus muscle of the same child during ankle dorsiflexion four weeks after injection of Botulinum toxin type A. The EMG was silent or substantially reduced from pre-injection values

A	
B	
C	
	Figure 3.20. In each panel the upper trace shows soleus EMG and the lower trace shows the pressure applied to dorsiflex the ankle. Panel A shows the EMG activity in the soleus muscle during repeated ankle dorsiflexion one week before Botulinum toxin type A injection. Panel B shows the EMG four weeks after injection. Panel C shows the EMG six weeks after injection. This is an example of good data recorded from a cooperative child

A



B



C

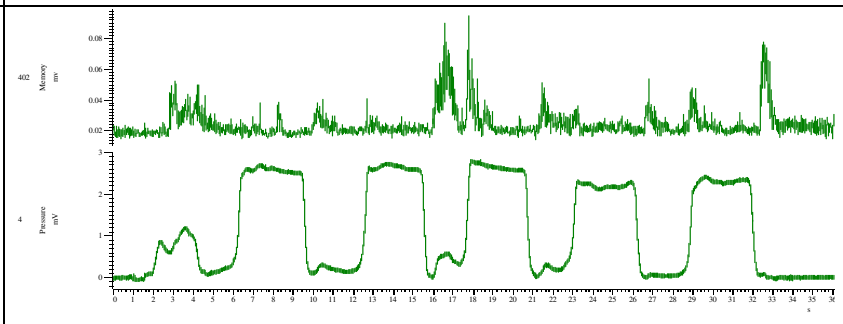


Figure 3.21.

In each panel the upper trace shows soleus EMG and the lower trace shows the pressure applied to dorsiflexion of the ankle.

Panel A shows the EMG activity in the soleus muscle during repeated ankle dorsiflexion one week before Botulinum toxin type A injection. Panel B shows the EMG four weeks after injection.

Panel C shows the EMG six weeks after injection.

This is an example of poor data recorded from uncooperative child

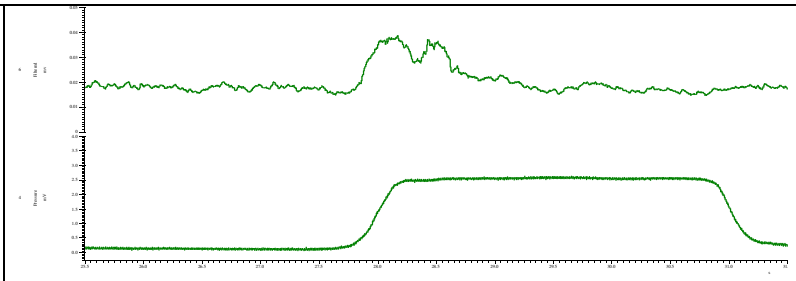
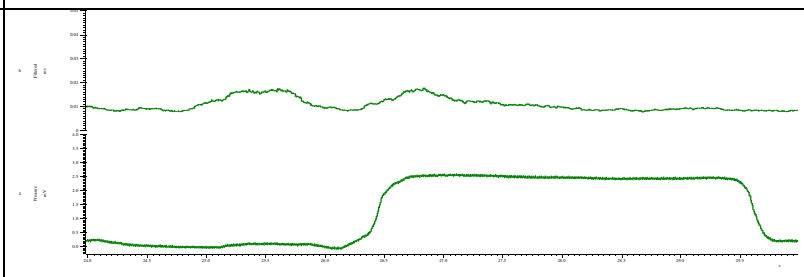
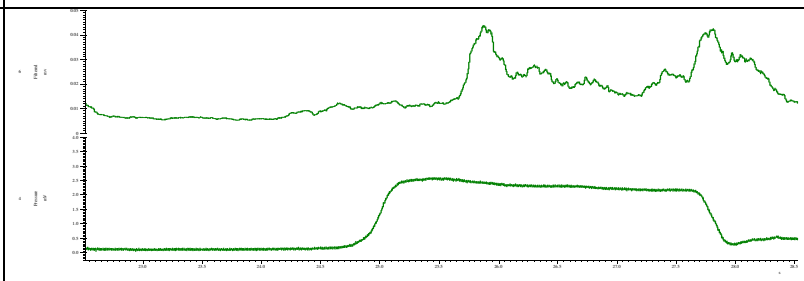
The examples shown in figure 3.20. illustrate that the stretch reflexes vary in amplitude even in the most favourable conditions when consistent stretches are applied. The commonly observed pattern was that the amplitude of the reflex declined over the series of stretches.

It was observed that the 4th stretch in the sequence elicited the most consistent reflexes. This was probably because the children were more relaxed.

Consistent data were found for the 4 most cooperative children and these are described below.

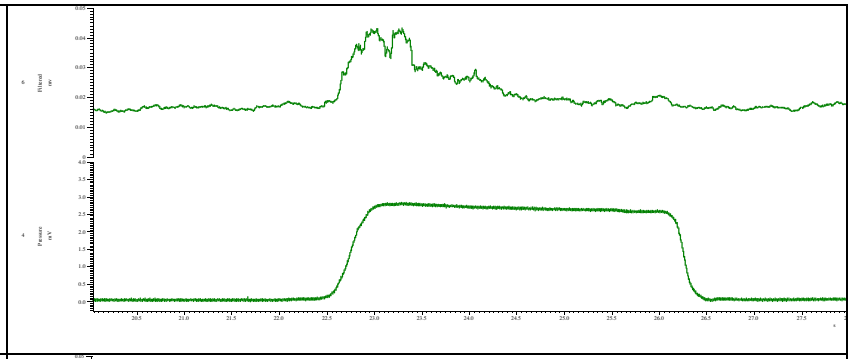
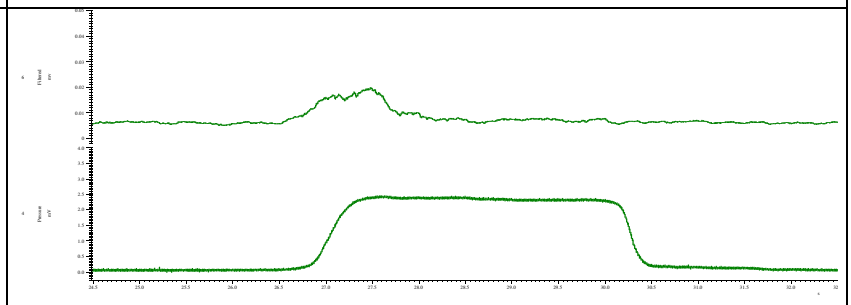
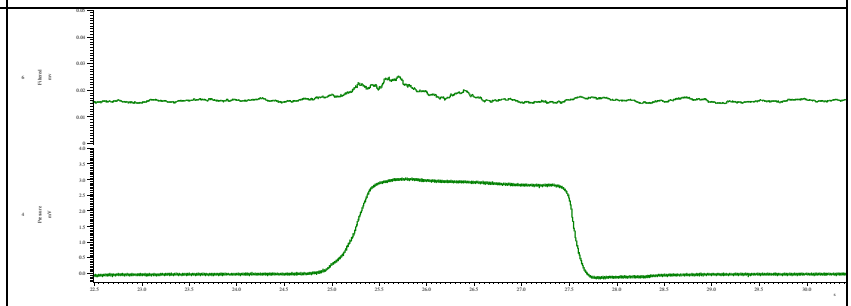
Examples for Group 1

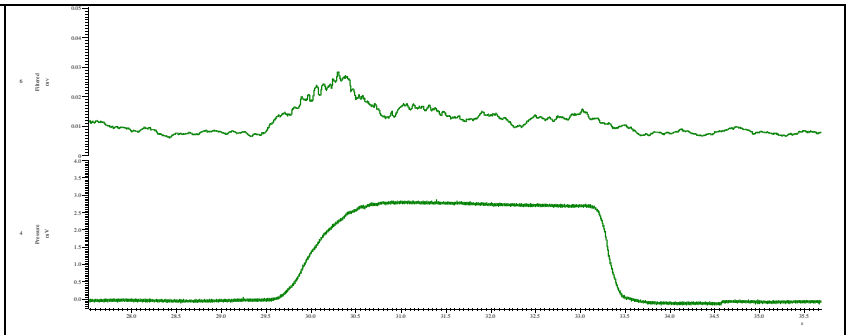
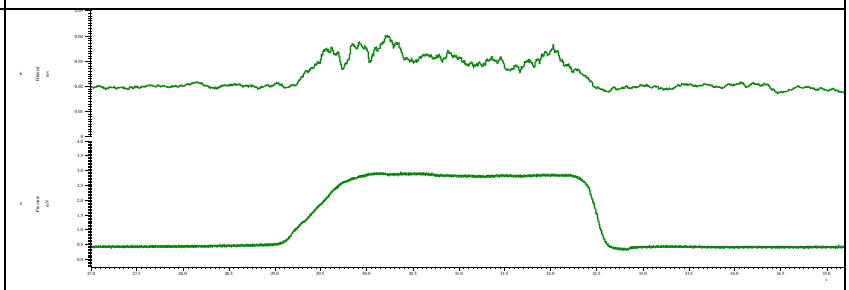
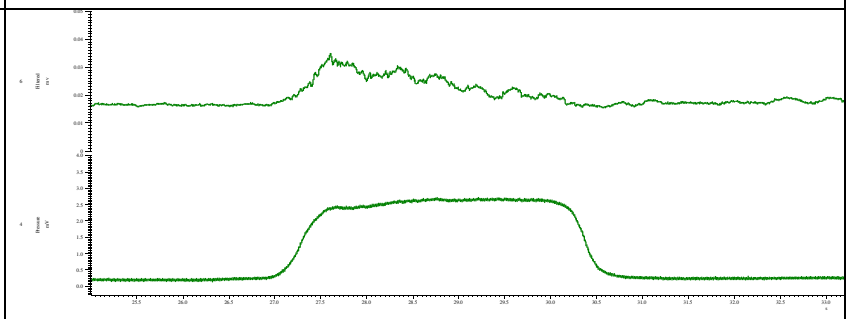
One set of suitable data was identified in this group. The EMG activity in soleus and strong stretch reflexes before the Botulinum toxin type A treatment. Figure 3.22 shows data from this child. The top panel shows a strong stretch reflex in the integrated EMG elicited by the ankle dorsiflexion. The middle panel shows recording made 4 weeks after the Botulinum toxin type A injection. A similar stretch elicits a smaller stretch reflex. In this case the reflex is preceded by a period of EMG activity which could be either involuntary or a voluntary preparation for the anticipated dorsiflexion. The bottom panel shows the response to a stretch applied 6 weeks after the Botulinum toxin type A injection. The EMG shows a very large period of activity some seconds after the stretch is applied. This is too slow developing to be a classical stretch reflex.

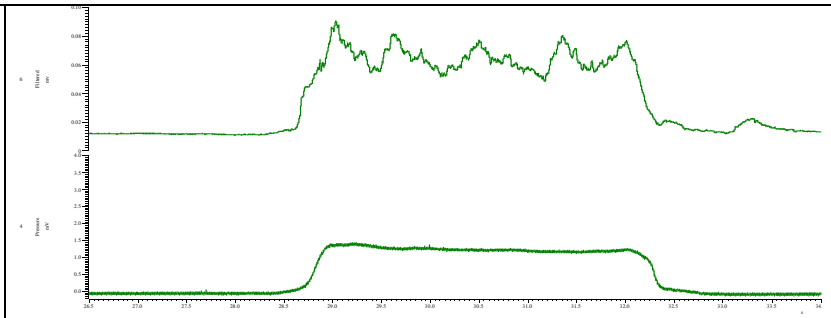
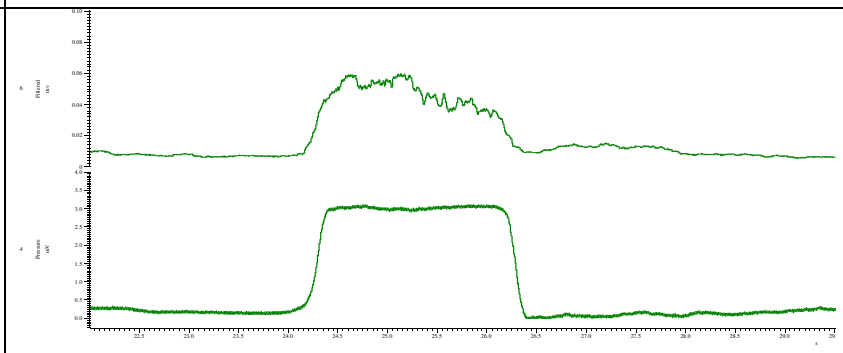
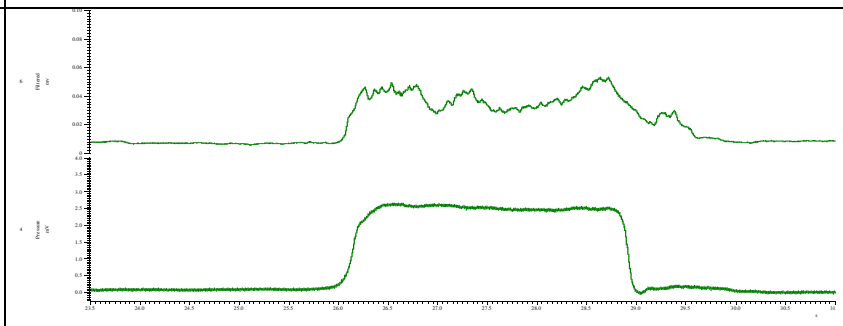
A	
B	
C	
	Figure.3.22. Panel A shows the integrated EMG activity one week before Botulinum toxin type A injection. The lower trace is the pressure applied to dorsiflex the ankle. The stretch reflex elicited was big. Panel B shows similar data form the same child four weeks after injection. The stretch reflex is smaller. Panel C shows similar data in the same child six weeks after injection. All records shown with the same amplification and time scale. Childs ID No. 23

Examples from Group 2.

3 children were selected from this group. They cooperated well and had EMG activity and clear stretch reflexes on al three recording sessions. Examples of their data are shown in figures 3.23, 3.24, and 3.25.

A	
B	
C	
	Figure 3.23. Similar layout to fig 3.22: Panel A, a clear stretch reflex in the integrated EMG activity and pressure one week before Botulinum toxin type A injection. Panel B shows similar data form the same child four weeks after injection. Panel C shows similar data in the same child six weeks after injection. Childs ID No. 19

A	
B	
C	
	Figure 3.24. Similar layout to previous figures. Panel A, integrated EMG activity and pressure one week before Botulinum toxin type A injection. Panel B shows similar data form the same child four weeks after injection. Panel C shows similar data in the same child six weeks after injection. In this child the stretch reflex was modest in amplitude and similar on all three days. Patient ID No. 4

A	
B	
C	
	Figure 3.25. Similar layout to previous figures. Panel A, integrated EMG activity and pressure one week before Botulinum toxin type A injection. Panel B shows similar data form the same child four weeks after injection. Panel C shows similar data in the same child six weeks after injection. In this child the stretch reflex was large in amplitude and similar on all three days. Patient ID No. 27

The data in figure 3.23. shows that the child had a strong stretch reflex in soleus before the treatment began. The initial phasic reflex is clear and the tonic components are less well developed. The Botulinum toxin type A injection had not fully paralysed the muscle at week 4 and a smaller phasic stretch reflex was recorded. The tonic components of the reflex are not present. In this example the EMG increases slightly before the pressure is applied and the child may have made some preparatory muscle contraction. This again illustrates the difficulty of working even with the more cooperative children. There was little change in the stretch reflex from week 4 to week 6.

Figure 3.25. shows a child who displays moderate stretch reflexes on all three occasions. The phasic reflex is small but the tonic components last throughout the stretch. The Botulinum toxin type A appears to have had very little effect on their stretch reflexes. A similar pattern is seen in the data in figure 3.26. The stretch reflexes may be a slightly reduced at 4 and 6 weeks but there is a strong sustained reflex each day.

These figures illustrate the problems of testing stretch reflexes in clinical populations in a clinical environment. There are many variables even in the same child. It was not possible to produce identical stretch profiles and that is seen in figure 3.22. In addition, some children anticipated the applied forces, as seen in figure 3.23. There were frequent problems with the behaviour of some children who were uncooperative or were distracted during EMG recording.

3.8 Adverse effects observed during the study

Fortunately, no children were affected by allergic skin reactions to the tapes, gels etc. used during the study.

No significant side effects of Botulinum toxin type A injections were recorded by any of the children. Most children reported pain at the time of injection. The clinicians did not use a topical anaesthetic before the injection and the children were often apprehensive before the injection began.

Two children showed generalized weakness during 1-2 weeks after Botulinum toxin type A injection. Four other children reported minor weakness in their legs following botulinum toxin injection. All of these effects were short lived and none required medical intervention.

Chapter 4

Discussion

4.1 Introduction

Cerebral palsy is the commonest cause of severe disability in childhood. It consists of a heterogeneous group of motor disorders including spasticity, muscle weakness, incoordination and dystonia. Muscle spasticity is one major factor that can interfere with normal walking.

Both conservative and surgical treatments are available to a child with cerebral palsy in an effort to reduce spasticity and its effects in the lower limb. The non-surgical interventions include: physical therapy, orthoses, casts and drug therapy. It is not clear which treatment or treatments are most effective (Flett, 2003), (Rethlefsen et al, 1995), (Middleton, Hurley and Mcllwain, 1988), (Koman, 1996), (Ubhi, 2000), (Gracies, Elovic, McGuire and Simpson, 1997), (Kita, 2000), (Davis and Barnes, 2000), (Koman, 1993), (Wall, 1993), (Scott, 1981), (Graham, 2000)). Empirical observations suggest that the combination of treatment modalities may be more effective than the use of one treatment.

