



THE USE OF BOTULINUM TOXIN TYPE A INJECTIONS IN COMBINATION WITH PHYSIOTHERAPY APPROACHES IN CHILDREN WITH CEREBRAL PALSY

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ABSTRACT

AIM: to assess treatment effect of lower limb botulinum toxin type A (BTX-A) in combination with physiotherapy approaches on gross motor functions in children with cerebral palsy compared with only physiotherapy treatment.

METHOD: A literature search was conducted in the following databases: Cochrane, PEDro, PubMed, MEDLINE, AMED and EMBASE. The searches were limited to the period from July 2009 to July 2015. The intervention had to contain BTX-A into the lower limb plus physiotherapy approaches and be compared with only physiotherapy. Inclusion criteria consisted of studies with (1) participants aged 18 or under, (2) participants with CP in GMFCS levels I, II and III, (3) studies published in English-language, (4) study design was a randomized controlled trial. The methodological quality and clinical relevance were independently assessed by two of the authors (MY, TT).

RESULTS: The database search resulted in a total of 1521 studies, of which 4 (Level II of evidence) trials were included in this review. The population represented by were age between from 11 month to 15 years. Overall there were 153 children all diagnosed with CP (87 Male, 66 Female).

INTERPRETATION: The use of BTX-A injections in addition to physiotherapy approaches seems to have positive effect on spasticity and ROM. However, the question of whether the treatment of BTX-A plus physiotherapy has a greater improvement on functional capacity, such as gross motor function or gait parameter than only physiotherapy treatments, was inconclusive. Further investigation by rigorous studies is required.

ABBREVIATIONS

BTX: Botulinum toxin

BTX-A: Botulinum toxin type A

BTX-E: Botulinum toxin type A injection guided via electrical stimulation

BTX-P: Botulinum toxin type A injection guided via palpation

CI: Confidence interval

CP: Cerebral Palsy

CSS: Composite Spasticity Scale

DTI: Diffusion Tensor Imaging

GMA: General Movements' Assessment

GMFM: Gross Motor Function measure

GMFCS: Gross Motor Function Classification System

ICF-CY: International classification of functioning, disability and health: children & youth version

MRI: Magnetic Resonance Imaging

NDT: Neurodevelopmental treatment (Bobath)

PEDro: Physiotherapy evidence database

PT: Physiotherapy/ Physiotherapist

RCT: Randomised controlled trial

ROM: Range of Motion

SR: Systematic review

US: Cranial Ultrasound

WHO: World Health Organization



1. CHAPTER I

INTRODUCTION & REVIEW OF LITARATURE

1.1.INTRODUCTION

This project is conducted as a master thesis according to the principles of University of Nottingham, Physiotherapy handbook. This project is written in three chapters namely; extended literature review, manuscript and critical reflection.

In first chapter, this study examines the literature and critically appraises the evidence of botulinum toxin type A (BTX-A) injection in children with CP. In this context, this chapter provides an opportunity to demonstrate a deeper understanding for CP in the terms of definition, risk factors, diagnosis, and classification. Then, this study covered the content and management of spasticity that commonly seen characteristic for CP population in the ratio of %80 by critically evaluating the methodological knowledge and existing evidence. This chapter is concluded by justifying the relevance of the study, the use of a systematic review (SR) to answer the research question, the choice of study design and choice of journal for publication.

In the 2nd chapter of the dissertation, the manuscript is a SR of the evidence investigating the effectiveness of BTX-A in combination with physiotherapy approaches on gross motor functions impairments in children with CP to answer research question that synthesises all the available evidence by providing the highest level of evidence. The Manuscript is written in the format for publication in the *Developmental Medicine and Child Neurology* journal explaining the step by step methodology, results and synthesis of findings.

The third and also final chapter of the study was titled as the reflection part. In this part, the author critically evaluated the reflections on the entire research process, including acquirements from the study. This part also contains reflections on the results of the research, how the results identify new meaning and suggest how this experience can impact and inform future study.

1.2.BACKGROUND

1.2.1. Cerebral palsy: Definition

Cerebral palsy (CP) was originally described as “a disorder of posture and movement due to a defect or lesion of the immature brain” (Bax, 1964, p. 295). In subsequent years the definition has developed; currently CP is defined as “a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of cognition, sensation, perception, communication, and/or behaviour, and/or by a seizure disorder” (Bax et al., 2005, p. 572). The motor impairment of CP was also associated with epilepsy and secondary musculoskeletal problems (Rosenbaum et al., 2007). In this context, limitation of movement and postural problems lead to activity limitations throughout daily life (Hidecker et al., 2011). Additionally, individuals with CP might have several musculoskeletal problems which were related to muscle spasticity, abnormal physical growth, and ageing (Mintaze Kerem et al., 2014).

Many researchers (Wu et al., 2011, Christensen et al., 2014, Kirby et al., 2011, Odding et al., 2006, Himmelmann et al., 2010, Fidan and Baysal, 2014) have considered the global extent of CP prevalence and the authors reported the CP

prevalence as between 2-5 per 1000 live births. For instance, a recent SR (Oskoui et al., 2013) of CP prevalence in the developed countries stated that CP disorder effect 2.11 per 1000 live births (95% confidence interval [CI] 1.98–2.25). Prevalence of CP in developing countries was reported greater than developed country (Fidan and Baysal, 2014). In this context, Serdaroglu et al. (2006) stated that the prevalence of CP in Turkey was 4.4 per 1000 live births and origin of CP was classified in the ratio of postnatal 5.9%, perinatal/neonatal 18.5%, prenatal 26.6%, and unclassifiable in 48.9%. In summary, the overall prevalence of CP has remained constant in recent years throughout the world (Himmelman et al., 2010, Oskoui et al., 2013). Hence, health professional focus on management of the motor disturbances to improve quality of the life in children with CP.

Economic aspects of CP management are another important issue for families and governments. Despite the fact that there is lack of evidence on cost of CP management, some literature is available. For example in 2004, Centre's for Disease control and Prevention (CDC) organization in US estimated the lifetime costs for the population of those born in 2000 with CP to be \$11.5 billion (CDC, 2004). In this study, cost of CP management is divided into three subheading; Indirect costs (80.6%, or \$9.241 billion), direct medical costs (10.2%, or \$1.175 billion), direct non-medical costs (9.2%, or \$1.054 billion). In another study, a child with CP incurred mean total Medicaid expenditures of \$22,143, whereas a child without CP incurred a mean total Medicaid expenditure of \$1729 for one year in US (Kancherla et al., 2012). This data shows that families, tax payers, and governments should provide approximately 13 times more economic funding to compensate health expense for those with CP. Kruse et al. (2009) firstly analyzed the life time cost of CP in a European country (Denmark) in regard with health care costs, productivity

costs, and social costs (N: 2367). The authors concluded that the lifetime costs of CP lie within the range of €737 783 to €1 115 376 for women and €802 771 to €1 206 232 for men (Kruse et al., 2009). This study gives beneficial information about lifetime cost for CP individual. The authors conducted the analysis of their study by sex and 5-year age groups and they truncated data at age 70 that may cause bias in analysis due to life expectancy for individuals with CP (Holmes et al., 2013). To sum up, to determine effectiveness of treatment methods comes into prominence to manage either individual or government level of economic source.

1.2.2. Cerebral palsy risk factors

By the effect of developing evidence based medicine many researchers evaluated the CP risk factor. CP disorder might occur in antenatal, intrapartum, or neonatal period, and also, may be caused by maternal origin, by developmental abnormalities, or by genetic malformations (McIntyre et al., 2013, Himmelmann et al., 2011). This part of the chapter analyzes the risk factors for CP according to occurring time.

1.2.2.1. Antenatal period

Antenatal refers to the period of pregnancy until the onset of labour resulting in delivery (Himmelmann et al., 2011). Additional to this, preconceptional factors such as maternal diseases or age and genetic factors are also included in antenatal period. In a SR, McIntyre et al. (2013) reported the preconceptional strong risk factors for CP as prior maternal diagnoses of seizures, intellectual disability or thyroid disease for children born at term in developed countries. Additionally, a range of other maternal diseases such as coagulation disorder, asthma, diabetes, surgical history, poor obstetric history, mental illness were also reported to increase the overall risk of CP (McIntyre et al., 2013). The authors also stated that maternal obstetric history of stillbirth or neonatal death was more strongly associated with CP.

There is a controversy about association between maternal age and CP disorder. Kulak et al. (2010) conducted a retrospective study of CP risk factors. They argued that there was no significant relation between maternal age (either age > 30 years or age < 30 years) and CP. However, there were some flaws in this study. First, there was no justification why the authors decided age of 30 as reference points. Additional to this, the authors referenced the two studies (Hemming et al., 2008, Jacobsson et al., 2002) which argued to have similar findings with their results. However, these studies investigated the association between gestational age and CP which did not specifically make an inference on the issue of maternal age. On the other hand, McIntyre et al. (2013) concluded that maternal age has critical impact on development of CP in the range of point estimates for maternal age <20y; 1.5–1.9, and >40y; 1.3-3.7. In interrelating with the results, they stated that maternal age <20 years and >40 years are risk-increasing factor in antenatal period. The variable results obtained from two studies may relate to differences in maternal age groups included and study design.