The particular aim of the project was to investigate the use of Botulinum toxin type A toxin with intensive physiotherapy in children with cerebral palsy. Botulinum toxin type A treatment is used to improve the motor function in children. This study made quantitative measure of motor function in two groups of children. One group was treated with Botulinum toxin type A alone and the second group received Botulinum toxin type A and intensive PT. The outcomes of the two treatments were compared at intervals of up to 52 weeks.

4.2. Objective of study

The aims of the present study were:

1. To survey the characteristic features of children in KSA with cerebral palsy.
2. To recruit two groups of children to the study.
3. To establish baseline data for GMFM, ROM and stretch reflexes in these groups and to repeat the measures at intervals of up to one year.
4. To record the clinical outcomes for the children in the two groups.

The first aim was fully achieved and the survey of Saudi children with cerebral palsy is contained in the chapter 3 section 3.2. The second aim was also achieved. One group of children was recruited from families living in more rural areas near Taif and the other group was recruited from families living in the cities of Mecca and Jeddah. In total, 163 children were assessed and 47 were recruited to the study.

The third aim was also achieved and GMFM and ROM measurements were made for all these 46 children at intervals up to one year after they entered the study. However, it was much more difficult to get consistent data on the stretch reflexes. Only six examples of these are shown in the results section. It was difficult to make concurrent recordings of soleus EMG, ankle joint position and apply consistent stretches to the ankle. The children were frequently uncooperative during these measurements and it was rare to have a complete set of data over four recording sessions. The final was almost completely achieved. Sufficient data was collected to allow a good statistical analysis of the GMFM and ROM data. The stretch reflex data obtained is compared to case studies because of the relatively small data set.

4.3. Characteristics features of children with cerebral palsy in KSA

In 2002 a major report on the prevalence and characteristics of European children with cerebral palsy was published (SCPE, 2002). This included data on 6000 children with cerebral palsy from 13 geographically defined populations. The overall average prevalence for this study was 2.08 cases per 1000 live births. The highest prevalence was found in eastern Denmark with (2.63/1000), Northern Ireland (2.26/1000) and the Viterbo region in central Italy at (2.21/1000). The lowest rates were found in France, in the regions of Isere (1.78/1000) and Garonne (1.66/1000) and in Scotland (1.62/1000). There is no obvious geographical pattern amongst the European data. In north-east England in the period 1964-1993 the rate of has risen in spite of falling perinatal and neonatal mortality rates, and this is probably because of the effect of modern health care. It is probable that babies with a low birth weight, who would have formerly been unlikely to survive, now survive perinatal period with severe cerebral palsy. (Colver, Gibson, Hey, Jarvis, Mackie and Richmond, 2000).

In the USA there are approximately 550,000 persons with cerebral palsy. The number of new cases has increased from 1.5-1.8 cases per 1000 live births in 1990 to 2.0-2.5 cases per 1000 live births in 2000 (UCP, 2002). The reasons for this change are unclear. However, Dale and Stanley, (1980) and Volpe, (1994) found the increased survival of infants born before full term has translated into an increase in the clinical subtypes of cerebral palsy more commonly seen in ex-preterm infants, e.g. spastic diplegia.

In Saudi Arabia, several studies have investigated children with cerebral palsy, other neurological disorders and other disabilities (Al-Naquib, (1981), Taha and Mahdi, (1984), El Rifai, Ramia and Moore, (1984), Al Frayh and Al Naquib, (1987), Al-Naquib, (1988), Al-Rajeh, Bademosi, Awada, Ismail,

al-Shammasi and Dawodu, (1991), Al-Triki, (1997), Ansari, (2001), Al-Asmari, (2006), Rajab, Yoo Seung-Yun, Abdulgalil, Kathiri, Riaz, Mochida, Bodell, Barkovich and Walsh, (2006)).

A population survey in Saudi Arabia on the prevalence of child disability found the rate to be 1.2 per 1000 and this accounted for 0.04% of the total population (Ansari et al, 2001) An independent study from Saudi Arabia reported a 2.5-fold increase in the occurrence of cerebral palsy in consanguineous families (Al-Rajeh et al, 1991).

The major risk factors identified were a history of disease in a sibling and consanguinity of the parents. Low birth weight, typically less than 2 kilos, gestational age less than 32 weeks, twin pregnancy and respiratory distress were significantly more frequent among cerebral palsy cases than controls. The antenatal factors, including inherited ones, play a major role in the pathogenesis in Saudia Arabia (Al-Rajeh et al, 1991). Al-Turaiki, (1997) also found a strong relationship between handicaps including cerebral palsy and marriage within close relatives.

The SCPE report found that only 7.8% of the total number of cerebral palsy cases in Europe could be attributed to postnatal causes. In the USA 10% of cerebral palsy cases could be attributed to postnatal causes (UCP, 2002). However, in Saudia Arabia in Al Riyadh 17% of the cases of cerebral palsy were attributed to postnatal events.

Several other studies of Saudi and Iraqi populations have found that postnatal events were responsible for between 15 and 32% of all cases. Al-Naquib, (1981) produced data, which showed that cerebral palsy, is more common in Arab populations than in Europe and the USA. The opposite

pattern is seen in the frequency of pre-natal causes. The USA studies find almost half the cases were known to have pre-natal causes but the Arab studies gave much lower frequencies.

Al-Naquib, (1988) found the prenatal factors include a high incidence of a positive family history and consanguinity in cerebral palsy in Saudia Arabia. Thus, similar features are common to both the pre natal and postnatal causes Al-Turaiki, (1997).

Country	Saudia Arabia	Saudia Arabia	Saudia Arabia	Saudia Arabia	Iraq	USA	USA	USA
Author	Al-Naquib	El Rifai	Taha & Mahdi	Al Frayh & Al Naquib	Al Naluib	Holm	O'Reilly & Nowiz	UCP
Year	1988	1984	1984	1987	1981	1982	1981	2002
Numbers	1716	190	202	260	—	142	—	—
Prenatal	22	33	23.5	27.96	24.5	50	38.5	70
Perinatal	9	49	48	12.68	27	33	46.4	20
Postnatal	22	17	28.4	32.3	15.5	10	15.2	10
Mixed	4	—	7	3.88	2.5	7	—	—
Un known	43	—	13. 0	20.38	30.5	—	—	—

Table 1.4.
The etiology of cerebral palsy. This study compared to other studies in Saudia Arabia and other countries. Modified from Al-Naquib, (1988).

Cerebral palsy has many effects on the development of the central nervous system (Levitt, 1995). Some of these are widespread and affect higher brain functions such as the intellectual development of the children. In this study 57 % of the children had problems with mental retardation. This ranged from mild to severe. Only 7% were classified with severe retardation). In Europe one in five children with cerebral palsy was found to have a severe intellectual deficit (SCPE, 2002).

Sensory developmental problems are also frequent. In this study 15 % of the children had vision abnormalities and 6% had auditory impairments. In Europe over one in ten children had severe visual impairments (SCPE, 2002). In England and Scotland 8.9% of cerebral palsy cases had severe visual disability and 12% had severe hearing disability (Pharoah et al, 1998). The frequency of sensory impairment seems similar in these studies.

4.4. Frequency of Spasticity

The group of children recruited for this study was also representative of the cerebral palsy population in terms of the motor disability. The dominant motor problem in children with cerebral palsy is spasticity: 90% of the children in this study had spasticity predominantly in gastrocnemius and soleus. This is very similar to the SCPE study, which showed that 86% of the children with cerebral palsy had spasticity

The most common type of cerebral palsy in this study was spastic diplegia. It represented 65% of the cases. Al-Naquib (1988) found spastic diplegia to be the most common form of cerebral palsy in his study of children in KSA. These data are similar to the European statistics. The SCPE report found that the European frequency was 55%.

The next largest group are the cases of spastic hemiplegia. They represent 29% of the cases in this study. A study by Al Frayh and Al Naquib (1987) found 19% of the cases to have spastic hemiplegia in sample of 260children. The European rate was reported to be 29% (SCPE, 2002). The studies all agree that spastic dyskinetias and ataxias are found at a low frequency.

Spasticity causes many problems with mobility, poor posture and self-care. The main functional difficulty for children lies in impaired walking. In this study 70% of the children had a walking disability. 14 children did not walk at all. Kuban and Levition, (1994) reported around 25% of the patients with

cerebral palsy were unable to walk. This paper did not give the ages of the patients. Their patients were a mixed population identified in France and the UK. In Europe, 31% of children with cerebral palsy are not able to walk. In England and Scotland 33% of children with cerebral palsy have severe ambulatory disability and no independent walking (Pharoah et al, 1998).

One important question is: is improvement in spasticity linked to improved walking?

Several studies have suggested that intramuscular injections of botulinum toxin type A can be both safe and effective in relieving spasticity. This ultimately leads to better walking in children with cerebral palsy (Koman et al, (1993), Cosgrove et al, (1994), Koman et al, (1994), Wong, (1998), Flett et al, (1999), Boyed, Graham, Nattrass and Graham, (1999), Corry et al, (1999), Sutherland et al, (1999), Yang et al, (1999), Ubhi et al, (2000), Barwood et al, (2000), Bakheit et al, (2001), Linder et al, (2001), Bottos et al, (2003))

Many people believe that physical therapy may help children with cerebral palsy to learn better ways to move and balance. It may help children learn to walk, use their wheelchair, stand by themselves, or go up and down stairs safely. Children may also work on other skills in physical therapy like running, kicking and throwing a ball or learning to ride a bike.

In this study 18 and 28 children were enrolled into group 1 and group 2 respectively. The demographic and clinical characteristics of the two groups were comparable at baseline. Children in both groups showed improvements in the joint ROM and the GMFM scores, but the improvement in-group two was bigger. Furthermore, between groups comparison showed a significantly better improvement in children who received Botulinum toxin type A and physiotherapy.

4.5. Discussion of the study design

Ultimately, the aim of this project was to investigate the efficacy of Botulinum toxin type A and Botulinum toxin type A in combination. with physical therapy.

The study was of the `open label `type, i.e. the clinical staff, the researcher and patient's family were aware of the treatment programme used. It is considered that this was the only practical design. The main action Botulinum toxin type A is to paralyse muscles and this cannot be concealed from those taking part in the experiment. Whilst the children and their parents knew that treatment was used, it is not clear that they had sufficient information to introduce any deliberate bias into the study. It is possible that the clinical staff could have done this accidentally. The physiotherapy programme was standardised to ensure consistent delivery. In addition, only one group of children was treated at any one centre and so the clinicians would not have been aware of the progress made by the parallel group. The GMF observations made by the researcher are the ones most likely the very structured GMFM questionnaire and this probably represents the best defence against accidental bias. The introduction of a second observer who is blinded to the study does not always help in such cases because of the possibility of discrepancies in the operation of two or more observers.

Many other studies of the efficacy of Botulinum toxin type A have used the same design (Koman et al, (1993), Cosgrove et al, (1994), Thompson et al, (1998), Koman et al, (1999), Boyd et al, (1999), Eames, Baker, Hill, Graham, Taylor and Cosgrove, (1999), Corry et al, (1999), Boyd et al, (2000), Bakheit et al, (2001), Linder et al, (2001), Fragala et al, (2002). Cerebral palsy is such a heterogeneous condition that it is difficult to recruit matched controls with similar degree of spasticity and motor disturbances (Wong, 1998).

The study did not allocate the children to the two groups in a randomised way. All the children at one site received one treatment and all the children at the other site received the alternative treatment. The primary reason for this was to respect family wishes. The parents who brought their children to the Centres of the Disabled Children's Association in Mecca and Jeddah clinic did not wish their children to attend the residential centre at Rehabilitation Centre of The Prince Sultan Military Hospital in Al Hada where the intensive physical therapy was delivered. Ultimately, the allocation to treatment groups was made by the parent's decision to enter or not enter the residential hospital. This could have introduced problems with the creation of dissimilar experimental groups. However, the post hoc analysis reported in section 3.3 and figures 3.8 showed that this was not a significant problem. It would be better if any future study were designed to ensure a balanced study. One advantage of the design used was that the families were happy to keep their children in the study and this is seen in the very low drop out rate and this improved the statistical power of the study.

One other feature of the recruitment was the decision to exclude children with severe disabilities. This initial decision was intended to avoid the problems of testing children who could not understand the instructions during the GMFM tests and to allow a focus on children who could walk independently or with assistance. The data shown in table 3.2 shows that this eliminated 7% of the children who were initially screened. The post hoc analysis shown in figure 3.15 shows that the children with the highest initial GMFM scores, i.e. those least affected, benefited most from treatment. Thus the recruitment policy probably biased the study in favour of detecting an effect though this was accidental.

In retrospect, it may be fairer to describe the sampling strategy as a 'stratified' i.e. the population is divided or stratified on some characteristic

(the initial classification of severity) before random selection on the sample (Thomas, Nelson and Silverman (2005)).

Any future developments of this study should consider using a crossover design where the all the volunteers get both treatments in sequence. This contrasts with the parallel groups design used. The crossover design can be used in situations where it is not possible to identify a separate comparison group. In effect, each subject serves as his/her own control. Also, since the same subject receives both treatments, there is no possibility of covariate imbalance. Ideally in a crossover design, a subject is randomly assigned to an each treatment order.

It is worth recognising that despite their potential to provide greater statistical power, crossover studies have well known limitations. Persistence of effect of first treatment can be a problem and this could be a significant problem since the treatment effects seen in this study were still significant 12 months after the treatment started and 6 months after the last injection. In addition, the crossover design requires each volunteer to remain in the study for longer periods and this can cause high dropout rates than in shorter duration parallel group studies.

This was an 'open label' prospective study. The clinicians, physical therapists and parents knew which treatment was delivered. It is impossible to blind those involved to the nature of the treatment.

In addition, it is difficult to blind patients or clinicians to the nature of treatment since the Botulinum toxin type A produces a very obvious paralysis.

However, some authors have been used a randomized controlled trial design, e.g. Koman et al, (1994), Flett et al, (1999), Wissel, Heinen, Schenkel, Doll, Ebersbach, Muller and Poewe, (1999), Sutherland et al,

(1999), Barwood et al, (2000), Ubhi et al, (2000), Boyd, et al, (2001) and Baker et al, (2002).

This study tested 46 children. Thus size of the study sample is larger than most previous studies. There are two larger studies: (Reddihough et al, 2002) with 49 children and (Koman et al, 1999) with 48 children. The smaller studies include Koman et al,. (1993) 26 children with dynamic deformities, Cosgrove et al, (1994) 26 children, Koman et al, (1994) 12 children, Eames et al, (1999) 39 children, Flett et al, (1999) 20 children, Ubhi et al, (2000) 40 children and (Boyd, et al, (2001) 39 children.

4.6. Children Age

In this study the children were between 25-154 months. This is similar to other studies. Some have tested children as young as 18 months (Barwood et al, 2000) but the great majority concentrated on children between 2 and 15 years (Flett et al, (1999), Ubhi et al, (2000), Linder et al, (2001), Reddihough et al, (2002), Bottos et al, (2003), Fragala et al, (2002), Boyd et al, (2001), Wong, (1998)).

The optimal time to treat spasticity with Botulinum toxin type A appears to be after the age of 2 years to coincide with the child motor development and learning to walk.

4.7. Dose of the Botulinum toxin A

In present study all the Botulinum toxin type A injections were made by Dr Shakfa, the head of Orthopaedic Surgery department at Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre, at Saudi Arabia. All injections were prepared by following a standard procedure. The dose administered was 6 units/kg of body weight per child. There was a maximum of 200 units per child for the lower limb the dose

calculation takes into account the mass of the child, the number of muscles targeted (see Chapter 2, section 2.5).

In this study the Botulinum toxin type A dose was too small to block the muscle contraction at 4 weeks. In some children the EMG in soleus returns by 6 weeks after Botulinum toxin type A. This is clearly seen in table 3.18. This return of EMG is observed in other studies (Gordon, (1999), Koman, (1993) Carr, Cosgrove, Geringrass and Neville, (1998) and Bakheit, (2001)). However, a clinical response was achieved in this study without excessive weakness or systemic side effects.

There is no consensus in either paediatric or adult practice about the appropriate dose of Botulinum toxin type A in spasticity. The dose is generally determined by the size of the muscle to be injected. The aim is to achieve a clinical response without excessive weakness or systemic side effects (Carr et al, 1998). The doses used in this study appeared to be adequate for the treatment of spasticity as confirmed with the neurophysiological test.

4.8. Muscle injected

The choice of muscles selected for injection depended on the degree of spasticity in the lower limb. The orthopaedic surgeon identified the target muscles by manipulation of the limbs without electromyography guidance. The soleus, gastrocnemius, hamstring and adductor muscle were injected by using appropriately sized syringe under antiseptic conditions, without using anaesthetic before administering the Botulinum toxin type A injection (Tables 2-3 and 2-4 in chapter 2).

4.9. Study duration

The duration of the current study was 52 weeks. This comparable is with the other studies. Linder et al, (2001), Reddihough et al, (2002), M Bottos et al, (2003), Barwood et al, (2000), Fragala et al, (2002), Boyd et al, (2001) and Flett et al, (1999) all carried out their final assessment after 12 months Only three studies have longer duration follow ups. Glanzman et al, (2004) waited 24 months and Wong, (1998) waited between 10-24 months. Sutherland et al, (1996) conducted a trial over 3 years.