Pregnancy is an important phase of the antenatal period where the foetal neurodevelopment is vulnerable. The high risk factors for CP during the pregnancy was defined as small for gestational age status, low birth weight, lower socioeconomic status, intrauterine growth, placental abnormalities, multiple gestation, maternal disease in pregnancy, bleeding in the second and third trimesters, pre-eclampsia, and intrauterine infection during pregnancy (McIntyre et al., 2013). Among intrauterine infections, bacterial Chorioamnionitis was most frequently associated with CP (Girard et al., 2009, Yoon et al., 2003, Bracci and Buonocore, 2003). In a SR, Wu (2002) stated that Chorioamnionitis, which is a type

of bacterial intrauterine infection, is a risk factor for CP both in premature and full term infants (RR 1.9, 95% CI 1.5–2.5).

Additionally, several researches evaluated the theory that multiple genetic factors contribute to the cause of CP (Lynex et al., 2004, Lerer et al., 2005, Verkerk et al., 2009, Moreno-De-Luca et al., 2010, Jamra et al., 2011). Moreno-De-Luca et al (2012) conducted the relevant articles about genetic contribution of CP that six genes (GAD1, KANK1, AP4M1, AP4E1, AP4B1, AP4S1) were identified to cause Mendelian forms of CP. On the other hand, despite the fact that several single-gene mutations have been identified in idiopathic CP, mutations in multiple genes result in Mendelian disorders that present with CP-like features which may cause misdiagnosis (Moreno-De-Luca et al., 2012, Schaefer, 2008).

Consequently, the antenatal period is an at risk period for developing foetus. Many pregnancy and preconceptional risk factors are widely defined in literature. Although some of risk factors might be curable or inhabitable such as infections, the others may be untreatable such as genetic heritage. Within this scope, antenatal and pre-pregnancy periods are important for monitoring and treatment as relevant in order to limit or prevent CP.

1.2.2.2. Intrapartum

The term of intrapartum includes period of labour and birth. Birth asphyxia, mode of delivery, meconium aspiration, membrane ruptures, length of labour, abnormal fetal presentations were associated with CP (McIntyre et al., 2013). However, there is no consensus whether caesarean delivery reduced risk of CP or not. Although some researchers argue that elective caesarean delivery might be a risk of CP, some researchers did not associated the elective or emergency caesarean delivery for

prevention. For example, in a SR, O'Callaghan and MacLennan (2013) concluded that caesarean delivery was not associated with a reduced risk of CP, whether the caesarean be elective or emergency. According to meta-analysis of the study of McIntyre et al. (2013), Despite their results did not support an overall increase or decrease in the risk of CP with caesarean delivery (OR 1.29; 95% CI 0.92–1.79), they found that emergency caesarean delivery was associated with an increased risk (OR 1.80; 95% CI 1.62–1.99). Therefore, McIntyre et al. (2013) included emergency caesarean delivery in Intrapartum risks factors. However, emergency cesarean delivery is performed when the labor has commenced and a variety of fetal or maternal risk factors might accompany the caesarean delivery such as birth stress or delay delivery (O'Callaghan and MacLennan, 2013). Therefore, decision to have an emergency caesarean delivery may be matter of the life and death of both/or mother and child, however; parallel risk factors associated with such procedures should be carefully considered to prevent a permanent damage such as CP.

1.2.2.3. Neonatal period

The term of neonatal refers to the period of time after birth of a baby until when the first two years of the postnatal period. The neonatal risk factors are defined as respiratory distress syndrome, meningitis, neonatal seizures, hypoglycaemia, and jaundice (Kulak et al., 2010, McIntyre et al., 2013).

1.2.3. Diagnosis of cerebral palsy

The diagnosis of CP is based on neuroimaging, laboratory testing (genetic or metabolic testing), clinical assessment performed by health professionals (Palmer, 2004, Sankar and Mundkur, 2005, Bosanquet et al., 2013). In clinical practice, physical examination, and observations of parents are important components to diagnose CP disorders (O'Shea, 2008). Health professionals' assessment can gather

information about deep tendon reflexes, muscle tone, posture, and motor milestones such as sitting, pulling to stand, and walking (O'Shea, 2008, Sankar and Mundkur, 2005). For instance, general movements' assessment (GMA) is the one of the assessment tool used in clinic by health professionals. Bosanquet et al. (2013) included six studies, with a total of 1358 participants in a SR, and they reported that sensitivity and specificity of GMA were 98% (95% confidence interval [CI] 74–100%) and 91% (95% CI 83–93%) respectively. Despite the fact that these clinical assessment tools provide evidence and strength for predictive accuracy for CP, these methods are not appropriate to obtain information the aetiology of CP (Sankar and Mundkur, 2005).

Further examinations identify the CP pathoanatomy, in this context; Serial Cranial Ultrasound (US) and Magnetic Resonance Imaging (MRI) are commonly used to detect the cerebral abnormalities associated with diagnosis of CP (Palmer, 2004). Mirmiran et al. (2004) reported that US and MRI demonstrate high specificity as a predictor of outcome for CP (MRI sensitivity, specificity: 71%, 91% at 20 month, and 86%, 89% at 31 months). The sensitivity and specificity of US for predicting CP were 29% and 86% at 20 months and 43% and 82% at 31 months (Mirmiran et al., 2004). Similar findings has been reported in a SR of elucidating the pathogenesis of CP which MRI was defined as a high potential screening to identify pathogenesis of CP, in particular spastic and dyskinetic subtypes of CP (Krägeloh-Mann and Horber, 2007).

Despite the fact that most (83%) of children with CP had abnormal neuro-radiological findings, 17% have no cerebral abnormality detectable by conventional neuroimaging methods including MRI (Korzeniewski et al., 2008). Therefore, these methods might be insufficient to elucidate for genetic conditions, such as

malformations. In this context, genetic testing can identify the genes which cause Mendelian forms of CP (chapter 1.2.2.1.). On the other hand, several single-gene disorders, inherited as autosomal or X-linked, often present with clinical features similar to CP (Moreno-De-Luca et al., 2012). In such cases, some of these genetic conditions, which have similar clinical features alike CP, can be successfully treated with available drugs. Hence, laboratory testing methods should be considered as part of the diagnostic assessment of individuals with suspected CP.

Consequently, observations of the family members are the key component throughout diagnosis process. Additionally, doctors' and physiotherapists' clinical observations and assessment methods take important place in diagnosis of babies with suspected CP. Neuroimaging and genetic testing methods provide better understanding for aetiology and pathogenesis of CP.

1.2.4. Classification of CP

The current definition of CP involves a broad range of degrees of activity limitation, epidemiologic and clinical features. Therefore, it is useful to further categorize individuals with CP into groups or classes (Bax et al., 2005). In this respect, many classification methods are used throughout the years which may cause difficulties for clinicians and researchers (Cans, 2000). Therefore, this chapter of the study will analyze the commonly used classification systems used in clinical area. Additionally, the limitation and context of those will be discussed with the current evidence.

Topographical classification of the CP is focused principally on the distributional pattern of affected limbs (e.g. hemiplegia or diplegia) (Minear, 1956). This traditional method is also commonly used to classify the adult individuals with neurologic disorders such as stroke. Addition to this method, physiological classification system

which describes the predominant type of tone or movement abnormality in CP (e.g. spastic or dyskinetic) is combined with topographical classification in clinical practice (e.g. spastic diplegic) (Minear, 1956, Bax et al., 2005). However, neither the combination of them nor each method separately inform about effectiveness of treatment programs or intervention in CP management (Wood and Rosenbaum, 2000). Additionally, motor development of individuals cannot be tested by these classification methods.

In this context, researches needed to develop motor classification system for CP populations such as Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997), Manual Ability Classification System (MACS) (Eliasson et al., 2006). In subsequent years the content of GMFCS has been expanded and revised as GMFCS-ER version (Rosenbaum et al., 2008). GMFCS-ER describe level of gross motor function from level 1 (most able) to level 5 (most limited) and each level is separately defined for five different age ranges. The researchers reported that GMFCS is a practical, easy, simple, and widely used classification of the functional status of children with CP in clinical areas (Gunel et al., 2009, Rosenbaum et al., 2008). Additionally, this classification system is translated into different languages, and is commonly used around the world. Those are also defined as reliable and valid for assessment for children with CP (Shi et al., 2014, El et al., 2012). However, there is still no consensus to use a standard classification system for individuals with CP among the researchers that lead to difficulties for pooling available data in a study.

In 2007, World Health Organization (WHO) developed a conceptual framework to constitute a common language between health professionals. *International Classification of Functioning, Disability and Health; Children & Youth Version (ICF-*

CY) also can be used as a classification system that defines health and functioning of children using a uniform coding system to guide holistic and interdisciplinary approaches (WHO, 2007). ICF-CY organizes the information in two parts; firstly, Functioning and Disability includes Functions and Structure of Body, Activities and Participation components, while the second part, covers contextual factors (WHO, 2007). In a SR, Schiariti et al. (2014) stated that ICF-CY provides a universal framework for defining and classifying functioning and disability in children with CP. According to their findings, current outcome measures in the field of CP primarily focus on assessing the body functions and activity and participation components of the ICF-CY (Schiariti et al., 2014).