In this study the results were statistically significant at 12 months. The effects were also significant at 4 and 6 weeks after injection.

Nerve sprouting and muscle re-innervation lead to functional recovery within 2 to 4 months (Rosales, 1996). There is evidence that partially functional neuromuscular junctions are re-established within 4 weeks (Angaut-Petit, Molgo, Comella, Faille and Tabit, 1990). The periods of clinically useful muscle relaxation is usually 12-16 weeks (Graham et al, 2000). (Duchen and Strich, 1968).

Because nerve sprouting and muscle re-innervations lead to functional recovery within 2 to 4 months, this study used the measurements after Botulinum toxin-A injection at 4,6 and 52 weeks.

4.10. Outcomes of the study

4.10.1. Gross Motor Function Measure (GMFM)

The primary outcome measure in this study was GMFM. This is commonly used to measure gross motor performance in children with cerebral palsy. It

establishes the baseline performance and to detects change over time (Leach, (1997), Russell et al, (2000), Graham, (2000) and Linder, (2001)).

In this study the GMFM technique worked well. The technique was sufficiently sensitive to detect changes in the motor behaviour of the children in group 2. In addition, it can produce a stable state in the children in group 1. However, the time taken to administer the tests was a problem since it took approximately 45-60 minutes per session per child. It also depended on the ability level of the child and the child's level of cooperation and understanding. In this study some data was unobtainable when working with uncooperative children. These operational problems probably explain why only nine studies have used GMFM outcomes after Botulinum toxin type A injection: (Flett et al, 1999), (Yang et al, 1999), (Wissel et al, 1999), (Ubhi et al, 2000), (Linder et al, 2001) (Reddihough et al, 2002) (Boyd et al, 2001) (Bottos et al, 2003) and (Mall et al, 2006).

Overall, this study worked well. The sample size, measurement techniques and duration were adequate to deliver statistically significant results as can be seen in table 3.12 and table 3.17. In addition, the study size and duration are similar to the largest and longest duration studies already published.

GMFM is a valid measure of the motor function in children. This study found GMFM sensitive to change after long-term from treatment and at 4, 6 and 52 weeks post injection it was statistically significant difference in the mean of the GMFM in Group1 and Group 2 after 4 weeks ($P < 0.002$), 6 weeks ($P < 0.001$). and at 52 weeks ($P < 0.000$). Both groups' treatments showed evidence of improvement in GMFM over the period of the study and particularly at 52 weeks. The observed improvement in GMFM was also evident to the treating therapists and the children's parents.

Group 2 had Botulinum toxin type A and physical therapy showed a significant average advantage in GMFM over group 1 had Botulinum toxin type A only at all times in the study.

This advantage in average GMFM scores increased from 4 through to 52 weeks with a clear and significant difference between 4 and 52 weeks

This benefit of treatment appeared to increase the higher the child's baseline GMFM, this was not statistically significant difference in the mean of the GMFM score in Group 1 and Group 2 before the Botulinum toxin type A injections ($P = 0.952$).

These results substantially agree with previous studies by Yang et al, (1999) Ubhi et al, (2000), Linder et al, (2001) and Bottos et al, (2003).

The GMFM approach is the most fully validated objective outcome measure of motor function. It is more appropriate for assessing children in the mid-range of disability Graham, (2000), Linder et al, (2001) It may not be sensitive enough to detect changes in children with mild disability. In this study the biggest improvement in GMFM scores occurred in children with the highest initial scores. (Refer to results chapter 3 table 3.8). This is most likely a genuine effect because the changes will be hardest to detect in the children with milder disabilities. In addition, Linder et al, (2001) found improvements in GMFM scores were most clearly evident in children with moderate impairment and the result of this study agrees with Graham et al, (2000) and Linder et al, (2001), Graham, (2000).

The present study confirmed that the combination of physiotherapy with Botulinum toxin type A is more effective than Botulinum toxin type A alone. By contrast, Reddihough et al, (2002) found there were no statistical differences between GMFM scores after treatment with the Botulinum toxin type A and PT or treatment with physical therapy alone at either 3 or 6

months post injection. Similar results were reported by Flett et al, (1999), Boyd et al, (2001) and Mall et al, (2006) they found it not significant between the two groups.

4.10.2. Electromyography (EMG)

The main aims of using electromyography (EMG) in this study were to investigate how effective the Botulinum toxin type A injections were in paralysing the muscles and to investigate the effects on the stretch reflexes in soleus.

Electromyography (EMG) is a technique for evaluating and recording the activation signal of muscles. Two main types of electrodes used for the study of muscle behaviour are surface electrodes and needle electrodes inserted through the skin. Each has its advantages and its limitations. The most common needle electrode is the concentric electrode is record deep-1-2 mm of needle tip, small sample single motor units 5 MU. Surface electrodes records up to 1 cm into the muscle, bigger volume 100 MU (Basmajian 1985).

Advantages of the needle its clear record, single motor unit and its useful with isometric experiments on the other hand its disadvantages difficult to ensure same position on different days, sampling problem are these 5 motor units like the rest of muscle and the needle in isometric experiment painful when muscle stretch with high forces high velocities. In this study the family and children were thought very unlikely to accept needle EMG because of local pain.

Surface electrodes offer the advantages giving a wider sample of motor units and being well tolerated movement. It was till difficult to make consistently good EMG recordings. The main difficulty was caused by children who would not relax and much spurious EMG was recorded. Indeed only eleven of the forty-three children had complete set of good EMG data for the initial tests and the repeats a 4 and 6 weeks. When good EMG was recorded during ankle dorsiflexions it was clear that significant muscle activity was present on some children at weeks 4 and 6, after the Botulinum toxin type A.

I recommended that future studies continue using of EMG recording. It may be easier to use in ore mature children. Only two authors have published reports using EMG to assess spasticity, Sutherland et al, (1996, 1999) and Bottos et al, (2003). They found no significant differences in their EMG data.

(Basmajian, 1974) EMG is widely used to investigate muscle activity. Most studies of reflex function require stable EMG recording for 10 to 100 minutes. In this study short-term EMG recordings were made. Examples can be seen in figures 2.5, 2.6 in chapter 2. These short term recording did allow investigation of how complete the paralysis was after Botulinum toxin type A injections. These data are in table 3.18 chapter 3. The EMG activity returned to normal after Botulinum toxin type A injection by 6 weeks. In some children, it had returned by 4 weeks. This agrees with the results of Gordon, (1999), Koman, (1993), Carr, (1998) and Bakheit, (2001).

However, in many children, it was very difficult or impossible to make EMG recordings because some hyperactive children kicked and protested. They could not relax and much spurious EMG was recorded. Indeed only eleven of the forty-three children had a complete set of good EMG data for the initial tests and the repeats at 4 and 6 weeks. Only two authors have

published reports using EMG to assess spasticity, Sutherland et al, (1996, 1999) and Bottos et al, (2003). They found no significant differences in their EMG data.

In this study EMG it not work very good with CP children. However it spent long time with 46 children to fixed EMG electrode. However, it returns after 4 and 6 weeks in some children. See table 3.18 in chapter 3

4.10.3. Goniometry

Like GMFM and EMG goniometry is well-established technique. It has been frequently used to study spasticity (refer to Literature review). The goniometry measurement shared some of the same problems with uncooperative children but it was easier to use than EMG. Sufficient data were obtained to allow statistical analysis. These are shown in table 3.13, 3.15.in chapter 3

The results of this study showed a significant increase in the range of motion at the ankle and this indicates a reduction in spasticity. This increase in ROM was found when the pre Botulinum toxin type A values were compared with the values 4 weeks later. The difference was significant in both groups of children. This difference was larger in group 2. This result agrees with Koman, (1993), Cosgrove, (1994), Koman, (1996), Sutherland, (1999), Suputtitada, (2000), Ubhi, (2000), Fragala, (2002) and Bottos, (2003).

The increase in the ROM correlated with clinical improvement. Ubhi et al, (2000) found the range of passive ankle dorsiflexion movement did not change between the weeks 2 and 12 after Botulinum toxin type A injection. All the previous studies and this one, measure changes before and after

botox. Indeed in this study, the children's parents or guardians often mentioned spontaneously that the spasticity had reduced within 24 hours of the injection. It is likely that Ubhi made all their measurements after the Botulinum toxin type A had taken effect.

4.11. Limitations of the study

The present study has some limitations. In terms of the design of the study, it would have been more satisfactory to achieve larger groups with similar ages and gender balance. In addition, for logistical reasons the assignment to the two groups could not be done randomly. The children in group 2 received two-weeks of intensive physical therapy treatment. This was best delivered if the families lived in the residential accommodation at the Rehabilitation Centre. The children were available for 1 to 2 hours each day and the families did not have to travel to the centre. Additional benefits were that treatments were delivered in a consistent manner by the same therapists in the same setting. The children in group 1 lived at home and came to the clinic for assessment and treatment like fitting of shoes and casts. Thus, the allocation to groups was done by the social and domestic factors influencing the families. One very positive result of using this allocation procedure was that the children and parents were happy to continue in the study and the dropout rate was very small. Four families did not return for the final assessment at one year and one child withdrew from the study after the initial assessment. Despite the recruitment difficulties the two study groups were very well matched for age, gender and baseline GMFM.

A second area of experimental difficulty lay in the interaction with the children. The clinical staffs involved were all experienced in working with children and the parents and at least one parent was present at all sessions.

However, it was frequently difficult to gain full cooperation from the child throughout the whole session. In an ideal world, the child would lie still on a bed in a prone position for parts of the assessment. The posture of limb would be constant and the knee of the target leg flexed to 90 degrees. The investigator could then apply controlled flexion movements to the ankle. However, some hyperactive children did not cooperate even when encouraged to do so by their parents. Kicking, shouting, crying and even on occasions vomiting confounded the tests. These movements could dislodge the skin mounted EMG electrode-amplifiers and the electrogoniometers. This caused the gaps in the experimental data as shown in table 3.18 and 3.19 of the results section. Even if the equipment stayed in place, the additional muscle contractions often rendered any measurements valueless. However, these difficulties would not have affected the primary outcome measure of the study.

One of the strongest features of the GMFM scoring was that it was much less affected by the child's immediate behaviour. GMFM scores were almost always successfully completed and the failure rate was in 4 children only.

4.12. Conclusion

In conclusion, this study has shown that Botulinum toxin A is safe and easy to administer, can be given as an outpatient procedure, and results in an improvement in walking and increase in range of motion. It offers an alternative to surgical intervention and our study supports its use with intensive physiotherapy programme following Botulinum toxin A injection, to maximise muscle lengthening and thus provide improved long-term benefit in children with cerebral palsy, to capitalise on the muscle relaxation more easily.

Botulinum toxin A should not be considered as a replacement for physiotherapy or orthotics. It should be viewed as an adjunct to current therapeutic strategies. Indeed the data in this thesis make an argument for an increased physical therapy programme following, Botulinum toxin A injection to enhance the child's motor performance.

4.13. Recommendation

1. Future studies of the effectiveness of the combined use of BTX-And physiotherapy in the management of spasticity in children with cerebral palsy should use a randomised controlled study design. This is the gold standard method in medical research.
2. The use of laboratory gait-analysis may provide useful additional information in studies that assess the benefits of treatment in ambulatory children with cerebral palsy.
3. Need to initiate data base included all cerebral palsy children in Saudia Arabia to know the incidence and prevalence of cerebral palsy in Saudia Arabia.

References

1. Al-Asmari, A., Al Moutaery, K., Akhdar, F. and Al Jadid, M. (2006). Cerebral Palsy: Incidence and Clinical Features in Saudi Arabia. Disability and Rehabilitation. **28** (22): 1373-1377.

2. Al-Frayh, A. and Al Naquib, N. (1987). The pattern of central nervous disease in children in King Khalid University Hospital in Riyadh. Saudi Arabia. Journal of Tropical Pediatrics. **33** (3): 124-130.

3. Al-Naquib, N. (1981). An analysis of 200 handicapped children in a teaching hospital in Iraq. An outline of etiological factors type of handicap. Courrier. **31**: 263-70.

4. Al-Naquib, N. (1988). Neuro-developmental Problems in Children in Riyadh, Saudi Arabia: 1-Year's Experience in a Family Practice Centre. Journal of Tropical Pediatrics. **43** (6): 294-300.

5. Al-Rajeh, S., Bademosi, O., Awada, A., Ismail, H., al-Shammasi, S. and Dawodu, A. (1991). Cerebral Palsy in Saudi Arabia: a case-control study of risk factors. Developmental Medicine & Child Neurology. **33** (12): 1048-52.

6. Al-Triki, M. (1997). National project researches for handicapped rehabilitation and re-rehabilitation in Kingdom of Saudia Arabia. The joint Centre for Research in Prosthetics & Orthotics and Rehabilitation Programmes (JCRPO) in Collaboration with Ministry of Health, Riyadh.

7. Angaut-Petit, D., Molgo, J., Comella, J., Faille, L. and Tabit N. (1990). Terminal sprouting in mouse neuromuscular junctions poisoned with

botulinum type A toxin: morphological and electrophysiological features. Neuroscience. **37**: 799-808.

8. Ansari, S., Sheikh, A., Akhdar, F. and Moutaery, K. (2001). Towards improving care in cerebral palsy. Disability & Rehabilitation. **23** (13): 592–595.

9. Baker, R., Jasinski, M. and Maciag, I-Tymecka, J. (2002). Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double blind, placebo-controlled, dose-ranging study. Developmental Medicine & Child Neurology. **44**: 666-675

10. Bakheit, A., M O, Pittock, S., Moore, A., P., Wurker, M., Otto, S., Erbguth and Coxon, L. (2001). A randomized, double blind, placebo-controlled study of the efficacy and safety of Botulinum toxin type A in upper limb spasticity in patients with stroke. European Journal of Neurology. **8**: 559-565.

11. Bakheit, A., M O., Severa, S., Cosgrove, A., Morton, R., Rousso, S., H., Doderlein, L. and Lin, J., P. (2001). Safty profile and efficacy of botulinum toxin A (Dysport) in children with muscle spasticity. Developmental Medicine & Child Neurology. **43**: 234-238.

12. Bakheit, A., M O. (2001). Botulinum toxin treatment of muscle spasticity. Black hall publishers, Dublin ISBN 1-842180-28-2

13. Barwood, S., Bailiew, C., Boyd, R., Brereton, K., Low, J., Nattrass, G. and Graham, H., K. (2000). Analgesics effects of Botulinum Toxin A: a randomized, placebo-controlled clinical trial. Developmental Medicine & Child Neurology. **42**: 116-121.

14. Basmajian, J.V., and Newton, W.J.: Feedback Training of Parts of Buccinator Muscle in Man, Psychophysiology 11 (1): 92, 1974.

15. Batshaw, M. and Perret, Y, Kurtz, L., A. (1992). Children with disabilities (3rd Ed.), Paul H. Brookes Publishing Co. Baltimore, Maryland. Chapter 24. ISBN 1-55766-102-2.

16. Barry, M. (1996). Physical Therapy interventions for patients with movement disorders due to cerebral palsy. Journal of Childhood Neurology. **11** (1): 51–60.

17. Berman, B., Vaughan, C., L. and Peacock, W., J. (1990). The effect of rhizotomy on movement in patients with cerebral palsy. American Journal of Occupational Therapy. **44** (6): 511-516.

18. Bertoti, D., B. (1986). Effect of short-leg casting on ambulation in children with cerebral palsy. Physical Therapy. **66** (10): 1522-1529.

19. Bly, L. (1991). A historical and current view of the basis of NDT. Paediatric Physical Therapy. **3**: 131-135.

20. Bobath, K. (1980). A neurophysiological basis for the treatment of cerebral palsy. Clinics in Developmental Medicine. **75**: 77-78.

21. Bobath, B. and Bobath, K. (1984). The Neuro-development treatment, in Scrutton D (ed): Management of the Motor Disorders of Children with Cerebral Palsy. Philadelphia, Lippincott. 6-18.

22. Bohanon, R., W. and Smith, M., B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. Physical Therapy. **67**: 206-207.

23. Boyed, N., Barwood, S., A., Baillieu, C., E. and Graham, H., K. (1998). Validity of a clinical measure of spasticity in children with cerebral palsy in a double blind randomised controlled clinical trail. American Academy of Cerebral Palsy and Developmental Medicine, Portland (AACPDM). Developmental Medicine & Child Neurology. **40**: 7.

24. Boyed, N., Graham, J., E., A., Nattrass, G., R. and Graham, H., K. (1999). Medium term outcome response characterisation and risk factor analysis of botulinum toxin type A in the management of spasticity in children with cerebral palsy. European Journal of Neurology. **6** (4): 37-45.

25. Boyd, N., Dobson, F., Parrott, J., Love, S., Oates, J., Larson, A., Burchall, G., Chondros, P., Carlin, J., Nattrass, G. and Graham, K. (2001). The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. European Journal of Neurology. **8** Suppl 5:109-19.

26. Borodic, G., Ferrante, R., Pearce, L. and Smith, K. (1994). Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic Botulinum A toxin injections. Journal of the Movement Disorders Society. **9**: 31-39.

27. Bottos, M., Azienda, USL, Benedetti, M., G., Salucci, P., Gasparroni, V. and Giannini, S. (2003). Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and functional assessment. Developmental Medicine & Child Neurology. **45**: 758–762.

28. Buckon, E., C., Thomas, S., S., Huston, J., S., Moor, M., Sussman, M., and Aiona, M. (2001). Comparison of three ankle-foot orthosis configurations

for children with spastic hemiplegia. Developmental Medicine & Child Neurology. **43**: 371-378. 193.

29. Butler, P., B., A. (1998). Preliminary report on the effectiveness of trunk targeting in achieving independent sitting balance in children with cerebral palsy. Clinical Rehabilitation. **12**: 281–293.

30. Carr, J., and Shepherd, R. (1998). Neurological Rehabilitation: Optimizing Motor Performance. The Bath Press plc, Bath.

31. Carr, L., J., Cosgrove, A., P., Geringrass, P. and Neville, B., G., R. (1998). Positions paper on the use of botulinum toxin in cerebral palsy. Archive of Disease and Childhood. **79**: 271-273.

32. Cherry, D., B. (1980). Review of physical therapy alternatives for reducing muscle contracture. Physical Therapy. **60**: 877–881.

33. Colver, A., F., Gibson, M., Hey, E., N., Jarvis, S., N., Mackie, P., C. and Richmond, S. (2000). Increasing rates of cerebral palsy across the severity spectrum in north-east England 1964-1993. Archives of Disease in Childhood - Fetal and Neonatal Edition. **83**: F7–F12.

34. Corry, I., S., Cosgrove, A., P., Duffy, C., M., Taylor, T., C. and Graham, H., K. (1999). Botulinum toxin A in hamstring spasticity. Gait & Posture. **10**: 206-10.

35. Cosgrove, A., P., Corry, I., S. and Graham, H., K. (1994). Botulinum toxin in the management of the lower limb in cerebral palsy. Developmental Medicine & Child Neurology. **36**: 386-396.

36. Coward, D., M. (1981). Selective muscle relaxant properties of tizanidinc and examination of its mode of action. Triangle. **20**: 151-158.

37. Dale, A. and Stanley, F., J. (1980). An epidemiological study of cerebral palsy in Western Australia, 1956-1975. II: spastic cerebral palsy and perinatal factors. Developmental Medicine & Child Neurology. **22**: 13-25.

38. Daniels, L. and Worthingham, C. (1980). Muscle Testing Technique of Manual Examination (4th Ed.), WB Saunders Co, Philadelphia, PA. ISBN 0-7216-1854-5.

39. Davis, C., E., and Barnes, P., M. (2000). Botulinum toxin and spasticity. Journal of Neurology, Neurosurgery and Psychiatry, London. **69**: (2): 143-151.

40. Delwaide and Young. R.R Editors. (1985). Wiesendanger chapter 1. Clinical neurophysiology in spasticity contribution to assessment and pathophysiology. Elsevier science publishers B.V. (Biomedical Division). The Netherlands. ISBN 0-444-80653-9.

41. Denhoff, E. and Robinault, I., P. (1960). Cerebral palsy and related disorders: A developmental approach to dysfunction. New York: McGraw-Hill

42. Desloovere, K., Molenaers, G., Jonkers, I., J., Cat, De, Borre, L., Nijs, J., Eyssen, M., Pauwels, P. and De Cock, P. (2001). A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. Journal of Neurology. **8** (5): 75-87.

43. Dogu, O., Apaydin, D., Sevim, S., Talas, DU. and Aral, M. (2004). Ultrasound-guided versus 'blind' intraparotid injections of botulinum toxin t-A for the treatment of sialorrhoea in patients with Parkinson's disease. Clinical Neurology and Neurosurgery **106**: 93-96.

44. Duchen, L., W. and Strich, S. (1968). The effects of Botulinum toxin on the pattern of innervation of skeletal muscle in the mouse. Q I Experimental Physiology. **53**: 84-9.

45. Dunevsky, A. and Pere, A. (1998). Gabapentin for relief of spasticity associated with multiple sclerosis. American Journal of Physical Medicine & Rehabilitation. 77, 451-4.

46. Eames, N., Baker, R., Hill, N., Graham, K., Taylor, T. and Cosgrove, A. (1999). The effect of Botulinum A toxin into the gastrocnemius length: magnitude and duration of response. Developmental Medicine & Child Neurology. **41**: 226-232.

47. Eiben, R., M. and Crocker, A., C. (1983). Cerebral Palsy within the spectrum of developmental disabilities. In G.H. Thompson, I L.Rubin, & R.M. Bilenker (Eds.), comprehensive management of cerebral palsy (pp. 19-23). New York: Grune &Stratton.

48. El Rifai, M., R., Ramia, S. and Moore V. (1984). Cerebral Palsy in Riyadh, Saudi Arabia: I. Aetiological factors. Ann Tropical Paediatric. **4** (1): 7-12.

49. El Rifai, M., R., Ramia, S. and Moore, V. (1984). Cerebral Palsy in Riyadh, Saudi Arabia: II. Associations between gestational age, birth weight and Cerebral palsy. Ann Tropical Paediatric. **4**(1): 13-7.

50. Etnyre, B., Chambers, C., S., Scarborough, N., H. and Cain, T., E. (1993). Preoperative and postoperative assessment of surgical intervention for equinus gait in children with cerebral palsy. Journal of Pediatric Orthopaedics. **13** (1): 24-31.

51. Flett, P., J., Stern, M., Waddy, H., Connell, M., Seeger, D. and Gibson, K. (1999). Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. Journal of the Paediatrics and Child Health**. 35**: 71-77.

52. Flett, P., J., (2003). Rehabilitation of spasticity and related problems in childhood cerebral palsy. Journal of the Pediatrics and Child Health. **39**: 6-14.

53. Fowler, E., Nwigwe, AI and Wong, Ho, T. (2000). Sensitivity of the pendulum test for assessing spasticity in persons with cerebral palsy. Developmental Medicine & Child Neurology. **42**: 182–189.

54. Foran, J., Steinman, S., Barash, I., Chambers, H. and Lieber, R. (2005). Structural and mechanical alterations in spastic skeletal. Developmental Medicine & Child Neurology. **47**: 713–717.

55. Fragala, M., O'Neil, M., Russo, K. and Dumas, H. (2002). Impairment, Disability, and Satisfaction Outcomes after Lower-Extremity Botulinum Toxin A Injections for Children with Cerebral Palsy. Pediatric Physical Therapy. **14** (3): 132-144.

56. Friedman, A., Diamond, M., Johnson, M., V.and Daffner, C. (2000). Effects of Botulinum Toxin A on upper limp spasticity in children with cerebral palsy. American Journal of Physical Medicine & Rehabilitation. **79** (1): 53-59.

57. Frieden, J., and Lieber, R. (2003). Spastic muscle cells are shorter and stiffer than normal cells. Muscle & Nerve. 2 (27): 157 – 164.

58. Gage, J. (2004). The treatment of gait problems in cerebral palsy. Mac Keith Press. Chapter 16. ISBN 1-898683-37-9.

59. Gage J., R. (1991). Clinics in developmental medicine, No. 121. Gait analysis in cerebral palsy. Oxford: MacKeith Press.

60. Glanzman, A., Heakyung, M., K., Swaminathan, K. and Beck, T. (2004). Efficacy of botulinum toxic A, serial casting, and combined treatment for spastic equinus: a retrospective analysis. Developmental Medicine and Child Neurology. **46**: 807-811.

61. Gordon, N. (1999). The role of botulinum toxin type A in the treatment-with special reference to children. Review article. Brain & Development. **21**: 147-51.

62. Girolami, G., L. and Campell, S., K. (1994). Efficacy of neurodevelopmental treatment program to improve motor control in infants born prematurely. Paediatrics Physical Therapy. **6**: 175–84.

63. Gracies, J., M., Elovic, E., McGuire J. and Simpson, D. (1997). Traditional pharmacological treatment for spasticity. Part I: Local treatment. Muscle Nerve. **(6)**: S61-91. 108.

64. Graham, H., K. (2000). Pendulum test in cerebral palsy. The Lancet. 355, **9222**: 2184.

65. Graham, H., K., Aoki, K., R., Autti-Rämö I., Boyd, R., N., Delgado, M., R., Gaebler-Spira, D., J., Gormley, M., E., Guyer, B., M., Heinen, F.,

Holton, A., F., Matthews, D., Molenaers, G., Motta, F., Garcia, R., Pedro, J. and Wissel, J. (2000). Recommendations for the use of botulinum toxin type A in the management of cerebral palsy. Gait and Posture **11**: 67-79.

66. Hagberg, B., Hagberg, G. and Olow, I. (1982). Gains and hazards of intensive neonatal care: An analysis from Swedish cerebral palsy epidemiology. Developmental Medicine and Child Neurology. **24**: 13-19.

67. Hall, C., M. and Brody, L., T. (2005). Therapeutic Exercise: Moving Toward Function. 2nd Ed. Lippincott Williams & Wilkins.

68. Hanson, C., J. and Jones, L., J. (1989). Gait abnormalities and inhibitive casts in cerebral palsy. Journal of the American Podiatric Medical Association. **79**: 53-59.

69. Harris, S., R. and Lundgren, B., D. (1991). Joint mobilization for children with central nervous system disorders: indications and precautions. Physical Therapy. **71**: 890-896.

70. Henry, G. (1997). The surgical treatment of spasticity. Muscle & Nerve. **(6)**: 121-129.

71. Horwath-Winter, J., Bergloeff, J., Floegel, I., Haller-Schober, E-M and Schmu, O. (2003). Botulinum toxin A treatment in patients suffering from blepharospasm and dry eye. British Journal of Ophthalmology. **87** (1): 54-56.

72. Humphrey, F. (1985). Therapeutic recreation. In D. A. Umpired (Ed.), Neurological Rehabilitation. **3**: 653-662. St. Louis: C.V. Mosby

73. Johnson, A. (2002). National Perinatal Epidemiology Unit, Institute of Health Sciences Surveillance of Cerebral Palsy in Europe (SCPE). Prevalence and characteristics of children with cerebral palsy in Europe. Developmental Medicine & Child Neurology. **44**: 633–640.

74. Jongerius, P., Rotteveel, J., van, Limbeek, J., Gabreëls, F., J., Hulst, van, K. and Hoogen, F. (2004). Botulinum toxin effect on salivary flow rate in children with cerebral palsy. Neurology. **63**: 1371-1375.

75. Jones, J., A. (Ed). (1987). Training guide to cerebral palsy sports (3rd ed.) Champaing, IL: Human Kinetics Publishers.

76. Jitpimolmard, S., Tiamkao, S. and Laopaiboon, M. (1998). Long term results of botulinum toxin type A (Dysport) in the treatment of hemifacial spasm: a report of 175 cases. Journal of Neurology Neurosurgery and Psychiatry. **64**: 751-757.

77. Kathleen, A. (1997). Physical and occupational therapy considerations in adult patients receiving Botulinum toxin injections for spasticity. Muscle & Nerve. **20** (6): S221-S231.

78. Katz, R., T. (1988). Management of spasticity. American Journal of Physical Medicine Rehabilitation . **67**: 108-116.

79. Kita, M., Goodkin, D., E. (2000). Drugs used to treat spasticity. Drugs. **59** (3): 487-95.

80. Kluzik, J., Fetters, L. and Coryell, S., K. (1990). Quantification of control: a preliminary study of neurodevelopmental treatment on reaching in children with cerebral palsy. Physical Therapy. **70**: 65–78.

81. Koman, L., A., Mooney, J., F., Smith, B., Goodman, A. and Mulvaney, T. (1993). Management of cerebral palsy with Botulinum toxin-A. Preliminary investigation. Journal of Paediatric Orthopaedic. **13**: 489-495.

82. Koman, L., A., Mooney, J., F., 3rd, Smith, B., P., A Goodman and Mulvaney T. (1994). Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial. Journal of Paediatric Orthopaedic. **14** (3): 299-303.

83. Koman, L., A., Mooney, J., F. and. Smith, B., P. (1996). Neuromuscular blockade in the management of cerebral palsy. Journal of Child Neurology. **11** (1): 23-28.

84. Koman, L., A., Smith, B., P., Tingey, C., T, Mooney, J., F., Slone, S. and Naughton, M., J. (1999). The effect of botulinum toxin type A injections on the natural history of equinus foot deformity in paediatric cerebral palsy patients. European Journal of Neurology. **6** (4): 19-22.

85. Koman, L., A., Brashear, A., Rosenfeld, S. and Chambers, H., B. (2001) Paediatrics, - Am Acad Paediatrics. Botulinum Toxin Type A Neuromuscular Blockade in the Treatment of Equinus Foot Deformity in Cerebral Palsy: A Multi center, Open-Label Clinical Trial. Paediatrics **108** (5): 1062-1071.

86. Kuban, K., C., K. and Levition, A. (1994) Cerebral Palsy. The New England Journal of Medicine.**20** (330): 188-195.

87. Lance, J., W. (1981). Symposium synopsis. In: R.G. Feldman, R. R. Young and W. P. Koella, Eds. Spasticity: Disorder motor control, pp.450-494. Yearbook Publishers, Chicago, London.

88. Lance, J., W. (1980). Pathophsiology of spasticity and clinical experience with baclofen. In: Feldman RG, Young RR, Koella WP, editors. Spasticity: Disordered Motor Control. Chicago: Year Book Medical.185-230.

89. Levitt, S. (1995). Treatment of cerebral palsy and motor delay. (3rd Ed.), Blackwell Publishing. USA. ISBN**:** 9781405101639.

90. Leach, J., P., T. (1997). Children Undergoing Treatment With Botulinum Toxin: The Role of the physical therapist. Department of Pediatric Orthopaedics Children's Hospital San Diego, CA Muscle & Nerve. **20** (6): 194-207.

91. Lieber, R., Steinman, S., Barash, I. and Chambers, H. (2004). Structural and functional changes in spastic skeletal muscle. Muscle & Nerve. **5**, (29): 615-627.

92. Linder, M., Schindler, G., Michaelis, U., Stein, S., Kirschner J., Mall, V., Berweck, S., Korinthenberg, R. and Heinen, F. (2001). Medium-term functional benefits in children with cerebral palsy treated with Botulinum toxin type A: 1-year follow-up using gross motor function measure. European Journal of Neurology. **8** (5): 120-126.

93. Mall, V., Heimen, F., Siebel, A., Bertram, C. and Hafkemeyer, U. (2006). Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double blind, placebo-controlled study. Developmental Medicine & Child Neurology. **48** (1): 10-13.

94. Massin, M. and Allington, N. (1999). Roll of exercise testing in the functional assessment of cerebral palsy children after botulinum toxin injection. Journal of Paediatric Orthopaedics. **19**: 362-365.

95. Middel, B., Kuipers-Upmeijer, H., Bouma, J., Staal, M., Oenema, D., Postma, T., Terpstra, S. and Stewart, R. (1997). Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. Journal of Neurology, Neurosurgery and Psychiatry. **63**: 204-209.

96. Middleton, E., A., Hurley, GRB and Mcllwain. J., S. (1988). The role of the rigid and HAFO Polypropylene ankle-foot-orthosis in the management of cerebral palsy: a case study. Prosthetic and Orthotics International. **12**: 129-135.

97. Mutch, L., Alberman, E. and Hagberg, B. (1992). Cerebral Palsy epidemiology: where are we now and where are we going? Developmental Medicine & Child Neurology. **34**: 547-551.

98. Nuzzo, R., M. (1980). Dynamic bracing: Elastic for patients with cerebral palsy, muscular dystrophy and myelodysplasia. Clinical Orthopaedics and Related Research. **148**: 263-273.

99. Ordia, J., I., Fischer, E., Adamski, E. and Spatz, E., L. (1996). Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. Journal of Neurosurgery. **85**: 452-457.

100. Pal, P., Calne, D., Calne, S. and Tsui, J. (2000). Botulinum toxin A as treatment for drooling saliva in PD. Neurology. **54**: 244.

101. Paneth, N. Etiologic factors in cerebral palsy. (1986). Pediatric Annals. **15** (191): 194-195, 197-201.

102. Papadonikolakis, A., S., Vekris, M., D., Korompilias, V., Anastasios, K., P., J., Ristanis, E., S. and Soucacos, N., P. (2003). Botulinum A toxin for treatment of lower limb spasticity in cerebral palsy Gait analysis in 49 patients. Acta Orthopaedica Scandinavica. **74** (6): 749-755.

103. Park, T., S. and Owen, J., H. (1992). Surgical management of spastic diplegia in cerebral palsy. New England Journal of Medicine. **326**: 745-749.

104. Perin, B. Physical therapy for the child with cerebral palsy. (1989). In J. S. Tecklin (Ed), pediatric physical therapy (68-105). Philadelphia: J. B. Lippincott.

105. Pharoah, P., O., Cooke, T., Johnson, M., A., King, R. and Mutch, L. Epidemiology of cerebral palsy in England and Scotland. (1998). Archives of Disease in Childhood Fetal &Neonatal Edition. **79** (1): 21-25.

106. Preiss, R., A.; Condie, D., N., Rowley, D., I. and Graham, H., K. (2003). The effects of botulinum toxin (Botox-A) on spasticity of the lower limb and on gait in cerebral palsy. The Journal of Bone & Joint Surgery. **85** (7): 943-948.

107. Rajab, A., Yoo, S., Abdulgalil, A., Kathiri, S., Riaz, A., Ganeshwaran, H., Bodell, A., Barkovich, J. and Walsh, C. (2006). An Autosomal Recessive Form of Spastic Cerebral Palsy (CP) With Microcephaly and Mental Retardation. American Journal of Medical Genetics Part A. **140**A: 1504–1510.