Overall, the knowledge of health professionals on ICF-CY is important to develop common language for management and classification of individuals with CP (WHO, 2007). This is also useful when planning and selecting outcomes measures for future studies (Schiariti et al., 2014).

1.2.5. Spasticity: definition and pathophysiology

Spasticity is commonly seen characteristic feature in individual with upper motor neuron syndrome (Pandyan et al., 2005). Lance's (1980) definition is most commonly cited study and defines spasticity as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome" (p.485). In subsequent years, the definition of the spasticity has been redefined by the researches (Young, 1994, Pandyan et al., 2005). Pandyan et al. (2005) currently superseded the Lance definition and described the spasticity as "a disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary

activation of muscles” (p. 5). However, there is still no consensus for the spasticity definition and this reflects the diversity and the complexity of the phenomena.

The pathophysiology of spasticity is associated with increased muscular activation initially results from the excessive neural drive of spinal motor neurones (spindle Ia afferents) (Kheder and Nair, 2012). In spasticity, motor neurones respond to stretch at a lower threshold than normal, with long discharges: the ‘plateau potentials’ (Nielsen et al., 2007). This results from a change in balance between inhibitory and excitatory inputs to spinal motor neurones in favour of excitation. This process might end up with contractures and loss of joint mobility which cause pain and affect the quality of life (Ward, 2012, Sheean, 2002).

1.2.6. Spasticity in CP

Spasticity is the most common neurological signs resulted in movement disorder in individual with CP (Albright, 1995). Most of children with CP have spastic clinical feature either unilateral or bilateral type in the range between 70 to 80% (Cans et al., 2008, Geister et al., 2014). Most spasticity treatment methods in CP are aimed to improve function, but the literature in relationships between spasticity and function is limited in children with CP (Ross and Engsberg, 2007). Spasticity and contractures in CP are associated with pain, communication difficulties, drooling, motor functional impairments, osteopenia or osteoporosis, feeding difficulties, fractures, feeding difficulties, and functional gastrointestinal abnormalities such as vomiting, and constipation (Kriger, 2006). In this context, children with CP may experience difficulties in their ability to move, problem solve, socialize, and communicate in their daily life (Shikako-Thomas et al., 2015). Therefore, spasticity management is an important milestone in paediatric rehabilitation to improve motor functions and quality of life in children with CP.

1.2.7. Management of spasticity in CP

Spasticity is common seen clinical feature in CP as discussed above. The management of CP requires a multidisciplinary approach incorporating physiotherapists, occupational therapists, orthotists, speech therapists, and physicians. Treatment methods are commonly categorized two groups: conservative and surgical treatment. This part of chapter will analyse the conservative treatments including physiotherapy and pharmacological approaches, and surgical approaches.

1.2.7.1. Physiotherapy approaches

Physiotherapy is a key component in the treatment of children with CP. In this context, basic techniques, such as massage, stretching, muscle strengthening, balance training, weight-bearing exercises, and electrical stimulation are frequently used (Franki et al., 2012, Novak et al., 2013). These basic techniques usually target specific problems at muscle tone, range of motion (ROM), and strength within the scope of body structure and function. There is a recent SR (Franki et al., 2012) including total of 83 studies of basic physiotherapy methods targeting lower limb function in children with CP. The authors indicated level II evidence for the positive effect of passive stretching on spasticity and ROM. Additionally, stretching in combination with strengthening training or electrical stimulation may have positive effect on the ICF functioning and disability component such as gross motor function in children with CP (Franki et al., 2012).

There are a number of different conceptional physiotherapy techniques, including the Bobath technique or neurodevelopmental treatment (NDT), the Brunnstrom technique, proprioceptive neuromuscular facilitation, motor learning by Carr and Shepherd, conductive education by Pető, reflex locomotion therapy by Vojta, and sensory integration by Ayres (Molenaers et al., 2012, Novak et al., 2013, Barnes,

1998). NDT is more frequently used treatment method in paediatric rehabilitation; however, the effectiveness of NDT is still controversial regard with levels of the ICF domains. In this context, Molenaers et al. (2012) demonstrated in a SR including 13 studies (N: 181 children) that NDT has a positive effect at all levels of the ICF. However, nine of the included studies had moderate or low quality conduct score, which make their results argumentative. On the other hand, the recent umbrella review of interventions for children with CP (Novak et al., 2013) demonstrated that NDT is not effective method to normalise movement or to prevent contracture development in the ICF body function and structure. According to this evidence, the clinical use of NDT is still controversial in evidence based rehabilitation.

Physiotherapists also play a key role in the management and assessment of splinting and casting, seating, positioning, and the use of orthotic devices (Barnes, 1998). Hence, this study will include these approaches in conventional physiotherapy care in original manuscript part (chapter 2).

1.2.7.2. Pharmacological approaches

Pharmacological treatments are available for spasticity management in individuals with CP which are divided into two subheading; oral agents and muscular injections (Novak et al., 2013). While oral agents can be used for generalized spasticity, phenol or botulinum toxin injections are preferred for focal spasticity (Ward, 2002, Flett, 2003). This chapter of the study will analyze the oral agents and BTX intramuscular injections.

1.2.7.2.1. Oral medications

The oral agents most commonly used to treat spasticity are gabapentin, dantrolene, benzodiazepines, tizanidine, and baclofen (Ghai et al., 2013, Delgado et al., 2010,

Kita and Goodkin, 2000). For instance, Baclofen is a gamma-Aminobutyric acid (GABA) agonist that is used to reduce spasticity. Baclofen treatment is prescribed both oral and intrathecal use in individuals with CP, however; the use of oral baclofen is still controversial in clinical practice. In this context, Delgado et al. (2010) recommended in an evidence-based review (based on two class II studies and one Class IV study) that there was no sufficient evidence to refute or support the use of oral baclofen for improvement of motor function or to treat spasticity in children with CP. Addition to this, several researchers demonstrated that the use of baclofen (oral) therapy might be controversial due to side effects such as somnolence, vertigo, hypotonia (Thibaut et al., 2013, Krach, 2001, Dai et al., 2015, Ghai et al., 2013, Novak et al., 2013).

Diazepam is a benzodiazepine that provides the ability for postsynaptic action of GABA to reduce spasticity in children with CP (Tilton, 2009). An umbrella review of Novak et al. (2013) stated that the diazepam is an effective pharmacological treatment to reduce spasticity in children with CP. Addition to this, diazepam is also defined as a cheap and effective spasticity reduction drug regard with cost effectiveness aspect which is important factor to determine choice of treatment method (Mathew et al., 2005). This approach is effective for general spasticity in short-term, therefore; diazepam is particularly preferred for quadriplegic type CP. However, this medication may not be preferable to reduce local spasticity in children with CP (Chung et al., 2011, Delgado et al., 2010). Additionally, the long-term use of diazepam is still controversial due to side effect such as ataxia and drowsiness (Chung et al., 2011, Patel and Soyode, 2005).

Consequently, several oral medications are used to management of spasticity in CP which discussed above to have ability for spasticity reduction. However, the use of

oral medications is needed to clarify in relation with adverse effects and motor functional improvement.

1.2.7.2.2. Botulinum toxin

Botulinum toxin (BTX) is a powerful neurotoxin consists of a high molecular weight protein generated from clostridium botulinum (anaerobic bacteria). There are seven structurally similar BTX types (A-G) defined within literature (Erbguth, 2008). As a protein BTX includes heavy and light chains connected with disulphide bonds. The heavy chain binds to nerve terminals at the neuromuscular junction. The light chain travels into the nerve terminal and inhibits the release of acetylcholine. It is this inhibiting action which provides a blockade to the neuromuscular junctions so potentially helpful in neuromuscular pathologies such as CP (Brin, 1997, Kostrzewa and Segura-Aguilar, 2007).