108. Rosales, R., L., Arimura, K., Takenage, S. and Osame, M. (1996). Extrafusal and intrafusal muscle effects in experimental Botulinum toxin A injections. Muscle Nerve. **19**: 488-496.

109. Rose J., Haskell W., Gamble J., Hamilton R., Brown D., Rinsky L. (1994). Muscle Pathology and Clinical Measures of Disability in children with cerebral palsy. Journal of Orthopaedic Research U: 758-768 The Journal of Bone and Joint Surgery, Inc. Orthopaedic Research Society.

110. Reddihough, D., King, J., Coleman, G., Fosang, A., McCoy, A., Thomason, P. and Graham, K. (2002). Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. Developmental Medicine & Child Neurology. **44**: 820-827.

111. Rethlefsen, S., Dennis, S., W., Forstein, M., Reynolds, R.A.K, Tolo V.T and Antonelli, D. (1995). A comparison of the effects of fixed versus articulated ankle-foot orthoses on gait in subject with cerebral palsy. Gait and Posture. **3** (2): 90-90 (1).

112. Rosalind, J. Jefferson, (2004). Botulinum toxin in the management of cerebral palsy. Developmental Medicine and Child Neurology. **46** (77): 491-499.

113. Russell, D., J., Rosenbaum, P., L., Cadman, D., T., Gowland, C., Hardy, S. and Jarvis, S. (1989). The gross motor function measure: a means to evaluate the effects of physical therapy. Developmental Medicine & Child Neurology. **31**: 341-352.

114. Russell, D., J., Avery, L., M., Rosenbaum, P., L., Raina, P., S., Walter, S., D. and Palisano, R., J (2000). Improved scaling of the Gross Motor

Function Measure for children with cerebral palsy: Evidence of Reliability and Validity. Physical Therapy. **80** (9): 873-885.

115. Russell, D., J., Rosenbaum, P., L., Avery, L., M. and Lane, M. (2002). Function Measure (GMFM-66&GMFM-88) User's Manual, McMaster University, Hamilton, Ontario, Canada, Mac Keith Press ISBN 1-89868329-8.

116. Sarioglu, B., Serdaroglu, G., Tutuncuoglu, S. and Ozer, E., A. (2003). The use of botulinum toxin type A treatment in children with spasticity. Pediatric Neurology. **4** (29): 299-301.

117. Scott, A., B. (1981). Botulinum toxin injection of eye muscles to correct strabismus. Transactions of the American Ophthalmological Society. **79**: 734-770.

118. Seib, T., P., Price, R., Reyes, M., R. and Lenhmanan, J., F. (1994). The quantitative measurement of spasticity- effect of cutaneous electrical stimulation. Archive of Physical Medicine Rehabilitation. **75**: 746-750.

119. Sloan, R., L., Sinclair, E., Thompson, J., Taylor, S. and Pentland, B. (1992). Inter-rater reliability of the modified Ashworth Scale for spasticity in hemiplegic patients. International Journal of Rehabilitation Research. **15** (2): 158- 161.

120. Smelt, H., R. (1989). Effect of an inhibitive weight-bearing mitt on tone reduction and functional performance in a child with cerebral palsy. Physical and Occupational Therapy in Pediatrics. **9**: 53-80.

121. Smith, L., H. and Harris, S., R. (1985). Upper extremity inhibitive casting for a child with cerebral palsy. Physical and Occupational Therapy in Pediatrics. **5**: 71-79.

122. Speelman, D, Van Manen, J. Cerebral palsy and stereotactic neurosurgery: long term results. Journal of Neurology, Neurosurgery and Psychiatry 1989; 52:23-30.

123. Sutherland, D., Kaufman, K., Wyatt, M. and Chambers, H. (1999). Double blind study of botulinum a toxin injection into the gastrocnemius muscle in patients with cerebral palsy. Gait Posture. **1** (10): 1-9.

124. Sutherland, D., Kaufman, K., Wyatt, M. and Chambers, H. (1996). Injection of Botulinum A toxin into the gastrocnemius muscle of patients with cerebral palsy: a 3- dimensional motion analysis study. Gait Posture. **4**: 269-279.

125. Suputtitada, A. (2000). Managing spasticity in pediatric cerebral palsy using a very low dose of botulinum toxin type A. Preliminary Report. American Journal of Physical Medicine & Rehabilitation l. **79**: 320-326.

126. Taha, S., A. and Mahdi, A., R. (1984). Cerebral palsy in Saudi Arabia: A clinical study of 120 cases. Ann Tropical Paediatric. **4** (3): 155- 158.

127. Thomas, J., Nelson J., Silverman, S. (2005). Research Methods in Physical Activity. Fifth Edition. Human Kinetics Publishers. Leeds. ISBN 0-7360-5620-3.

128. Thompson, S., Baker, J., Cosgrove, P., Corry, S. and Graham, K. (1998). Musculoskeletal modelling in determining the effect of Botulinum toxin on the hamstring of patients with crouch gait. Developmental Medicine & Child Neurology. **40**: 622-625.

129. Ubhi, T., B., Bhakata, B., B., Ives, H., L., Allgar, V. and Roussounis, S., H. (2000). Randomised double blind placebo controlled trial of the effect of Botulinum toxin on walking in cerebral palsy. Archives of Disease in Childhood. **83**: 481-487.

130. Valvono, J. and Long, T. (1991). Neurodevelopmental treatment: a review of the writing of the Bobaths. Pediatric Physical Therapy. **3**: 125–129.

131. Vaile, L. and Finlay, F. (2006). Is injection of botulinum toxin type A effective in the treatment of drooling in children with cerebral palsy? Archives of Disease in Childhood. **91**: 862-863.

132. Volpe, J., J. (1994). Brain injury in the premature infant- current concepts. Preventive Medicine. **23**(5): 638-645.

133. Wall, S., A., Chait, L., A., Temlett, J., A., Perkins, B., Hillen, G. and Becker, p. (1993). Botulinum A chemodenervation: a new modality in cerebral palsied hands. British Journal of Plastic Surgery. **46**: 703-706.

134. Whittle, M. (1996). Gait Analysis an introduction. Elsevier Ltd. Oxford. Fourth Edition. Butterworth Heinemann Elsevier. Chapter 3. ISBN 0-7506-8883-1.

135. Whyte, J. and Glenn, M., B. (1990). The Practical Management of Spasticity in children and adult. Philadelphia: Lea & Febiger. ISBN: 0812112970 9780812112979.

136. Whyte, J. and Robinson, K., M. (1990). Pharmacologic management. In the practical management of spasticity in children and adults. Glenn MB, Whyte J, Eds. Lea & Febiger Philadelphia. 201-226.

137. Wissel, J., Heinen, F., Schenkel, A., Doll, B., Ebersbach, G., Muller, J. and Poewe, V. (1999). Botulinum Toxin A in the Management of Spastic Gait Disorders in Children and Young Adults with Cerebral Palsy: A Randomized, Double-Blind Study of "High-Dose" versus. Low dose treatment. Neuropediatrics. **30**: 120-124.

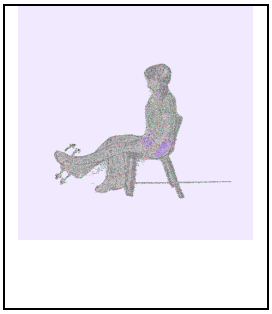
138. Wong, V. (1998). Use of botulinum toxin in 17 children with spastic cerebral palsy. Paediatric Neurology. **18**: 124-31.

139. Yang, T., F., Chan, R., C., Chuang, T., Y., Liu, T., J. and Chiu, J., W. (1999). Treatment of cerebral palsy with botulinum toxin: evaluation with gross motor function measure. Journal of the Formosan Medical Association. **98** (12): 832-836.

140. Yasukawa, A. (1990). Upper extremity casting: Adjunct treatment for a child with cerebral palsy hemiplegia. American Journal of Occupational Therapy. **44**: 840-846.

Appendix 1

Summary description of the rehabilitation programme used in this project



This is the physical therapy programme (PT) was used in this study after BTX-A injection for 2 weeks/2 hours daily. This PT programme based on Daniels and Worthingham (1980), Gage, J. (2004), Hall, C. and Brody L., T. (2005). Also, PT programme drawing by the author.

Introduction

One of the important steps in ensuring a positive outcome of a rehabilitation program is the child or the parent's ability to understand the therapist's instructions. Many variables affect this aspect of the childcare, including cultural barriers, hearing impairment and clarity of instructions. The best-designed rehabilitation program may fail (Brody, 2005). Consequently, this study required the children to stay in accommodation for the duration of the 2 week rehabilitation program.

The children in the study had cerebral palsy, diplegia, spasticity of the ankle planter flexors and significant gait problems. This study assessed of the effects of BTX- A alone and in combination with intensive physical therapy in the treatment of these children.

Definition of Physical Therapy

Physical therapy as defined by the GPT (2001) includes:

1. the diagnosis and management of movement dysfunction and the enhancement of physical and functional abilities
2. the restoration, maintance and promotion of optimal physical function, optimal fitness and wellness, and optimal quality of life as it relates to movement and health
3. the prevention of the onset, symptoms, and progression of impairment, functional limitations, and disabilities that may result from diseases, injuries, conditions, or disorders.

Physical therapy, as provided by or under the direction and supervision of a physical therapist, includes:

1. Examining patients with impairment, functional limitation, and disability or other health-related condition to determine a diagnosis, prognosis, and intervention
2. Examination within the scope of physical therapy practice include, but are not limited to, tests and measures of four categories of condition; musculoskeletal (e.g., range of motion, muscle performance, joint mobility, posture), neuromuscular (e.g., reflex integrity, cranial nerve integrity, neuromotor development, sensory integration), cardiovascular/endurance, ventilation, circulation), and integumentary (e.g., integumentary integrity)
3. Alleviating impairments and functional limitations by designing implementing, and modifying therapeutic interventions. Interventions include, but are not limited to, procedural interventions such as therapeutic exercise; manual therapy techniques; prescription, fabrication, and application of assistive, adaptive, supportive, and protective devices and equipment; airway clearance techniques; physical agents and mechanical and electrotherapeutic modalities; and functional training in self-care, home management, work (job/school/play), community and leisure activities.
4. Preventing injury, impairments, functional limitations, and disability, including the promotion and maintenance of fitness, health and quality of life in all age populations.
5. Engaging in consultation, education, and research (APTA, 1995).

Physical therapy programme after Botulinum toxin A injection

Specific therapy programmes should be used based on every subject's individual requirements for stretching or strengthening exercises and gait training with or without assistance. Rehabilitating after BTX-A injections

should be done in a stepwise incremental way starting with non-weight-bearing exercises, moving to resisted exercises and to then weight bearing activities.

1 Range of Motion Exercises - Non-Weight Bearing

These exercises are used to increase range of motion typicallya t the ankle joint. All exercises should be performed whilst the patient is sitting with their legs fully extended, knees straight out in front.

1.1 Dorsiflexion

1. Pull the child foot back toward himself by moving his ankle. Remember to keep the child's knees straight. Continue until you can no longer pull your foot back.
2. Ask child to hold this position for 10 seconds
3. Return to neutral position
4. Repeat above steps 10 more times

1.2 Plantarflexion

As above but with the ankle plantarflexed by ask the child to push the child foot forward away from him Ask the child to hold this position for 10 seconds

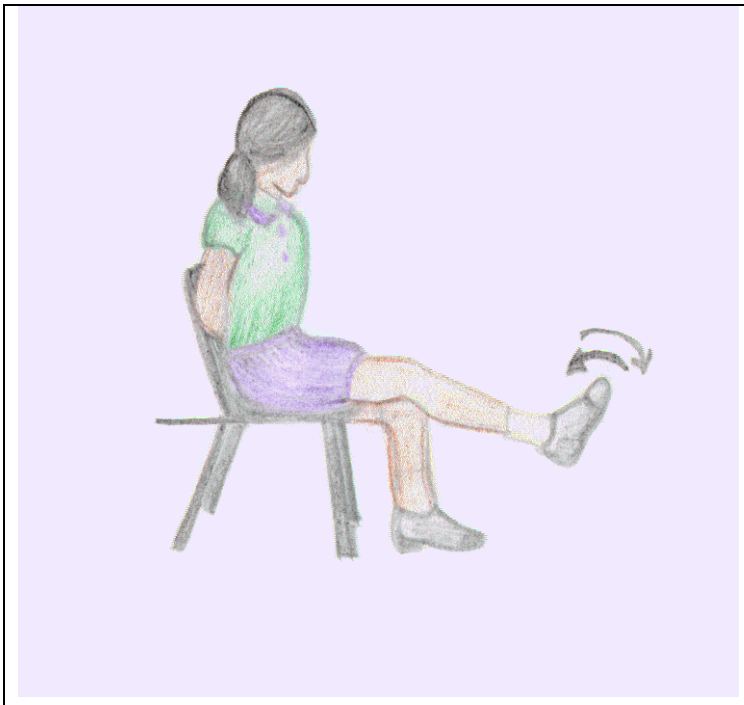


Figure 1.

This picture shows the child position during plantarflexion and dorsiflexion of the ankle joint. Non-weight bearing exercise.

1.3.Inversion

1. Ask the child to turn the foot inward by moving his ankle. Continue until he can no longer turn his foot inward.
2. Ask the child to hold this position for 10 seconds
    1. Return to neutral position.
    2. Repeat above steps 10 more times.

1.4 Eversion

As above but ask the child to turn the foot outward by moving his ankle.

Figure 2

This picture shows the child position during eversion and inversion of the ankle joint. Non-weight bearing exercise.

1.5 The Alphabet

3. Ask the child to sit on a chair with the foot dangling in the air or on a bed with the foot hanging off the edge
4. Draw the alphabet one letter at a time by moving the ankle and using the great toe as a "pencil."

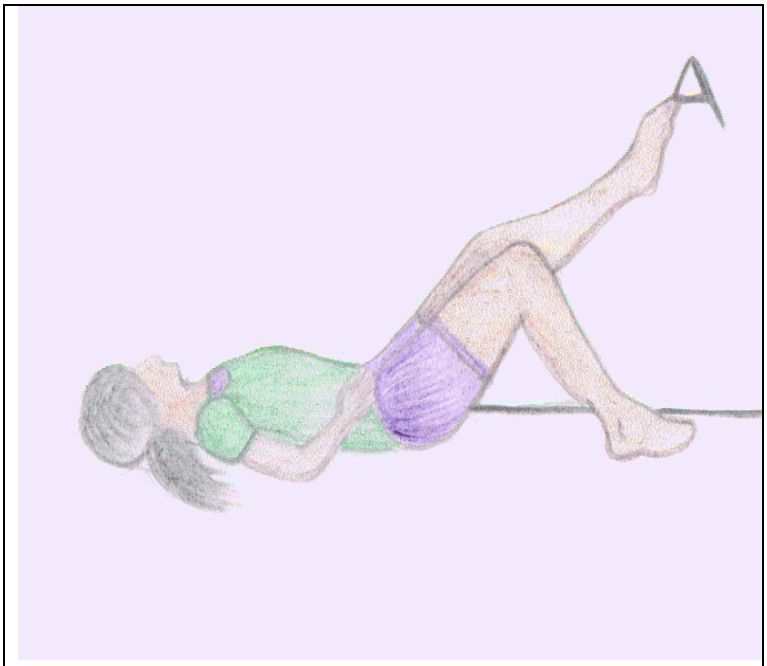


Figure 3

This picture shows the child position during non-weight bearing exercise Alphabet. the ankle joint moving the great toe as pencil.

2 Isometric Strengthening Exercises

These exercises to strengthen the muscles around your ankle, this will provided added support to the joint.

2.1 Eversion Isometrics

1. While the child seated place the outside of the foot against a table leg or a closed door.
2. Ask the child to push outward with his foot against the object the foot is touching, (the ankle joint should not move) causing a contraction of the child muscles.
3. Ask the child to hold this muscle contraction for 10 seconds.
4. Relax for 5 seconds.
5. Repeat 5 times, increasing to 10 repetitions.

2.2 Inversion Isometrics

As above but with inversion of the ankle.

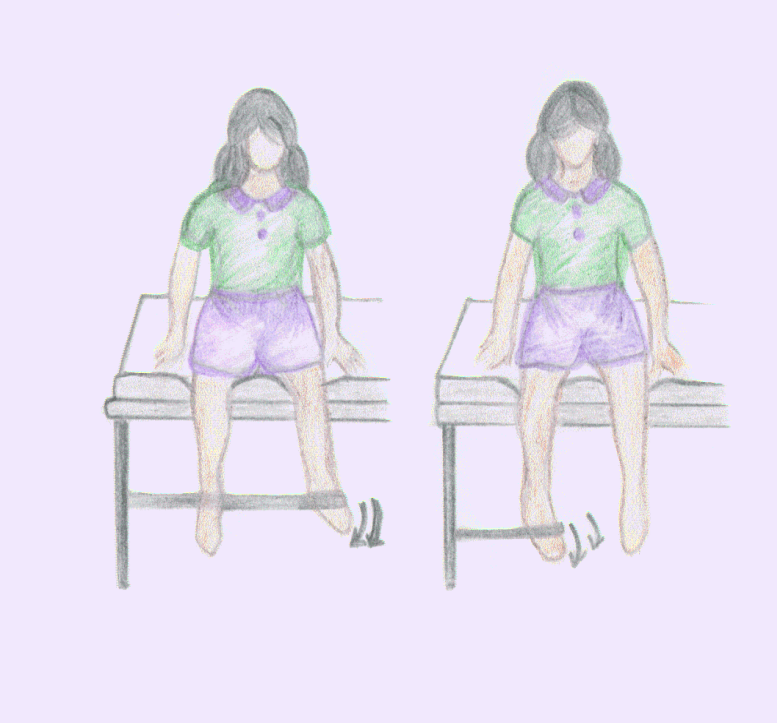


Figure.4

This picture shows the child position during inversion and eversion of the ankle joint against resistance.

3 Resisted Strengthening Exercises

These exercises work to strengthen the muscles around the ankle joint. This will provided added support to the joint. Each exercise should be performed with a towel or belt around the ankle providing resistance to the movements. To provide the own manual resistance to each movement

3.1 Dorsiflexion

1. Ask the child to pull his/here foot back toward him self, against the resistance of a belt (while keeping knees straight), by moving the ankle joint.
2. Ask the child to hold this position for 10 seconds
3. Return to neutral position

4. Repeat above steps 10 more times

3.2 Plantar flexion

As above but with plantar flexion of the ankle.

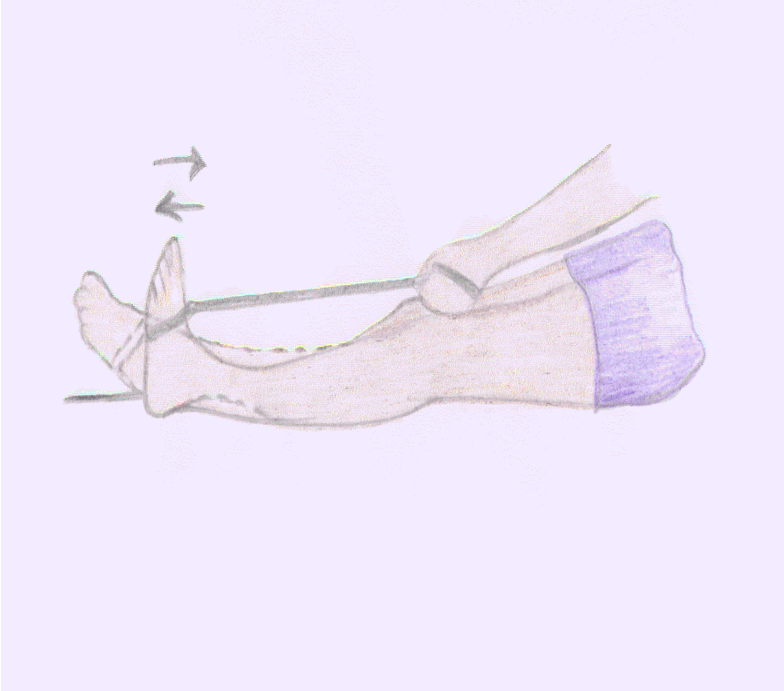


Figure 5.
This picture shows the child position during dorsiflexion and planter flexion of the ankle joint against a belt resistance.

3.3Inversion

1. Turn your foot inward by moving your ankle, against the resistance of the belt.
2. Hold this position for 15 seconds
3. Return to neutral position
4. Repeat above steps 10 more times

3.4 Eversion

As above but with eversion.

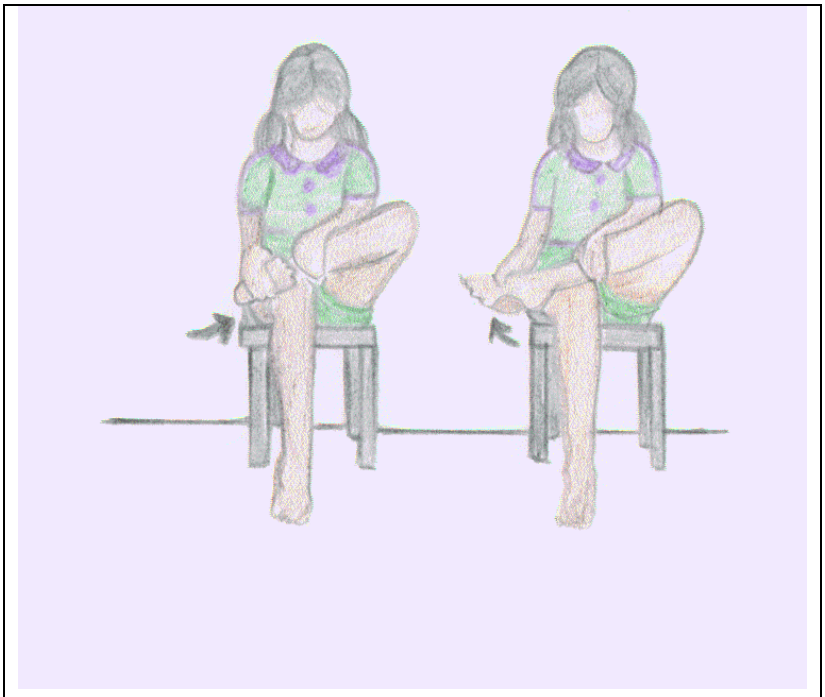


Figure 6.
This picture shows the child position during inversion and eversion of the ankle joint against the child resistance

4 Single Leg Stand

1. Ask the child to stand upright while holding onto a stable object like a table or chair.
2. Shift some of their weight onto one foot, if the child can.
3. Hold for the position for 10 seconds.
4. Relax and put weight back onto another foot.

5. Repeat 10 times also we can do these exercise with a belt resistance as in a figure 5.

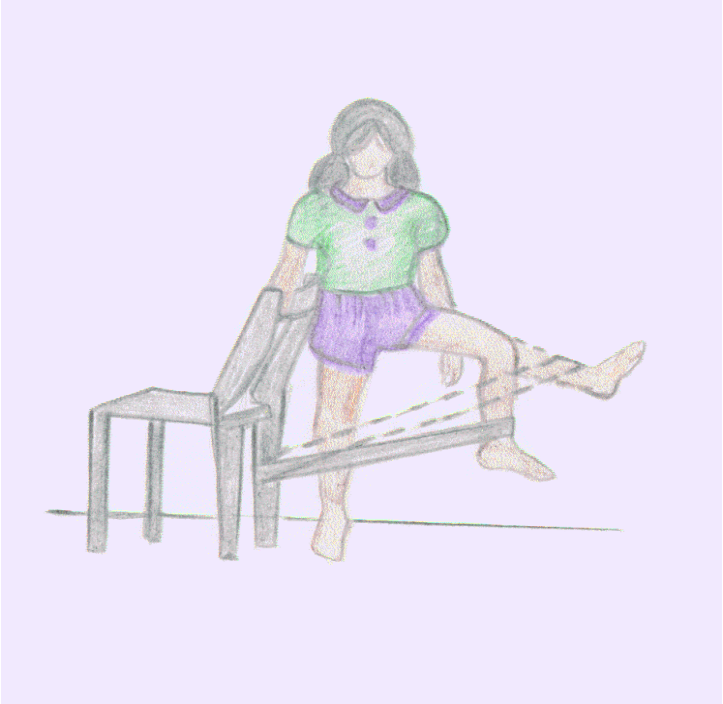


Figure 7.
This picture shows the child position during dorsiflexion and planterflexion of the ankle joint against a belt resistance

5 Full Weight Bearing Exercises

These exercises will help put more weight on the foot as well as strengthen it.

1. Ask the child to stand upright and place only the amount of weight on his leg as he can and avoid hyperextending the child knee.
2. Relax and put weight back onto another foot.
3. Repeat 10 times alternatively.

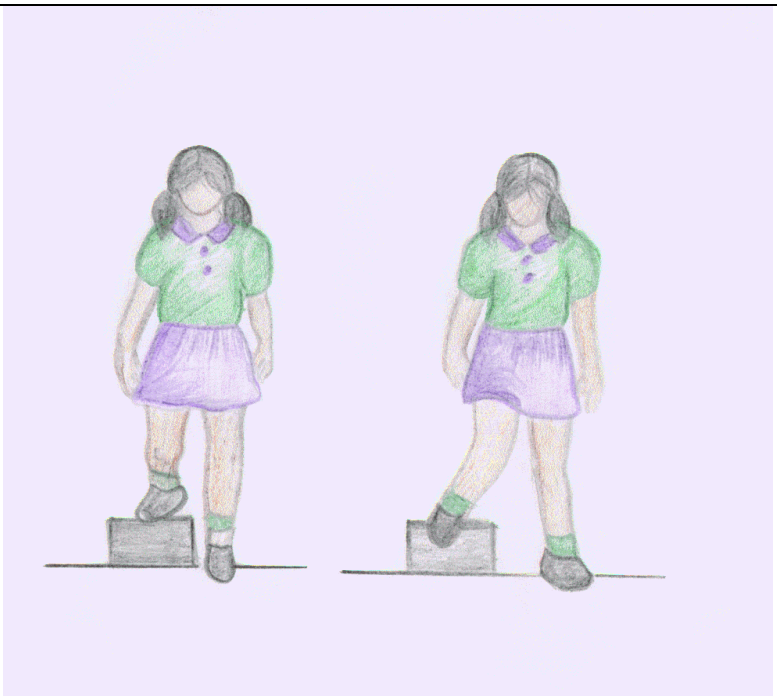


Figure 8

This picture shows the child position during full weight bearing exercises. The position on the left is correct. That on the right is incorrect.

6 Balance Activities

Shortening of Achilles tendon can often result in decreased balance ability. Towards the end of rehabilitation performing balance activities is an important way to prevent future injury.

6.1 Single Leg Stance

1. Ask the child to stand on one foot while raising another foot off the ground if he/she can.

2. Maintain full weight bearing on one foot for 10 seconds
3. Return to resting position.
4. Repeat above exercise 10 more times for the other foot.

Figure 9.

This picture shows the child's position during single leg stance

6.2 Sitting balance on unstable surface

To increase postural stability and trunk balance:

1. Child sitting on the therapeutic ball.
2. Ask the child to hold a ball by his/here hands with extended arms.

3. Practice reaching hands forward, overhead, and to the side.

4. Repeat 5 times

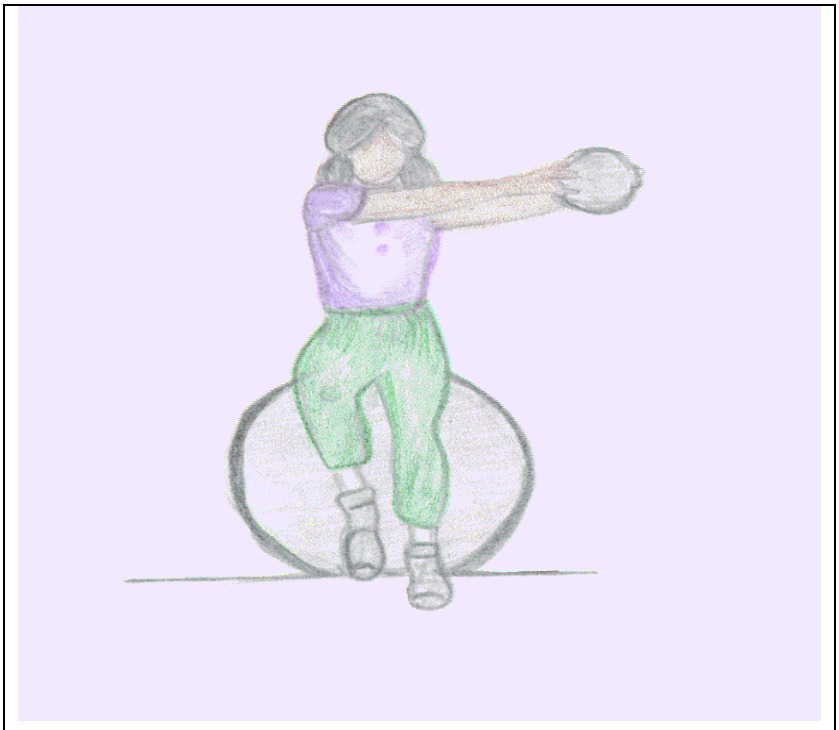


Figure 10.

This picture shows the child's position during balance exercise on the therapeutic ball.

6.3 Minitrampoline balance

To improve stability in single leg stance

1. Ask a child to stand on the minitramp with a stable object at hand.

2. Let the child practice standing on one leg, make sure that a child's knee is slightly bent if he/she can.

3. Ask a child to jump, with hand support if he/she need.

4. Repeat above 5 more times

Figure 11.

This picture shows the child position during balance exercise on minitrampoline.

7 Single Leg Stance on a Towel

1. Fold a towel into a small rectangle and place on the ground

2. Ask a child to stand with his/here left heel on the towel, half on the floor.

3. Lift the right leg off the ground standing only on the towel with the left leg if he/she can do it.

4. Ask a child to curl the toes, pull the towel toward him all the way to the arch.

5. Hold for 5 seconds

6. Repeat above 10 more times

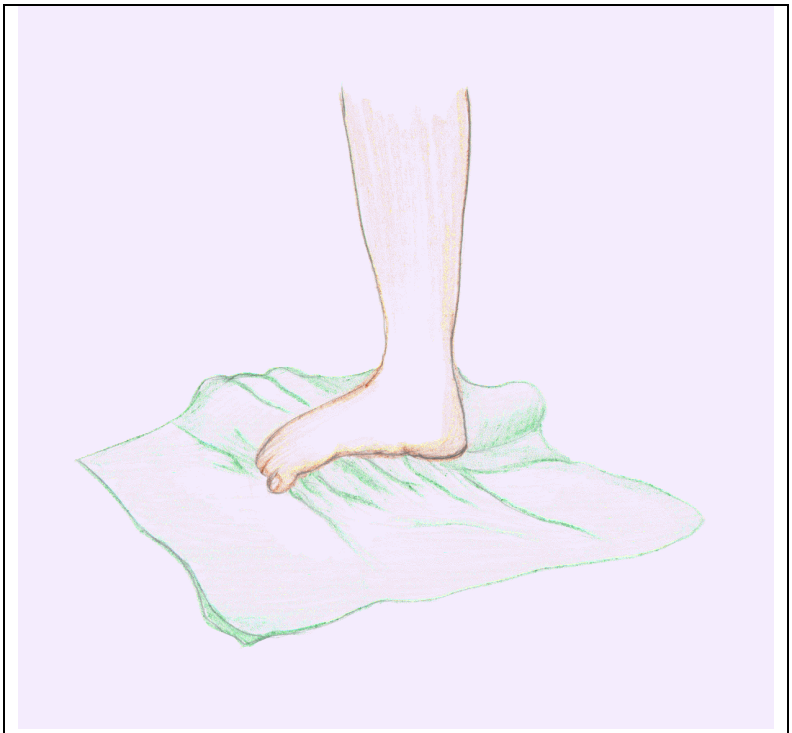


Figure 12.

This picture shows the ankle position during exercise of the single leg stance on a towel

8 Walk up and down stairs

To increase flexibility of the plantar fascia

1. Ask a child to stand with the toes extended against the vertical part of a step and the heel on the floor

2. Ask the child to bend the knee slowly above the toes

3. Walk up 4 step and walk down 4 step-alternating feet.

Figure 13.

This picture shows the child position during walking up and down stairs.

9 Foot orthoses

Orthoses are useful in the management of deformity because they apply a sustained stretch to a hypertonic muscle/tendon group and by positioning one joint can gain better posture and muscle activity elsewhere. Orthoses may be articulated to allow movement about a specific joint, thereby allowing muscles to be more active. (Burtner, Woollacott, Qualls, 1999)

The functions of foot orthoses

1. To even the distribution of weight-bearing forces.

2. To reduce stress on proximal joint.

3. To control foot motion at the subtalar and mid-tarsal joints, including magnitude, end range, and rate.

4. To balance intrinsic foot deformities if necessary.

10 Walking with crutches

When a child walks with crutches, taking some of his weight on the involved knee, several guidelines should be followed:

1. Make sure the child's weight is on his hands, not under his arms. His arms should be slightly bent if his crutches fit properly.

2. When the child walks, place his crutches out first, followed by his involved leg and then his uninvolved leg.

3. Place his involved heel down first. Let his knee bend slightly and allow his foot to roll toward his toes as he begins to bring his uninvolved leg forward.

4. As he brings his uninvolved foot through, ask a child to bend his involved knee, and pick it up behind him. Straighten the involved knee as he brings it past his cruches to place it on the floor in front of him. His knee should be straight just before his heel contacts the ground.

5. When a child using a single crutch, be sure to ask him to use it on the side opposite his injured knee.

Figure 14.

This picture shows the crutches and the hand positions during walking with assistance of crutches.