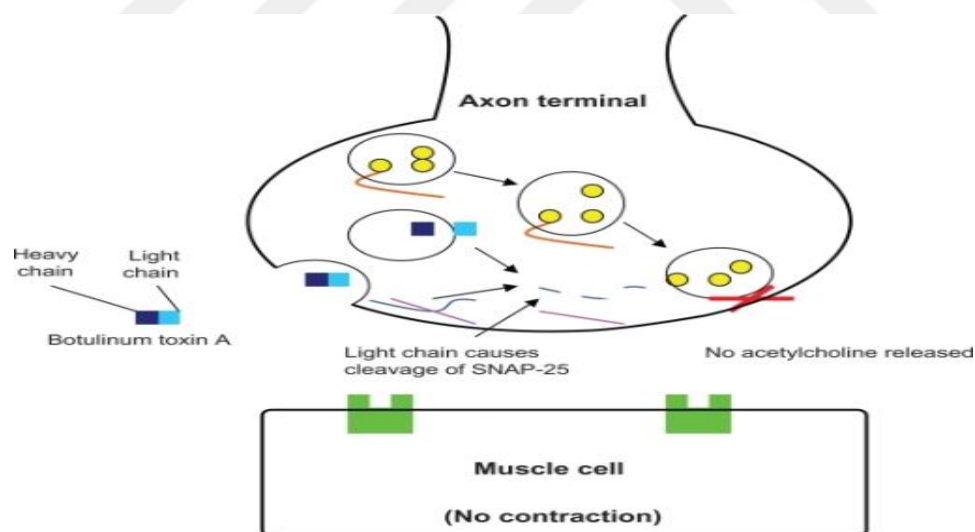


Figure 1 Physiologic action of BTX-A injection cited from Tremaine (2010)

Historically, first therapeutic use BTX was defined by Justinus Kerner (1786-1862) (Blumetti et al., 2009). However, Dr. Brookes accomplishedly demonstrated that the BTX A has a potential to reduce spasticity as an intramuscular injection (Brooks, 1954). In subsequent years the use of BTX-A developed further with the first

successful practice in children with CP in 1993 (Ryll et al., 2011). BTX-A injections are increasingly used and are often complemented by adjunctive rehabilitation therapies (Esquenazi et al., 2010, Kinnear et al., 2014). Despite the fact that several studies showed that BTX-A injection is a spasticity reduce injection method in CP management, the controversy of BTX-A injections in individuals with CP keep up to date with regard to functional capacity.

In this context, several independent systematic reviews on the use of BTX-A for lower limb spasticity have been written by various authors (Boyd et al., 2001, Garces et al., 2005, Cardoso et al., 2006, Lannin et al., 2006, Simpson et al., 2008). Ade-Hall and Moore (2000) were the first to bring all gold standard evidence on BTX-A for lower leg spasticity in a SR. Three RCT (total participants; 52 children) were combined in the study of the results and they concluded that a BTX injection in children with CP has no significant improvement on gait parameters (Ade-Hall and Moore, 2000). Due to small sample size and current available literature, this study is not up-to-date for clinical implications. There are two current SR are available in literature (García Salazar et al., 2014, de Souza et al., 2014). For instance, Souza et al. (2014) included six controlled trials addressing the effect of the effect of BTX-A and spasticity was primary outcome. The authors concluded that BTX-A combined with either physical therapy or plaster casts lead to improvement in motor function in children with CP. However, due to quality of the included studies, the result of study is controversial (mean PEDro score; 4). Additionally, in four of included studies, the all participants received the botulinum toxin injections, whereas the other has placebo or physiotherapy control group which may cause bias in design.

Another current SR including 17 studies is titled “Intrinsic properties and functional changes in spastic muscle after application of BTX-A in children with CP” (García

Salazar et al., 2014). The authors concluded that BTX-A injections has no changes in the passive stiffness of spastic muscle. Additionally, the effect of BTX-A was controversial in relation to functional level (García Salazar et al., 2014). However, most of included trials in this study investigated the effectiveness on lower limb muscles, whereas some of studies researched the changes in spastic upper limb muscles. In this context, the reliability of the study might affect due to the heterogeneous data.

Consequently, the literature questioning the effectiveness of BTX-A gradually increase in evidence base rehabilitation. However, the use of BTX-A injection in children with CP is still debate due to lack of evidence Therefore, further studies need to evaluate the effectiveness in specific gross motor level and for specific muscle group.

1.2.7.3. Surgical approaches

The surgical methods in spasticity management for children with CP are Intrathecal Baclofen (IB), Selective Dorsal Rhizotomy (SDR), and orthopaedic surgery. Single-event multilevel surgery (SEMLS) is the more common orthopaedic technique (Harvey et al., 2012, Lehtonen et al., 2015). SEMLS addresses several components of the progressive lower limb musculoskeletal pathology seen in CP; including joint stabilization procedures, rotational osteotomies, tendon transfers, and tendon lengthening (McGinley et al., 2012, Shore et al., 2010). In a SR included of 31 studies, McGinley et al. (2012) investigated the quality of the evidence for SEMLS for children with CP. Despite the evidence based is limited, this method might be an effective to improve motor functions of children with CP (McGinley et al., 2012). However, cost effectiveness for routine use in children is inconsistent around the

world due to benefit analysis being unsupportive that SEMLS remain somewhat debatable.

IB is another combined surgical pharmacological approach to spasticity management in CP which is administered with a programmable pump implanted in the abdominal wall (Francisco et al., 2009). Either oral or via a surgically implemented intrathecal space catheterised pump of Baclofen action on the body is to provide spasticity reduction. Pin et al. (2011) conducted a SR questioning the effectiveness of IB therapy on motor functional status in ambulant children with CP. the SR was included 16 study (15 level IV or V, 1 level II of evidence according to the AACPDm guidelines). The authors concluded that IB may be an effective method for spasticity or gross functional activities; however, the clinical use of IB is still inconclusive due to lack high qualified evidence (Pin et al., 2011). Additionally, adverse events or medical complications such as infection, and dosing problems were frequently reported for IB approach (Pin et al., 2011, Butler et al., 2000). Hence, further studies need to investigate the effectiveness and complications of IB in children with CP.

SDR is a non-reversible surgical intervention increasingly applied to children with CP (Dudley et al., 2012, Ailon et al., 2015). Sensory nerve fibers activating targeted spastic muscles are identified via an electrical stimulation in the spinal cord. They are then transacted; whilst other nerve roots critical for function (i.e. sphincter functions) are preserved (Grunt et al., 2014). Currently, there is limited evidence that SDR might have a positive long-term benefit on the ICF body' structure and function domains. SDRs' effect on the ICF activity and participation domains are inconclusive in children with spastic CP (Grunt et al., 2011). Further the authors highlight the potential for SDR to contribute to spinal deformities, such as lordosis and, scoliosis which need to gather in individuals with CP (ibid).

There is limited evidence that IB therapy is, which might be an alternative for SDR, might even be more costly (Tedroff et al., 2011). However, these procedures remain limited with regard to cost effectiveness, and short/long term adverse events aspects in children with CP. Overall, there is lack of evidence in particularly for RCT to compare between surgical approaches due to cultural or economic reasons (McGinley et al., 2012, Tedroff et al., 2011) .

1.2.8. Rational for review

CP remains a commonly diagnosis global ratio between 2 to 5 in 1000 life birth (chapter 1.2.1.). Spasticity related insufficiency of motor functional capacity takes an important place to achieve independence in daily life activities (Kirby et al., 2011). Therefore, reduce lower limb spasticity and improve functional capacity are crucial component of rehabilitation programmes. Researchers stated that the therapeutic use of BTX-A to improve functional ability by reducing lower limb spasticity might be effective treatment method in cerebral palsy (Balaban et al., 2012, Unlu et al., 2010, Liu et al., 2014). Therefore, a SR focused upon BTX-A intervention for lower limb function would bring together the several studies. SR such as this assists in making clinical decisions and guiding future research (Denyer and Tranfield, 2009, Higgins and Green, 2011).

Additionally, the author as a physiotherapist has worked in the area of Paediatric Physiotherapy for the past four years. The majority of patients are diagnosed with CP present with lower limb spastic motor functional disorders. Physiotherapist practitioners recognise limitations in their therapeutic approaches to address such as lower limb spasticity and functional impairments. Adjuncts to physiotherapy therapeutic methods such as BTX by reducing spasticity may offer opportunities to

optimise therapeutic effectiveness of physiotherapy approaches (Novak et al., 2013). From the author physiotherapist perspective, BTX injections are very popular in Turkish paediatric rehabilitation. However, according to the literature search (chapter 1.2.7.2.2.), there is no consensus on the effectiveness of BTX intervention for lower limb muscles and motor functional capacity. In Turkey, BTX intramuscular injections are the most frequently applied management approach for spasticity by orthopaedics, neurologists in an agreement with physiotherapist. Lack of high qualified evidence on the effectiveness of BTX intervention encourages the author to improve health professionals' knowledge on this issue. For these reasons, this study is conducted to focus on this specific area and to answer whether BTX A injection in combination with physiotherapy care improve motor functional capacity for children with cerebral palsy or not is required.

1.2.9. The aim and objectives

The aim of this project including SR is to critically appraise and synthesize the available evidence for the effectiveness of lower limb BTX-A injections in addition to physiotherapy care on gross motor functions in children with CP. The research question is framed with a population, intervention, comparison and outcome approach (PICO) (chapter 1.3.3.). It is as follows; "Does lower limb BTX-A injection in addition to physiotherapy approaches more effective than physiotherapy care alone on gross motor functions in children with CP (equivalent to GMFCS levels from I to III)?"

Order of objectives to;

- To devise and implement a SR search strategy including inclusion and exclusion criteria May 2015

- To critically appraise included articles using the appraisal tool recommended in journal guidelines July 2015
- To compile data from the included studies including quality ratings (DMCN TOC) by July 2015
- To write up synthesis and discussion of findings in the light of the literature review and the PICO question including recommendations as a journal article by July 2015
- To include a reflection chapter on how the SR findings and research process may impact clinical practice and my own knowledge and skill development by August 2015
- To submit the whole project as a written thesis by September 2015

1.3.METHODOLOGY

1.3.1. Introduction

In accordance with the requirement of the school of Health Science of the University of Nottingham, this dissertation will be include tree parts; 1) introduction and extended literature review, 2) the research paper (SR), 3) critical reflection. In this context, this chapter focuses on the methodology employed in carrying out the systematic review (chapter 2.). It starts with an introduction and discussion of the role of systematic reviews in evidence based practice. Then, this followed by the justification for scope of the review, the review question. The target journal is developmental medicine and child neurology. Therefore, The SR protocol and the methodology of the review will be detailed in accordance with targeted journal in chapter 2. to avoid duplication.

1.3.2. Systematic review methodology

RCT are quantitative studies, which measure and compare two interventions regarding random allocation (Higgins and Green, 2011). SR are secondary source of reviews of literature to evaluate and summarise primary research studies. A high level quality of SR should identify all relevant studies and select them regarding inclusion criteria. Then it should assess the quality of each study and summarize findings considering in an unbiased way. Finally, it should interpret and explore relevance clinical findings based on evidence. A SR that provides these criteria including RCTs are the strongest and most trustworthy evidence in the literature to evaluate effectiveness of any interventions because of using strategies to avoid bias and random error (Haines et al., 2008, Higgins and Green, 2011, Abuabara et al., 2012).

1.3.3. The research Question

By considering the qualities of a well-designed question, PICO framework is selected to create the research question;

- **P (population):** children under the age 19 diagnosed with CP (GMFCS I – III) in all type of topographical distribution.
- **I (intervention):** lower limb BTX-A injections in addition to physiotherapy approaches
- **C (Comparison group):** physiotherapy approaches (chapter 2.7.1.) with/without sham injections.
- **O (outcome measure) :**
 - Primary outcome: Gross motor functions

- Secondary outcomes: spasticity, gait, ROM.

According to this framework, research question has been decided as noted below:

“Does lower limb BTX-A injection in addition to conventional physiotherapy approaches more effective than usual physiotherapy care alone on gross motor functions as measured by GMFM in children with CP?”

1.3.4. Justification of Methodology

The choice of the design of this study is a SR including RCTs. This study aimed to understand whether BTX-A injections in addition physiotherapy approaches is more effective than physiotherapy methods alone in children with CP, RCTs were chosen if BTX-A injections plus physiotherapy were compared with physiotherapy care alone as control group. Therefore, among the several methods to answer research question, systematic review of randomized controlled trials was selected the best design because of justifications mentioned before. Additionally, gross motor functions were selected as a primary outcome measure in this review because GMFM is one of the primary interests to clinicians, patients and their families.

1.3.5. The choice of journal submission

This study is aimed to conduct a SR including RCTs in according to principles of *Developmental Medicine and Child Neurology* (DMCN) journal. This journal is the official journal of; American Academy for Cerebral Palsy and Developmental Medicine, the British paediatric neurology association, the British academy of childhood disability, the European academy of childhood disability. DMCN has defined the field of paediatric neurology and neuro-disability and is one of the world's leading journals in the whole field of paediatrics. DMCN aims to enhance the care of children by worldwide dissemination of clinical research into the wide range of

neurological conditions and disabilities that affect children (Impact Factor: 3.51). The breadth of DMCN includes many disciplines in pediatrics such as Paediatric Neurology, Physical, Occupational & Speech and Language Therapies. Therefore, the author used single-line spacing for all parts and Vancouver style reference system (Appendix 1.).



2. CHAPTER II

The Efficacy of lower limb Botulinum toxin A injections in addition to Physiotherapy approaches in children with cerebral palsy in Gross Motor Function Classification system level I-III: a systematic review

2.1. INTRODUCTION

Cerebral Palsy (CP) was defined as a number of permanent disorders pertaining to movement and posture development, which induces a number of restrictions attributed to non-progressive disturbances arising in the brain of the foetus or infant^(13, 14). CP-related motor disorders are commonly seen to go hand-in-hand with disturbances in various other areas, including behaviour, cognition, communication, perception and sensation, for example epilepsy, as well as secondary musculoskeletal issues^(13, 14). One of the most common causes of physical disability in children is recognised as CP, with prevalence on a global scale amounting to 2-5 per 1000 live births^(15, 16). CP classifications are commonly based on functional topographical distribution, types of muscle tone, and, motor abilities⁽¹⁷⁾.

When considering topographical classification, this may be explained as the distribution of those body parts affected, which can include, but are not limited to, diplegia (usually the lower extremities more affected), hemiplegia (unilateral distribution) and quadriplegia (involvement of all four limbs)⁽¹⁸⁾. Such a classification is widely implemented, regardless of the fact that validity and overall reliability are queried^(13, 19).

The expanded and revised Gross Motor Function Classification System (GMFCS-E&R) is recognised as valuable and reliable in categorising CP children in line with age-centred (0-18 age) gross motor function^(20, 21). The GMFCS-E&R may be defined as an ordinal grading system, comprising five distinct levels spanning I–V, in which there is the description of various self-initiated movement in relation to age group; movements include sitting, standing and walking, for example. Between-level distinctions are made on the basis of an evaluation concerning functional restrictions and capacities, along dependence on assistive technology, such as wheeled mobility and walking aids. Those children assigned to Level I and Level II are usually able to walk without the use of an aid, whilst those of Level III are able to walk with the use of aids but only for a short distance, and therefore commonly opt for wheeled mobility. Children at Level IV are recognised as having restricted motor ability when considering assisted stepping, standing and transfers, whilst those at Level V are entirely dependent on others for transportation, and therefore do not demonstrate antigravity postural control^(21, 22).

There is the general categorisation of muscle tone types as ataxic, dystonic/dyskinetic, spastic or mixed ⁽²³⁾. In specific regard to spasticity, this may be defined as a velocity-dependent increase in muscle resistance at a time at which there is the stretching or passive movement of the muscle ^(24, 25). This is the most common motor type, and is identified in as much as 80% of CP-diagnosed individuals ⁽¹⁷⁾. Those with spastic CP are known to experience a degree of limb stiffness as a result of focal muscular hyperactivity, which subsequently causes awkward or altogether restricted movement. Dystonia/dyskinesia is prevalent amongst 10%–20% of CP individuals, and is recognised by fluctuating muscle tone, which induces slow twisting, and writhing movements, abnormal posture and/or repetitive movement. The least common of CP types is ataxic, where individuals are seen to show poor levels of balance and coordination as a result of low levels of muscle tone ⁽¹⁷⁾.

The management of CP spasticity requires a variety of interventions aimed at improving functionality, quality of life, and sustained health, with such methods including physiotherapy, occupational therapy, pharmacological agents, and surgical interventions ⁽²⁶⁾. In regard to the pharmacological approach, botulinum toxin type A (BTX-A) is defined as a serotype of botulinum toxin, created by the Gram-positive bacterium *Clostridium botulinum* ⁽²⁷⁾. This potent neurotoxin restricts acetylcholine release from peripheral nerve terminals through synaptic vesicle binding ⁽²⁸⁾. Neuromuscular conduction interruption through BTX-A causes muscle weakness to be experienced temporarily, which subsequently might cause a reduction in focal spasticity. BTX-A effects are seen to have a duration of an estimated 3 months, with the muscle recovering through the creation of new neuromuscular junctions, referred to as proximal axonal sprouting, along with the regeneration of the original neuromuscular junctions ⁽²⁸⁾.

BTX-A efficiency in terms of spasticity management in CP is widely recognised in the literature ^(29, 30). Additionally, a number of past studies providing support for its effectiveness in CP children at levels IV–V ⁽³¹⁾. Previously there has been a lack of literature considering lower limb BTX-A injections on gross motor functions in ambulant CP however, more recently a number of studies have emerged exploring this area. Ryll et al 2011 did undertake a SR including low quality and small sample size of studies compared the BTX-A injection plus physiotherapy care versus usual care or physiotherapy ⁽³²⁾. Therefore this current study is required to provide current evidence in the light of the new literature and make recommendation for the clinical use of BTX-A injections in children with CP. Accordingly, this systematic review aims at completing an evaluation pertaining to the effectiveness of the evidence in direct consideration to the following question: When injected into the lower limb muscles, does BTX-A, combined with physiotherapy approaches, achieve a greater degree of efficiency than physiotherapy care alone in regard to gross motor functions in CP children at levels equivalent to GMFCS I–III?

2.2. METHOD

This systematic review (SR) was conducted according to principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^(33, 34) in combination with American Academy of Cerebral Palsy and Developmental Medicine (AAPDM) methodology for developing systematic reviews of treatment interventions⁽³⁵⁾.