Appendix 2

Consent To Participate in A research Investigation

Biomedical and Life Sciences Department, Glasgow University

Child Name: Child ID No:

Date:

Research Title: A comparison toxin-A combined with Physical Therapy and Botulinum toxin-A alone in Children with of Botulinum Spastic Cerebral Palsy Cerebral Palsy remains a significant issue for our medial and educational establishments and for society as a whole. Cerebral Palsy is the most common cause of childhood physical disability. The upper motor neuron injury that accompanies with cerebral palsy frequently results in muscle imbalance, spasticity, and dynamic joint deformity. Spasticity is the most common symptoms seen in cerebral palsy children. It interferes with function, standing balance and gait. Currently there are a number of interventions, both conservative and surgical, which are being offered to the child with cerebral palsy in an effort to reduce spasticity and its effects in the lower limb. Mediations frequently used in the treatment of spasticity-included baclofen, benzodiazepines, tizanidine, clonidine, dantroline and Botulinum toxin-A. Botulinum toxin-A, the most potent biologic toxin known, is one of seven antigenically different toxins produced by the bacteria clostridium Botulinum. Botulinum toxin-A acts at the neuromuscular junction by inhibiting the release of acetylcholine, which leads to decrease spasticity in injected muscle. There were no side effects for this injection in previous studies except pain and redness in injection site. You are being asked to participate in a research investigation as described in this form below. All such investigational projects carried out in Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre At Kingdome of Saudi Arabia. The investigator will explain to you in detail the purpose of the project, the procedures to be used, and the potential benefits and possible risks of participation. You an ask the investigator any questions you ay have to help you understand the project and you may expect to receive satisfactory answers to questions. A basic explanation of the project is written below.

There are two main objectives in this study:

1) To evaluate the effects of Botulinum toxin-A Spastic Cerebral Palsy by using gross motor function measurement, passive ankle range of motion.
2) To compare of botulinum toxin-A combined with physical therapy and botulinum toxin-A alone in children with spastic cerebral palsy.

The procedure to be used include:

The duration of this study fifty weeks, and there are four sessions assessment. First before injection and the second post four weeks, third post six weeks and last assessment post fifty weeks. Upper and lower limb muscle tone will be evaluated using special scale gross motor function measurement Passive ankle range of motion will be measured using electrogoniometer. A small skin mounted pre-amplifier with integrated electrodes, measuring 7mm in diameter, was used for recording the electromyography (EMG).

After pre injection assessment, each subject will be transferred to Prince Sultan Hospital and Al-Hada Armed Forces Hospital and Rehabilitation Centre in Al-Taief at Kingdome of Saudi Arabia. The injection will be under supervision neurologist consultant. After 2 weeks following the injection those children were given casts for 2 weeks. Post injection 2 weeks children will stay in the disabled children association Makkah or Jeddah centres accommodation under intensive physical therapy. I certify that I have read and fully understanding the above project. I willingly consent to participate.

Name of the guardian of child

……..

Signature

……

I certify that I have explained fully to the above the guardian of child the nature and purpose, the potential benefit and possible risk of botulinum toxin-A injection.

Signature of Investigator

……

Appendix 3

Patient's assessment form

Cerebral Palsy Assessment Form

Name: Age: Sex: □ Male □Female Guardian:……Tel.No:……..
Cerebral Palsy classification: □Spastic □Dyskinetic □Ataxic □Mixed □Diplegia□ □Hyperkinetic □Quadriplegic □Dystonic □Hemiplegic
Causes: □Prenatal (Specify if possible) □Perinatal (Specify if possible) □Postnatal (Specify if possible) □ Full term □ Preterm
Ambulation: □Independent □Walker □Wheelchair □Others
Speech: □Normal □Language delay □Dysartheria □Communications device
Vision: Normal □Poor □Blind Eye: □Nystagmus
Hearing: □Normal □Mild □Non □Hearing aids
Mental state: □Normal □ Mild retarded □Moderate □Severe

Previous surgery: □No □Yes (If yes specify)
Previous drug: □No □Yes
Present drug: □No □Yes
Deformity: □Hip Left□ Right□ □Knee Left□ Right□ □Ankle Left□ Right□
Physio therapy programme: □No □Yes Since ( ) □Improve □Stable □Worse If yes specify: □Ice □Stretching Exs □Active Exs □Positioning □Stretching Exs □Others (specify)
Gait: □Toe-to-toe □Occasional heel-to-toe □Heel-to-toe □Toe-to-heel
□This patient will be included in this study. □This patients has been excluded from this study because of: □Fixed contracture □Hemiplegic □Previous drug □Quadriplegic □Previous surgery □Patients can not walk □Sever mental retardation □Others…….
Investigator: Date:

Appendix 4

The Gross Motor Function Measurement

GMFM a standardised observational instrument designed and validated to measure the change in gross motor function over time in children with cerebral palsy. The scoring key gives a general guideline. However, most of the items have specific descriptors for each score. It is imperative that the guidelines in the manual are used for scoring each item.

Scoring is based on a four- point scale for each item using the following key:

0 = does not initiate

1 = initiates

2 = partially completes

3 = completes

NT = not tested

“Does not initiate” applies when the child is unable to begin any part of the activity.

“Initiates” (1) applies when less than 10% of the task is completed.

“Completes,” (3) applies when the task is completed fully.

“Not tested” is used when an item has not been administrated or when a child refused to attempt it. (Russell et al 2002)

The test includes 88 items grouped in five dimensions: (A) Lying and Rolling; (B) Sitting; (C) Crawling and Kneeling; (D) Standing; (E) Walking, Running, and Jumping.

GROSS MOTOR FUNCTION MEASURE (GMFM)
SCORE SHEET (GMFM-88 and GMFM-66 scoring)

Version 1.0

Child's Name: _____ ID #: _____

Assessment date: _____ year / month /day

Date of birth: _____ year / month /day

Chronological age: _____ years/months

GMFCS Level [1]

☐ ☐ ☐ ☐ ☐

I II III IV V

Testing Conditions (eg, room, clothing, time, others present)

_____

Evaluator's Name: _____

_____

_____

The GMFM is a standardized observational instrument designed and validated to measure change in gross motor function over time in children with cerebral palsy. The scoring key is meant to be a general guideline. However, most of the items have specific descriptors for each score. It is imperative that the guidelines contained in the manual be used for scoring each item.

SCORING KEY
0 = does not initiate
1 = initiates
2 = partially completes
3 = completes
NT = Not tested [used for the GMAE scoring*]

It is now important to differentiate a true score of "0" (child does not initiate) from an item which is Not Tested (NT) if you are interested in using the GMFM-66 Ability Estimator Software.

*The GMFM-66 Gross Motor Ability Estimator (GMAE) software is available with the GMFM manual (2002). The advantage of the software is the conversion of the ordinal scale into an interval scale. This will allow for a more accurate estimate of the child's ability and provide a measure that is equally responsive to change across the spectrum of ability levels. Items that are used in the calculation of the GMFM-66 score are shaded and identified with an asterisk (*). The GMFM-66 is only valid for use with children who have cerebral palsy.

Contact for Research Group:
Dianne Russell, *CanChild* Centre for Childhood Disability Research, McMaster University, Institute for Applied Health Sciences, McMaster University, 1400 Main St. W., Rm. 408, Hamilton, L8S 1C7
Tel: North America - 1 905 525-9140 Ext: 27850
Tel: All other countries - 001 905 525-9140 Ext: 27850
E-mail: canchild@mcmaster.ca Fax: 1 905 522-6095
Website: www.fhs.mcmaster.ca/canchild

[1] GMFCS level is a rating of severity of motor function. Definitions are found in Appendix I of the GMFM manual (2002).

Check (√) the appropriate score: if an item is not tested (NT), circle the item number in the right column

	Item	A: LYING & ROLLING	SCORE				NT
	1.	SUP, HEAD IN MIDLINE: TURNS HEAD WITH EXTREMITIES SYMMETRICAL	0 ☐	1 ☐	2 ☐	3 ☐	1.
*	2.	SUP: BRINGS HANDS TO MIDLINE, FINGERS ONE WITH THE OTHER	0 ☐	1 ☐	2 ☐	3 ☐	2.
	3.	SUP: LIFTS HEAD 45°	0 ☐	1 ☐	2 ☐	3 ☐	3.
	4.	SUP: FLEXES R HIP AND KNEE THROUGH FULL RANGE	0 ☐	1 ☐	2 ☐	3 ☐	4.
	5.	SUP: FLEXES L HIP AND KNEE THROUGH FULL RANGE	0 ☐	1 ☐	2 ☐	3 ☐	5.
*	6.	SUP: REACHES OUT WITH R ARM, HAND CROSSES MIDLINE TOWARD TOY	0 ☐	1 ☐	2 ☐	3 ☐	6.
*	7.	SUP: REACHES OUT WITH L ARM, HAND CROSSES MIDLINE TOWARD TOY	0 ☐	1 ☐	2 ☐	3 ☐	7.
	8.	SUP: ROLLS TO PR OVER R SIDE	0 ☐	1 ☐	2 ☐	3 ☐	8.
	9.	SUP: ROLLS TO PR OVER L SIDE	0 ☐	1 ☐	2 ☐	3 ☐	9.
*	10.	PR: LIFTS HEAD UPRIGHT	0 ☐	1 ☐	2 ☐	3 ☐	10.
	11.	PR ON FOREARMS: LIFTS HEAD UPRIGHT, ELBOWS EXT., CHEST RAISED	0 ☐	1 ☐	2 ☐	3 ☐	11.
	12.	PR ON FOREARMS: WEIGHT ON R FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0 ☐	1 ☐	2 ☐	3 ☐	12.
	13.	PR ON FOREARMS: WEIGHT ON L FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0 ☐	1 ☐	2 ☐	3 ☐	13.
	14.	PR: ROLLS TO SUP OVER R SIDE	0 ☐	1 ☐	2 ☐	3 ☐	14.
	15.	PR: ROLLS TO SUP OVER L SIDE	0 ☐	1 ☐	2 ☐	3 ☐	15.
	16.	PR: PIVOTS TO R 90° USING EXTREMITIES	0 ☐	1 ☐	2 ☐	3 ☐	16.
	17.	PR: PIVOTS TO L 90° USING EXTREMITIES	0 ☐	1 ☐	2 ☐	3 ☐	17.

TOTAL DIMENSION A ☐

	Item	B: SITTING	SCORE				NT
*	18.	SUP, HANDS GRASPED BY EXAMINER: PULLS SELF TO SITTING WITH HEAD CONTROL	0 ☐	1 ☐	2 ☐	3 ☐	18.
	19.	SUP: ROLLS TO R SIDE, ATTAINS SITTING	0 ☐	1 ☐	2 ☐	3 ☐	19.
	20.	SUP: ROLLS TO L SIDE, ATTAINS SITTING	0 ☐	1 ☐	2 ☐	3 ☐	20.
*	21.	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD UPRIGHT, MAINTAINS 3 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	21.
*	22.	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD MIDLINE, MAINTAINS 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	22.
*	23.	SIT ON MAT, ARM(S) PROPPING: MAINTAINS, 5 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	23.
*	24.	SIT ON MAT: MAINTAINS, ARMS FREE, 3 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	24.
*	25.	SIT ON MAT WITH SMALL TOY IN FRONT: LEANS FORWARD, TOUCHES TOY, RE-ERECTS WITHOUT ARM PROPPING	0 ☐	1 ☐	2 ☐	3 ☐	25.
*	26.	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S R SIDE, RETURNS TO START	0 ☐	1 ☐	2 ☐	3 ☐	26.
*	27.	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S L SIDE, RETURNS TO START	0 ☐	1 ☐	2 ☐	3 ☐	27.
	28.	R SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	28.
	29.	L SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	29.
*	30.	SIT ON MAT: LOWERS TO PR WITH CONTROL	0 ☐	1 ☐	2 ☐	3 ☐	30.
*	31.	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER R SIDE	0 ☐	1 ☐	2 ☐	3 ☐	31.
*	32.	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER L SIDE	0 ☐	1 ☐	2 ☐	3 ☐	32.
	33.	SIT ON MAT: PIVOTS 90°, WITHOUT ARMS ASSISTING	0 ☐	1 ☐	2 ☐	3 ☐	33.
*	34.	SIT ON BENCH: MAINTAINS, ARMS AND FEET FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	34.
*	35.	STD: ATTAINS SIT ON SMALL BENCH	0 ☐	1 ☐	2 ☐	3 ☐	35.
*	36.	ON THE FLOOR: ATTAINS SIT ON SMALL BENCH	0 ☐	1 ☐	2 ☐	3 ☐	36.
*	37.	ON THE FLOOR: ATTAINS SIT ON LARGE BENCH	0 ☐	1 ☐	2 ☐	3 ☐	37.

TOTAL DIMENSION B ☐

Item		C: CRAWLING & KNEELING	SCORE				NT
	38.	PR: CREEPS FORWARD 1.8m (6')	0 ☐	1 ☐	2 ☐	3 ☐	38.
*	39.	4 POINT: MAINTAINS, WEIGHT ON HANDS AND KNEES, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	39.
*	40.	4 POINT: ATTAINS SIT ARMS FREE	0 ☐	1 ☐	2 ☐	3 ☐	40.
*	41.	PR: ATTAINS 4 POINT, WEIGHT ON HANDS AND KNEES	0 ☐	1 ☐	2 ☐	3 ☐	41.
*	42.	4 POINT: REACHES FORWARD WITH R ARM, HAND ABOVE SHOULDER LEVEL	0 ☐	1 ☐	2 ☐	3 ☐	42.
*	43.	4 POINT: REACHES FORWARD WITH L ARM, HAND ABOVE SHOULDER LEVEL	0 ☐	1 ☐	2 ☐	3 ☐	43.
*	44.	4 POINT: CRAWLS OR HITCHES FORWARD 1.8m (6')	0 ☐	1 ☐	2 ☐	3 ☐	44.
*	45.	4 POINT: CRAWLS RECIPROCALLY FORWARD 1.8m (6')	0 ☐	1 ☐	2 ☐	3 ☐	45.
*	46.	4 POINT: CRAWLS UP 4 STEPS ON HANDS AND KNEES/FEET	0 ☐	1 ☐	2 ☐	3 ☐	46.
	47.	4 POINT: CRAWLS BACKWARDS DOWN 4 STEPS ON HANDS AND KNEES/FEET	0 ☐	1 ☐	2 ☐	3 ☐	47.
*	48.	SIT ON MAT: ATTAINS HIGH KN USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	48.
	49.	HIGH KN: ATTAINS HALF KN ON R KNEE USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	49.
	50.	HIGH KN: ATTAINS HALF KN ON L KNEE USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	50.
*	51.	HIGH KN: KN WALKS FORWARD 10 STEPS, ARMS FREE	0 ☐	1 ☐	2 ☐	3 ☐	51.

TOTAL DIMENSION C ☐

Item		D: STANDING	SCORE				NT
*	52.	ON THE FLOOR: PULLS TO STD AT LARGE BENCH	0 ☐	1 ☐	2 ☐	3 ☐	52.
*	53.	STD: MAINTAINS, ARMS FREE, 3 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	53.
*	54.	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND, LIFTS R FOOT, 3 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	54.
*	55.	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND, LIFTS L FOOT, 3 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	55.
*	56.	STD: MAINTAINS, ARMS FREE, 20 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	56.
*	57.	STD: LIFTS L FOOT, ARMS FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	57.
*	58.	STD: LIFTS R FOOT, ARMS FREE, 10 SECONDS	0 ☐	1 ☐	2 ☐	3 ☐	58.
*	59.	SIT ON SMALL BENCH: ATTAINS STD WITHOUT USING ARMS	0 ☐	1 ☐	2 ☐	3 ☐	59.
*	60.	HIGH KN: ATTAINS STD THROUGH HALF KN ON R KNEE, WITHOUT USING ARMS	0 ☐	1 ☐	2 ☐	3 ☐	60.
*	61.	HIGH KN: ATTAINS STD THROUGH HALF KN ON L KNEE, WITHOUT USING ARMS	0 ☐	1 ☐	2 ☐	3 ☐	61.
*	62.	STD: LOWERS TO SIT ON FLOOR WITH CONTROL, ARMS FREE	0 ☐	1 ☐	2 ☐	3 ☐	62.
*	63.	STD: ATTAINS SQUAT, ARMS FREE	0 ☐	1 ☐	2 ☐	3 ☐	63.
*	64.	STD: PICKS UP OBJECT FROM FLOOR, ARMS FREE, RETURNS TO STAND	0 ☐	1 ☐	2 ☐	3 ☐	64.