2.2.1. Search strategy

The literature search was performed by two independent researchers for studies published in English. The literature search used the following databases: The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), the Physiotherapy Evidence Database (PEDro), PubMed, OVID MEDLINE, AMED and EMBASE (via OVID). Search terms were designed to include the population of interest ('Cerebral palsy' OR 'CP' OR 'Children with cerebral palsy' OR 'Hemiplegic type cerebral palsy' OR 'Diplegic cerebral palsy' OR 'Quadriplegic cerebral palsy' OR 'Monoplegia cerebral palsy' OR 'Spastic type cerebral palsy') AND type of intervention ('Botulinum Toxin Type A' OR 'Botulinum Toxin' OR 'Botox' OR 'Dysport' OR 'Clostridium botulinum Toxin' OR 'Botulinum Neurotoxin A' OR 'Clostridium Botulinum Toxin Type A'). In 2011, Ryll et al.⁽³²⁾ investigated the comparison between BTX-A injection with physiotherapy care and physiotherapy alone in children with CP. Therefore, the database searched is limited for a period from July 2009 until July 21015 due to the period of their database search. Then, the duplication citations are excluded from initial search. The titles and abstracts of articles identified in the initial search were screened against inclusion and exclusion criteria separately by two authors (MY and TT). Additionally, the authors also reviewed the references of all retrieved articles for additional relevant literature. When in doubt, the full text of an article was read to determine its suitability. Any disagreement between the two authors was resolved by the third author (SWW).

2.2.2. Inclusion and exclusion criteria

The articles were included based on the following inclusion criteria:

- Study design was a randomized controlled trial;
- The studies were full text available in English;
- The participants were children aged 0 to 18 years;
- All participants were diagnosed with CP equivalent to GMFCS level of I, II, or III
- The studies were structured as the intervention group(s); Botulinum toxin type A applied to lower limb muscle(s) in addition to physiotherapy approaches, whereas the participants in comparison group only received the physiotherapy treatment(s)

- They reported the efficacy or effectiveness of the intervention, for improving gross motor function, using at least one outcome measure of motor function by GMFM.

The studies were excluded based on the following inclusion criteria:

- They were non-randomised studies or non-controlled studies
- The participants were adult or the data for children participants did not separately calculated
- They reported medical or surgical interventions
- They investigated or compared the effectiveness of different doses or type of Botulinum toxin injection.
- Participants were not classified according to their GMFCS level and if it was not possible to classify the participants accurately by the authors of this review with information provided in the studies.

2.2.3. Data extraction and quality appraisal

The AACPDM SR data extraction summary form was used to compile for research design, participants, intervention(s), outcome (categorized relative to ICF-CY domains), results and potential adverse effect. The level of evidence of included studies was graded according to the American Academy for Cerebral Palsy and Developmental Medicine Treatment Outcome Committee (AACPDM TOC) guidelines for the development of systematic reviews. According to this guideline, the quality of each included article was assessed in two steps:

1. Assignment of the level of evidence; the studies was rated from I to V according to the rating system (Table I). In this context, Level I studies produce results from which definitive conclusions can be made. Level II through Level IV studies report progressively less credible evidence from which only cautious conclusions can be drawn. No definite conclusion can be made from Level V evidence.
2. Evaluation of conduct; studies with the level of I, II, or III were also given a quality assessment score based on the scoring system of the AACPDMTOC guidelines. The evaluation of conduct for included studies was rated using a 7-item questionnaire, with studies scoring 'yes' on between 6 or 7 items rated as strong, on 4 or 5 items rated as moderate, and on three or less items rated as weak (Table III).

Table 1 AACPDM levels of evidence: hierarchy of research designs

Level	Intervention (Group) studies
I	Systematic review of randomized controlled trials (RCTs) Large RCT (with narrow confidence intervals) (n >100)
II	Smaller RCT's (with wider confidence intervals) (n<100) Systematic reviews of cohort studies "Outcomes research" (very large ecologic studies)
III	Cohort studies (must have concurrent control group) Systematic reviews of case control studies
IV	Case series Cohort study without concurrent control group (e.g. with historical control group) Case-control Study
V	Expert Opinion Case study or report Bench research Expert opinion based on theory or physiologic research Common sense/anecdotes

2.3. RESULTS

The search strategy was applied with limitation of date and language and this initial electronic search resulted in 1521 relevant studies. After duplicates were removed, the titles and abstracts of 851 articles were screened. Of these, 16 full-text articles met initial criteria and were retrieved for review, with 4 studies meeting final inclusion criteria. The flow of studies, and reasons for exclusion at final stage, is summarized in a PRISMA diagram (Fig. 1).

The summary of the included studies were tabulated based on AACPDM guidelines in Table II, including citation, design, evidence level and conduct rating, participants, experimental and control groups intervention. The population represented by were age between from 11 month to 15 years. Overall there were 153 children all diagnosed with CP (87 Male, 66 Female). Diagnosis of CP generally was not detailed; however, MRI was the most common diagnostic procedure in the included studies. In accordance with the inclusion/exclusion criteria there were no children equivalent to GMFCS levels IV and V included in the studies. Two ^(36, 37) of included studies specially classified the participants according to GMFCS levels (number of participants level I; 32, level II; 47, level III; 1). However, two ^(38, 39) of studies do not provide information detail about GMFCS level of participants. One ⁽³⁹⁾ of this studies stated that the participants' GMFM score was ranging from 50 to 60. In accordance with this information, the participants are equivalent to GMFCS levels II or III ⁽²¹⁾. Another study's inclusion criteria ⁽³⁸⁾ defined as the participant who can walk over 10 steps independently (i.e. GMFCS levels I or II) ⁽²¹⁾. The further information was asked via email from co-authors, however, they did not reply.

Researchers investigated the efficacy of BTX-A looked for changes in looked for changes in functional performance, muscle spasticity, ROM, and gait. The outcomes are commonly represented by the ICF-CY components of Functioning and Disability, which is provided in Table IV. For spasticity the Modified Ashworth scale (MAS) was most frequently used, additionally, one study ⁽³⁶⁾ is also used Composite spasticity scale (CSS). Range of motion (ROM) outcome of choice in two studies ^(36, 37) was the goniometer; however, one study ⁽³⁸⁾ is assessed extension angle of hip joints via video and digital imaging technology. Walking ability was evaluated with two outcomes; one study ⁽³⁷⁾ used Gillette Gait Index (GGI), another study ⁽³⁶⁾ assessed the waling velocity with 3m walking test. All included studies investigated the functional performance as measured with GMFM; however, due to variety of GMFM versions, the Meta-analysis was not suitable from provided data.



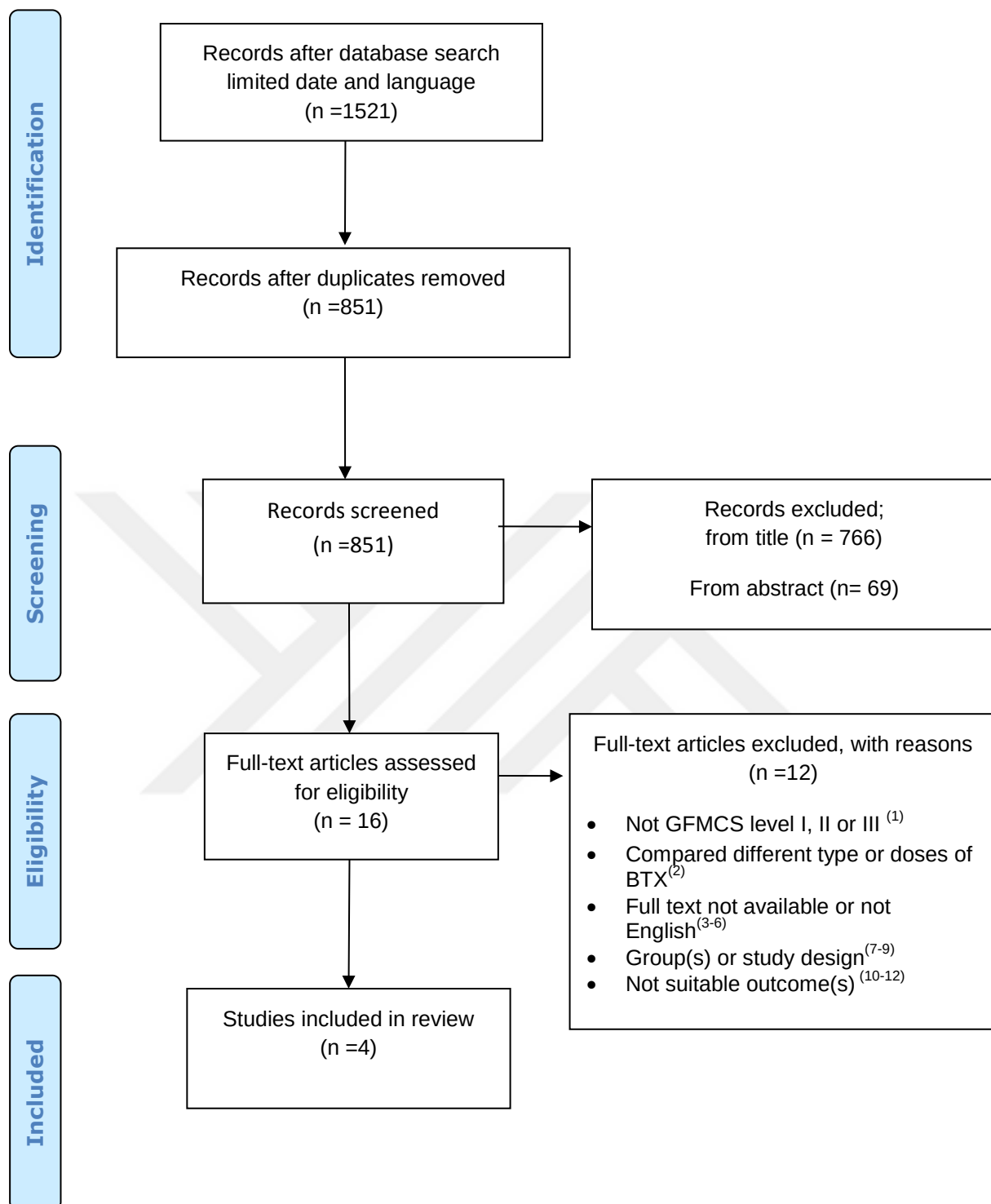


Figure 2 PRISMA flow diagram

Table 2 Summary of studies- interventions and participants

References	Research Design, evidence level, and conduct rating	Participants	Total N	Ages	Intervention group[s]	Comparison group
2009 Xu ⁽³⁶⁾	randomized controlled trials (RCT), Group design, level II, strong (5/7)	CP, spastic diplegic, and mild diplegic type, able to walk independently, GMFMCS level I and II	N=65 (44M, 21F) BTX via E; N=25 (16m, 9F) BTX via P; N=22 (15m, 7F) PT; N=20 (13M, 7F)	30 to 106 months Mean=56 months BTX via E; 55.3 months BTX via P; 59.4 months PT; 51.7 months	The dosages were 3–10 U/kg body weight limited to no more than 12 U/kg body weight. Total dose not exceeding at any one site was 10 U. The number of injection sites ranged from 6 to 8. Two type of method used to determine injection location; 1) electric stimulation, 2) palpation applied to plantar flexors	Neurodevelopment therapy, stretching, strength and coordination training and task-specific training, and neuromuscular electrical stimulation. Five days a week (60-90 min) for 2 week with a PT then taught to caregivers. Duration; 3 months
2010 Tedroff ⁽³⁷⁾	randomized controlled trials (RCT), Group design, level II, weak (3/7)	CP, uni- or bilateral type, GMFCS level I, II and III	N=15 (7M, 8F) BTX group n;6 (3M, 3F) PT group;9 (4m, 5F)	11 to 22 months Mean=16 months BTX group; 16.7 months Physio group; 15.6 months	In addition to stretching programme, Two BTX-A injection at a 6month interval applied to gastrocnemius muscle via palpation methods. Six units of Botox/kg body weight, diluted to 50 U/mL, Duration; 12 months	15-min daily stretching programmes focusing on gastrocnemius and soleus muscles. Duration: 12 months
2013 Chaturvedi ⁽³⁹⁾	randomized controlled trials (RCT), Group design, level II, weak (3/7)	CP, spastic diplegic type GMFM score ranging from 50 to 60. i.e. GMFM I, II or III	N=36 (23M, 13F) BTX group n;18 (11M, 7F) PT group;18 (12M, 7F)	2 to 8 years Mean age; 4.35 years BTX group; 4.4 years Physio group; 4.3 years	Addition to PT treatment, 100–500 units/muscle with total dose not exceeding 30 units/kg body weight BTX-A toxin Injection applied. Duration; 6 months Muscles: (medial hamstring hip abductors, gastrocnemius muscle and soleus)	Physiotherapy treatment including ; 30 minutes of stretching program, 30 minutes of strengthening and 30 minutes gait training Duration; 6 months

2014 Liu ⁽³⁸⁾	randomized controlled trials (RCT), Group design, level II, weak (3/7)	Cp, spastic diplegic type, able to walk over 10 steps independently i.e. GMFM I or II	N=37 (23M, 14F) BTX group n;17(11M, 6F) Physio group;20 (12M, 8F)	3 to 15 years Mean; 5.92 BTX group; 6.02 years Physio group; 5.86 years	Besides conventional PT training, they were injected BTX-A in iliopsoas muscle. The dose of BTX-A was according to the weight and the (MAS). Dose of injection ranged from 15 IU to 45 IU with average dose 31.2±13.9 IU.	Conventional physiotherapy rehabilitation training. Duration; 8 weeks
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Table 3 Conduct of Group Design Studies

Study	Design, evidence level, and conduct rating	1. Were inclusion and exclusion criteria of the study population well described and followed?	2. Was the intervention well described and was there adherence to the intervention assignment?	3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	4. Was the outcome assessor unaware of the intervention status of the participants?	5. Did the authors conduct and report appropriate statistical evaluation including power calculations?	6. Were dropout/loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	Total
2009 Xu ⁽³⁶⁾	Group, level II, strong (5/7)	Y	Y	N	Y	Y	N	Y	5
2010 Tedroff ⁽³⁷⁾	Group, level II, Moderate (4/7)	Y	N	Y	Y	N	N	Y	4
2013 Chaturvedi ⁽³⁹⁾	Group, level II, weak (2/7)	Y	N	N	N	Y	N	N	2
2014 Liu ⁽³⁸⁾	Group, level II, weak (2/7)	N	Y	N	N	Y	N	N	2

Table 4 Summary of studies: outcomes, measures, results, and adverse events

Study	Outcome of interest	Outcome measure	Component of health (ICF-CY)	Results/Comparison	Adverse events
2009 Xu ⁽³⁶⁾	ROM at ankle joint	Goniometer	BF(b710)	Three group showed groups showed significant improvement in passive ROM at ankle joint ($p<0.01$), however, the two botulinum toxin injection groups showed greater improvement than PT alone group at each follow-up session ($p<0.05$) and the greatest chance was observed from BTX-E group in BTX groups end of follow-up ($p=0.039$)	Pain at injection side and fall lasted up to one week. Then, no adverse event is reported ($p>0.05$).
	Muscle tone	MAS, and CSS	BF(b735)	all children showed significant decreases in spasticity according to MAS and CSS score ($p<0.01$), however, The two botulinum toxin injection groups showed greater improvement in both outcome measure than PT alone group ($p<0.05$) and greatest decrease was identified in BTX-E group between injection groups at three months($p=0.043$ for MAS, $p=0.043$ for CSS)	
	Gait (Walking velocity)	3m walking test	BF(b770)	significantly increase after two weeks of treatment for the three groups, and the results were maintained for three months ($p<0.01$) but No significant differences in walking velocity were detected among the three groups ($p>0.05$)	
	Functional performance	GMFM D&E dimensions	A&P (d410–d429, d455)	D and E dimensions score increased in three groups after two weeks and maintained for three months ($p<0.01$).The D and E dimensions of the GMFM scores increased more significantly in the BTX-E group than in the PT alone group at two and three months ($p=0.041$, $p=0.043$ respectively), however, No significant difference in Gross Motor Function Measure scores was found between the BTX-P and the physiotherapy only group after treatment ($p>0.05$).	
2010 Tedroff ⁽³⁷⁾	ROM at knee, and ankle joints	Goniometer	BF(b710)	Ankle joint; no significant difference between the changes in the two groups at any time, but the ES was 0.52 at 1 year and 0.47 at 3.5 years Knee joint; significant differences between two groups in popliteal angle change from baseline, both at 1 year ($p = 0.017$, ES = 1.86) and at 3.5 years ($p = 0.016$, ES = 0.88)	Weakness, dyesthesia, skin and pain at the injection side (N=3)
	Muscle tone	MAS	BF(b735)	Plantar flexors; reduction in muscle tone after 1 and 3.5 years that was significantly different from baseline at 3.5 years (mean Ashworth score -1.0; 95% CI: -1.4 to -0.6, $p = 0.04$). However, no significant differences in the changes of tone between the groups at any time Knee flexor; significant difference in knee flexor tone changes between groups ($p= 0.05$) at 3.5 years, with a larger reduction of tone in the BoNT-A group	