TOTAL DIMENSION D ☐

Item		E: WALKING, RUNNING & JUMPING	SCORE				NT
*	65.	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO R	0 ☐	1 ☐	2 ☐	3 ☐	65.
*	66.	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO L	0 ☐	1 ☐	2 ☐	3 ☐	66.
*	67.	STD, 2 HANDS HELD: WALKS FORWARD 10 STEPS	0 ☐	1 ☐	2 ☐	3 ☐	67.
*	68.	STD, 1 HAND HELD: WALKS FORWARD 10 STEPS	0 ☐	1 ☐	2 ☐	3 ☐	68.
*	69.	STD: WALKS FORWARD 10 STEPS	0 ☐	1 ☐	2 ☐	3 ☐	69.
*	70.	STD: WALKS FORWARD 10 STEPS, STOPS, TURNS 180°, RETURNS	0 ☐	1 ☐	2 ☐	3 ☐	70.
*	71.	STD: WALKS BACKWARD 10 STEPS	0 ☐	1 ☐	2 ☐	3 ☐	71.
*	72.	STD: WALKS FORWARD 10 STEPS, CARRYING A LARGE OBJECT WITH 2 HANDS	0 ☐	1 ☐	2 ☐	3 ☐	72.
*	73.	STD: WALKS FORWARD 10 CONSECUTIVE STEPS BETWEEN PARALLEL LINES 20cm (8") APART	0 ☐	1 ☐	2 ☐	3 ☐	73.
*	74.	STD: WALKS FORWARD 10 CONSECUTIVE STEPS ON A STRAIGHT LINE 2cm (3/4") WIDE	0 ☐	1 ☐	2 ☐	3 ☐	74.
*	75.	STD: STEPS OVER STICK AT KNEE LEVEL, R FOOT LEADING	0 ☐	1 ☐	2 ☐	3 ☐	75.
*	76.	STD: STEPS OVER STICK AT KNEE LEVEL, L FOOT LEADING	0 ☐	1 ☐	2 ☐	3 ☐	76.
*	77.	STD: RUNS 4.5m (15'), STOPS & RETURNS	0 ☐	1 ☐	2 ☐	3 ☐	77.
*	78.	STD: KICKS BALL WITH R FOOT	0 ☐	1 ☐	2 ☐	3 ☐	78.
*	79.	STD: KICKS BALL WITH L FOOT	0 ☐	1 ☐	2 ☐	3 ☐	79.
*	80.	STD: JUMPS 30cm (12") HIGH, BOTH FEET SIMULTANEOUSLY	0 ☐	1 ☐	2 ☐	3 ☐	80.
*	81.	STD: JUMPS FORWARD 30 cm (12"), BOTH FEET SIMULTANEOUSLY	0 ☐	1 ☐	2 ☐	3 ☐	81.
*	82.	STD ON R FOOT: HOPS ON R FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE	0 ☐	1 ☐	2 ☐	3 ☐	82.
*	83.	STD ON L FOOT: HOPS ON L FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE	0 ☐	1 ☐	2 ☐	3 ☐	83.
*	84.	STD, HOLDING 1 RAIL: WALKS UP 4 STEPS, HOLDING 1 RAIL, ALTERNATING FEET	0 ☐	1 ☐	2 ☐	3 ☐	84.
*	85.	STD, HOLDING 1 RAIL: WALKS DOWN 4 STEPS, HOLDING 1 RAIL, ALTERNATING FEET	0 ☐	1 ☐	2 ☐	3 ☐	85.
*	86.	STD: WALKS UP 4 STEPS, ALTERNATING FEET	0 ☐	1 ☐	2 ☐	3 ☐	86.
*	87.	STD: WALKS DOWN 4 STEPS, ALTERNATING FEET	0 ☐	1 ☐	2 ☐	3 ☐	87.
*	88.	STD ON 15cm (6") STEP: JUMPS OFF, BOTH FEET SIMULTANEOUSLY	0 ☐	1 ☐	2 ☐	3 ☐	88.

TOTAL DIMENSION E ☐

Was this assessment indicative of this child's "regular" performance? YES ☐ NO ☐

COMMENTS:

GMFM RAW SUMMARY SCORE

DIMENSION	CALCULATION OF DIMENSION % SCORES	GOAL AREA (indicated with ✓ check)
A. Lying & Rolling	$\frac{\text{Total Dimension A}}{51} = \frac{\quad}{51} \times 100 = \quad\%$	A. ☐
B. Sitting	$\frac{\text{Total Dimension B}}{60} = \frac{\quad}{60} \times 100 = \quad\%$	B. ☐
C. Crawling & Kneeling	$\frac{\text{Total Dimension C}}{42} = \frac{\quad}{42} \times 100 = \quad\%$	C. ☐
D. Standing	$\frac{\text{Total Dimension D}}{39} = \frac{\quad}{39} \times 100 = \quad\%$	D. ☐
E. Walking, Running & Jumping	$\frac{\text{Total Dimension E}}{72} = \frac{\quad}{72} \times 100 = \quad\%$	E. ☐

TOTAL SCORE = $\frac{\%A + \%B + \%C + \%D + \%E}{\text{Total \# of Dimensions}}$

$= \frac{\quad + \quad + \quad + \quad + \quad}{5} = \frac{\quad}{5} = \quad\%$

GOAL TOTAL SCORE = $\frac{\text{Sum of \% scores for each dimension identified as a goal area}}{\text{\# of Goal areas}}$

$= \quad = \quad\%$

GMFM-66 Gross Motor Ability Estimator Score [1]

GMFM-66 Score = _____ _____ to _____ 95% Confidence Intervals

previous GMFM-66 Score = _____ _____ to _____ 95% Confidence Intervals

change in GMFM-66 = _____

[1] from the Gross Motor Ability Estimator (GMAE) Software

TESTING WITH AIDS/ORTHOSES

Indicate below with a check (✓) which aid/orthosis was used and what dimension it was first applied. (There may be more than one).

AID		DIMENSION	ORTHOSIS		DIMENSION
Rollator/Pusher	☐	____	Hip Control	☐	____
Walker	☐	____	Knee Control	☐	____
H Frame Crutches	☐	____	Ankle-Foot Control	☐	____
Crutches	☐	____	Foot Control	☐	____
Quad Cane	☐	____	Shoes	☐	____
Cane	☐	____	None	☐	____
None	☐	____	Other	☐	____
Other	☐	____			

_____ (please specify)

_____ (please specify)

RAW SUMMARY SCORE USING AIDS/ORTHOSES

DIMENSION	CALCULATION OF DIMENSION % SCORES	GOAL AREA (indicated with ✓ check)
F. Lying & Rolling	$\frac{\text{Total Dimension A}}{51} = \frac{\quad}{51} \times 100 = \quad\%$	A. ☐
G. Sitting	$\frac{\text{Total Dimension B}}{60} = \frac{\quad}{60} \times 100 = \quad\%$	B. ☐
H. Crawling & Kneeling	$\frac{\text{Total Dimension C}}{42} = \frac{\quad}{42} \times 100 = \quad\%$	C. ☐
I. Standing	$\frac{\text{Total Dimension D}}{39} = \frac{\quad}{39} \times 100 = \quad\%$	D. ☐
J. Walking, Running & Jumping	$\frac{\text{Total Dimension E}}{72} = \frac{\quad}{72} \times 100 = \quad\%$	E. ☐

TOTAL SCORE = $\frac{\%A + \%B + \%C + \%D + \%E}{\text{Total \# of Dimensions}}$

$= \frac{\quad + \quad + \quad + \quad + \quad}{5} = \frac{\quad}{5} = \quad\%$

GOAL TOTAL SCORE = $\frac{\text{Sum of \% scores for each dimension identified as a goal area}}{\text{\# of Goal areas}}$

$= \quad = \quad\%$

GMFM-66 Gross Motor Ability Estimator Score [1]

GMFM-66 Score = _____ _____ to _____ 95% Confidence Intervals

previous GMFM-66 Score = _____ _____ to _____ 95% Confidence Intervals

change in GMFM-66 = _____

[1] from the Gross Motor Ability Estimator (GMAE) Software

Appendix 5

Tables to show in summary for the previous published work on the effect of BTX-A on children with cerebral palsy

The papers are arranged in chronological sequence.

Date & Author	Design of the study	Participants	Outcome	Results	Comment
1993 Koman et al	Preliminary, open-label study. The first reported successes of use of BTX-A	27 patients, dynamic deformities. 16 ambulatory, 11 more severe. 1–2 U/kg BTX-A/muscle group	Physician Rating Scale subjective assessment by careers	Spasticity significantly decreased after 12-72 h after injection Delayed surgery. Reduces spasticity for 3–6 months without major side effects	Spasticity of the target muscles then gradually returned BTX-A may delay orthopaedic surgery
1994 Cosgrove et al	Open-label study	26 patients, BTX-A in gastro-soleus /tibialis/ posterior/hamstrings. Dynamic contractures 5–28 U/kg body weight Dysport	Sagittal-plane kinematics ROM and electro-goniometry	Reduced tone , improved ankle kinematics with gains in dorsiflexion inversely proportional to the age of participant	Fixed contractures develop gradually with age
1994 Koman et al	Randomized double-blind placebo controlled, trial	Small trial: 6 children BTX-A, 6 placebo 1 U/kg BTX-A/leg	Physician Rating Scale for gait, muscle strength, physiotherapy career questionnaire	83% BTX-A group versus 33% placebo group showed improved gait	BTX-An effective treatment for dynamic deformity; effects last 3–6 month.
1996 Sutherland et al	Open-label prospective study 3 years period	26 children, 2-16 years, 4 U/kg of BTX-A in L and R gastrocnemius,	EMG, Gait analysis	Significant improvements in dynamic ankle dorsiflexion in both stance and swing phases, stride length, and EMG of tibialis anterior.	Future research should also compare BTX-A casting, orthotic devices, physical therapy, selective dorsal rhizotomy, and surgical lengthening. No complications
1998 Thompson et al	Open-label, study, hamstring spasticity	10 children with crouch gait 5–8 U BTX-A /kg/muscle 35 U/kg Dysport	Hamstring length and excursion from computer model	Increased muscle length with improved knee extension. Increased walking speed, pelvic tilt, and hip flexion	Short hamstrings over-diagnosed in crouch gait
1998 Wong et al	Open-label prospective study. Period of the study 10-24 months	17 children aged 25-177 months. 6 U/kg /child of BTX-A	Video gait analysis, Electrogoniometry, ambulatory state, modified Ashworth scale, and parental report.	BTX-A is useful as an adjunctive therapy in ameliorating spasticity in CP children	BTX-A is effective in younger ones.
1999 Boyd et al	Open-label cohort study	197 children 2–4 U BTX-A /kg/muscle	Response to BTX-A, time to next intervention Adverse effects	55% later surgery, 45% repeated BTX-A 80%, clinical responders with improved function	BTX-A safe and effective

1999 Corry et al	Open-label, study of hamstring spasticity	10 children dynamic hamstring spasticity 5–8 U BTX-A/kg 6 U/kg Dysport	Muscle tone, range of movement, 3D kinematics Oxygen uptake	Improved knee extension in stance; mean pelvic tilt increased. Energy cost of walking unchanged	Longitudinal muscle growth occurs after BTX-A injection
1999 Eames et al	Open-label prospective study	39 children, gastrocnemius injected. 8–10 U/kg BTX-A or 20–25 U/kg Dysport	3D kinematics as measure of changes in gastrocnemius length	Short-term muscle lengthening. Diplegia better response than Hemiplegia	Need for orthopaedic surgery delayed
1999 Flett et al	Randomised controlled trial, BTX-A vs serial casting One year	20 children, Aged 2-8 years 10 BTX-A, 10 placebo with dynamic calf tightness 4–8 U/kg BTX-A	Muscle tone, GMFM, ankle joint range of movement– gait Physician Rating Scale, parent satisfaction Questionnaire	Improved gait, muscle tone, passive ankle dorsiflexion in both groups at 6 months No significant difference in GMFM after 2, 4 and 6 months.	BTX-A and casting have similar effects, and costs. Parents preferred BTX-A.
1999 Heinen et al	Open-label prospective study	2 children with adductor spasticity No dose of BTX-A stated	Tone, joint mobility, GMFM, parent questionnaire	Improved function, positioning, gait and posture, facilitation of care	Beneficial effects of BTX-A on daily activities
1999 Koman et al	Open-label study	48 patients 4–7 U BTX-A/kg body weight	Response to BTX-A: Physician Rating Scale, progression to surgery	Improved gait and, function, sustained long term	BTX-A delayed need for surgery
1999 Massin et al	Open-label–prospective study	15 children, 6 U/kg BTX-A	Energy cost of walking: oxygen uptake in response to exercise	Reduced energy cost and improved endurance	–
1999 Sutherland et al	Double-blind placebo controlled trial	20 children, gastroc soleus complex injected. 2–4 U BTX-A/kg body weight	Gait studies with 3D kinematics/kinetics, EMG	Improvements in maximum dorsiflexion in both stance and gait. No significant differences in the EMG data in both groups	Short-term efficacy of BTX-A to improve
1999 Wissel et al	Randomised Double blind, high dose vs low dose	33 children, high dose: 40–80 U BTX-A /muscle. Low dose: 20–40 U BTX-A/muscle	Muscle tone, range of movement at knee and ankle, general gait parameters	High dose gives better response, Greater functional benefit in younger children	Dose-dependent functional improvement

1999 Yang et al	Open-label prospective study	38 children 28 had BTX-A and 10 in comparison group,	GMFM, Physical Rating Scale Ashworth scale.	BTX-A is effective treatment for reducing spasticity and improving gross motor function in CP children	GMFM provides objective evidence regarding functional improvement after BTX-A
2000 Barwood et al	Double-blind, randomised controlled trial clinical trail. 12 month period	16 patients undergoing hip adductor release surgery. age between 2-10 years 8 U BTX-A/kg body weight	Pain scores, analgesia requirements, length of hospital stay	Reduced: mean pain scores, analgesic requirements, length of hospital stay compared with the placebo,	Significant proportion of post-op pain from muscle spasm relieved by BTX-A
2000 Boyd et al	Open-label prospective study	25 children, 15 diplegia, 10 hemiplegia 4–9 U BTX-A/kg/muscle	Muscle tone, ankle range of movement. 3D kinetics: ankle joint	Improved patterns of ankle joint moment and power generation	Change in functioning of muscle post BTX-A
2000 Ubhi et al	Randomised; double-blind, placebo controlled, trial	40 children: aged 2-16 years 22 BTX-A, 18 placebo gastrosoleus injected 25 U/kg Dysport in diplegia, 15 U/kg in hemiplegia	Video gait analysis, GMFM, ankle dorsiflexion range Physiological Cost Index	Improved gait and function in BTX-A group. GMFM showed a statistically significant improvement in walking after BTX-A after 12 weeks. At 2,6 weeks no significant changes.	Effective adjunctive treatment to, improve spasticity and functional mobility. Intensive physiotherapy treatment blocks following BTX-A for long term benefit
2001 Bakheit et al	Multicentre retrospective study	758 patients undergoing. 1594 treatments Dysport	Adverse events from BTX-A	Increased adverse effects with higher doses. Multilevel treatments give better response than single level	Recommended maximum total dose 1000U Dysport
2001 Boyd et al	Randomised study. 1 year	39 children Age 2-5 years, Adductor and hamstring. Muscle, 4 –16 U BTX-A/kg,	GMFM GMFCS Orthosis (SWASH)	GMFM showed a similar improvement in both groups	A longer-term follow up of a larger cohort may be required to determine the effect of the combined treatment on hip displacement.
2001 Linder et al	Open-label, study, prospective study 1 year	25 children Age 1.5-15.5 years, adductor spasm, or pes equinus 12 U BTX-A/kg body weight 30 U /kg Dysport	GMFM, fine motor assessment, modified Ashworth scale,	Improvement in joint mobility and reduction of spasticity, significant improvement of GMF Scores after 12 months GMFM improvement in younger children	Improvement in GMFM is specifically related to BTX or represents at in part the natural course of motor development

2002 Baker et al	Multi-centre, randomised double-blind placebo controlled study	125 children with diplegic cerebral palsy and dynamic equinus spasticity during walking Patients randomised to receive 10, 20 or 30 U/kg Dysport	Electro-goniometry, change in dynamic component of gastrocnemius shortening at 4 weeks after injection	Dynamic component of spasticity most improved in 20U/kg group	Recommended optimal starting dose 20 U/kg
2002 Fragala et al	Multiple single-subject design study, over 12 month period	7 children, 3-11 years, 9.5-18 U/kg of body weight the dose depend on the child needed.	PROM, Ashworth scale, Canadian occupational performance measure. (COPM-performance Score), Parents satisfaction (COPM-Satisfaction Score)	All of the subjects demonstrated improvements in PROM or spasticity.	Further studies evaluating the effectiveness of specific physical therapist intervention after BTX-A injection are also needed.
2002 Polak et al	Double-blind comparison study	48 CP children with spastic hemiplegia. High dose (24 U/kg) versus low dose (8 U/kg) Dysport	Instrumented gait analysis, maximum ankle angle in stance and swing phases; gastrocnemius muscle length	Optimal dose range between 200 and 500 U with higher dose/kg more effective and longer lasting	–
2002 Reddihough et al	Cross-over study One year	49 children with spastic diplegia/quadriplegia BTX-A plus physiotherapy versus physiotherapy alone	GMFM, fine motor assessment, modified Ashworth scale, parental perception ratings	Unsustained improvements in gross motor function in both groups, small increase in fine motor ratings in BTX-A group. Parental ratings favoured BTX-A	Timing of formal assessments missed peak gross motor function response
2003 Bottos et al	Randomised controlled trial, vs BTX-A plus serial casting One year	10 children, 4-11 years, BTX-A injected bilaterally at multiple sites in the triceps sura 15-20 U/kg in each muscle	Ashworth scale, GMFM, fine motor assessment, modified, ROM range of motion measure, gait analysis, .EMG	Spasticity decreased significantly at 1 month in both, at 4 month, and 12-month in-group 2 only. GMFM significantly improved at 4 month for standing and walking.	BTX-A reduces spasticity and improves function performance in standing and walking with casting provides more marked result.

2004 Glanzman et al	Open-label prospective study 24 month	186 children 37 treated with BTX-A, 55 with casting, 86 treated legs and 32 received combined BTX-A with casting. .10-12 U/kg of BTX Mean age 7 years	ROM (goniometry), GMFCS,	The combined group showed a significant increase in passive (ROM) of the ankle joint in comparison of BTX-Alone.	Casting produced a significant increase in the ROM. More than BTX-A alone
2006 Mall et al	Multicentre, randomised double-blind placebo controlled study Study period 3 months,	61 children, aged between 18 months – 10 years 30 U/kg of BTX-A.	Ashworth scale, GMFM, GMFCS, GAS) Goal attainment Scale.	GMFM failed to detect the superiority of BTX-A treatment at week 4 and week 12	Most children with CP, reduction of adductor muscle tone with all its functional implication is achievable.