	Gait	Gillette Gait Index (GGI)	BF(b770)	Gait pattern at 5 years; No significant difference between GGI in the two groups ($p = 0.31$)	
	mobility, self-care and social function	PEDI	A&P (various)	Both groups had a significant increase in all six scales after 1 and 3.5 years. However, no significant differences between two groups at any time.	
	Functional performance	GMFM-66	A&P (d410–d429, d455)	BTX group; increased a mean of 13.6 points ($p < 0.0001$) at first year, 23.6 points ($p = 0.0002$) at 3.5 years, and PT group; increased a mean of 10.1 points ($p = 0.0001$) and 20.9 points ($p < 0.0001$) respectively No significant differences between two groups in any assessment at any time. ES at 1 year approached a high ES (0.76) and a moderate ES at 3.5 years (0.6)	
2013 Chaturvedi ⁽³⁹⁾	fractional anisotropy(FA) values of motor and sensory fiber bundles	DTI	BS(s110-s199)	Significant change in FA value in motor and sensory fiber bundle at 6 months compared to baseline study in both the groups ($p < 0.001$); however, delta change (motor; $p = 0.89$, and sensory; $p = 0.95$) and relative delta change (motor; $p = 0.98$, and sensory; $p = 0.83$) in FA values of sensory and motor fiber between PT and BTX groups were statistically insignificant.	NS
	Functional performance	GMFM	A&P (d410–d429, d455)	Significant increase as compared to baseline study in PT group ($p < 0.001$) and BTX group ($p < 0.001$); however, delta change ($p = 0.53$) and relative delta change ($p = 0.48$) between two groups were statistically insignificant.	
2014 Liu ⁽³⁸⁾	extension angle of hip joints	Video and digital imaging technology	BF(b710,b770)	The range of hip joint decreased in both PT group and BTX group, but the change in PT group was insignificant ($p = 0.239$), whereas the change in BTX group was statically significant ($p = 0.021$). The decrease of range between the two groups has significant difference ($p = 0.001$)	NS
	Muscle tone	MAS	BF(b770)	No significant difference in PT group ($p = 0.094$), but significant decrease in BTX group ($p = 0.004$). significant difference between PT and BTX groups ($p < 0.05$)	
	Functional performance	GMFM	A&P (d410–d429, d455)	Significant increase in PT group ($p = 0.038$) and BTX group ($p = 0.013$) compared with baseline; however, the increase in BTX group higher than PT group ($p = 0.002$)	

2.3.1. Changes in ROM

Of the three studies ⁽³⁶⁻³⁸⁾ investigating the effect of BTX-A on ROM (n=117 in total). Two studies ^(36, 38) reported that participants treated with BTX-A injection plus physiotherapy have showed statistically significant improvement than participants treated with only physiotherapy approaches (N=102). On the other hand, one study ⁽³⁷⁾ evaluated the ROM at two joints and they found that there were no significant changes at ankle joint in participants either treated BTX-A plus physiotherapy or physiotherapy alone, while there were significant different at knee joint in two groups (Table IV).

2.3.2. Changes in spasticity

Three studies ⁽³⁶⁻³⁸⁾ investigated the efficacy of BTX-A on the muscle spasticity (N=117), of two ^(36, 38) reported significant difference when compared the reduction of muscle spasticity between intervention and control groups, with a greater reduction in the participant treated BTX-A in addition to physiotherapy (N=102). One study ⁽³⁷⁾ (N=15) showed no statistically significant changes between groups in plantar flexor muscles; however, significant difference was reported in knee flexor tone changes between groups (Table IV).

2.3.3. Changes in walking

Of the two studies ^(36, 37) investigating the effects of BTX-A injections on gait parameters with two different outcomes (N=80). The results of studies showed a non-significant difference on gait parameters between intervention and control groups' participants (Table IV).

2.3.4. Changes in gross motor functions

There are four studies ⁽³⁶⁻³⁹⁾ evaluated efficacy of lower limb BTX-A injections on gross motor function in children with CP (N=153). Two studies ^(37, 39) found insignificant difference of GMFM score changes between BTX-A injection plus physiotherapy and physiotherapy alone groups. Liu et al. (2014) stated that the GMFM of all participants either treated with BTX-A plus physiotherapy or physiotherapy alone have shown significant difference compared with baseline and the increase of GMFM in BTX-A group was higher than physiotherapy group (Table IV). Xu et al. (2009) compared two different injection techniques and conventional physiotherapy approaches. The D and E dimensions of the GMFM scores increased more significantly in the BTX injection group guided by electrical stimulation (BTX-E) than in the physiotherapy group at two and three months. However, no significant

difference in GMFM scores was found between the BTX injection group guided by palpation (BTX-P) and the physiotherapy only group after treatment (Table IV).

2.4. DISCUSSION

The use of BTX-A injection in children with CP has been scrutinised in terms of its ability to treat children with CP ^(30, 40). The efficacy of BTX-A injection has been currently evaluated in CP as classified GMFCS levels IV and V for pain reduction and improvement in positioning or ease of hygiene ⁽³¹⁾. However, the use BTX-A injection in children with CP has a variety of aims at different functional capacity levels ⁽⁴¹⁻⁴³⁾; for example, BTX-A is primarily aimed at using the improvement of pain reduction, ease of hygiene in GMFCS level IV and V, whereas BTX-A is commonly used to improve gait parameters and gross motor functional capacity in ambulant children with CP ⁽⁴⁴⁻⁴⁶⁾. Therefore, this review is aimed at critically appraising the available evidence and filling the gap in terms of the effectiveness of BTX-A lower limb muscles injection, in addition to physiotherapy approaches on gross motor functions amongst children with CP (GMFCS levels from I to III).

In this context, we found four studies that examined the use of BTX-A in children with CP equivalent to GMFCS Levels I, II and III, which investigated the outcomes of gross motor function, spasticity, ROM and gait. All of the studies showed a high degree of evidence (Level II); however, the quality of the studies included showed variation: two ^(38, 39) study; weak, one ⁽³⁷⁾ study; moderate, and one ⁽³⁶⁾ study; strong in term of methodological quality (Table 3). All of the studies included reported the significant change on gross motor function, muscle tone, gait and joint range in children with CP (GMFCS levels I, II and III) treated with BTX-A in combination with physiotherapy approaches when compared with the baseline results of the participants. The results of current study was confirmed by the previous studies investigated the efficacy if BTX-A injections in children with CP ^(29, 30, 44, 47).

On the other hand, the studies comparing the effectiveness of BTX-A plus physiotherapy and physiotherapy alone on functionality, as measured by GMFM, showed different results in children with CP, classified as GMFCS levels I to III. Xu *et al* ⁽³⁶⁾ investigated the two different injection technique of BTX-A and physiotherapy approaches. The different injection technique showed different results when compared with the physiotherapy approaches. The participants treated with BTX-A injection guided by electrical stimulation has greater improvement on D and E dimensions of GMFM when compared with the physiotherapy approaches, including programmes based on the principles of neurodevelopment therapy, stretching, strength and coordination training, and task-specific and electric stimulation. However, the results of the participants treated with BTX-A injection guided by palpations did not show significant improvement on GMFM when compared with the physiotherapy alone group (Table IV). In accordance with this study's results, a firm conclusion cannot be drawn about the efficacy of BTX-A injection in children with CP. In another study, Liu *et al.* ⁽³⁸⁾ reported similar findings to those garnered in the study of Xu *et al.* In this study, the children (N=37) with spastic iliopsoas muscle were aged 3–15 years. The results demonstrated that the participants treated with

BTX-A injections in combination with physiotherapy showed statistically significant improvement in terms of GMFM when compared with the physiotherapy alone group participants. However, in this study, the context of rehabilitation programme has not been stated, which could mean the results fall under question.⁽⁴⁸⁾ Despite the fact that two^(37, 39) of the included studies reported statistically significant improvement on gross motor functions of the participants treated with either BTX-A plus PT or PT alone; however, the difference between intervention and comparison group results were not statistically significant. This difference results from the studies included, which may cause the included age range and study design. Additionally, the difference physiotherapy programmes in the included studies might show different results on the effectiveness of physiotherapy on gross motor function in children with CP⁽⁴⁸⁾. Overall, it seems that additional use of BTX-A injections are unlikely significant improve gross motor function compared to traditional physiotherapy approaches. Similar results have been reported in previous SR investigating the efficacy of BTX-A injections in ambulant children with CP. In this SR, including 4 RCTs, Ryll *et al.*⁽³²⁾ did not make a clear recommendation as to the use BTX-A in combination with physiotherapy.

Spasticity is a common problem amongst children with CP, which is identified in as much as 80% of the CP population⁽⁴⁹⁾. Three⁽³⁶⁻³⁸⁾ of the studies included were found to have investigated the effects of BTX-A on muscle tone changes, which is commonly reported with MAS outcome measure. Xu *et al.*⁽³⁶⁾ used two different objective outcome measures (MAS and CSS) to assess the spasticity changes between two BTX-A injection techniques and physiotherapy, and accordingly established a statistically significant reduction in these outcome measures for both injection techniques when compared with the physiotherapy group (Table IV). In another study, Liu *et al.*⁽³⁸⁾ compared MAS score between the BTX-A plus physiotherapy and physiotherapy alone groups results at the end of 8 weeks of follow-up (Level II of evidence). With the weak methodological rigour, this study reported the significant change on MAS score in participants treated with BTX-A muscle injection in combination with physiotherapy ($p < 0.05$). However, this study's post treatment was assessed only at 8 weeks after therapy, with the long-term effectiveness not shown in the study. Additionally, there was no report as to CI and whether the results were in the range of CI. Tedroff *et al.*⁽³⁷⁾ investigated the long-term efficacy of BTX-A injection in children under 2 years old, and reported significant differences from baseline at 3.5 years for plantar flexor muscle (mean Ashworth score -1.0 ; 95% CI: -1.4 to -0.6 , $p = 0.04$). despite the researchers reported that the spasticity score change in group of BTX-A plus physiotherapy at knee flexor was a non-significant reduction of muscle tone at both 1 and 3.5 years after treatment in relation to baseline level, there was a significant difference in knee flexor tone changes between BTX-A plus physiotherapy and physiotherapy alone group at 3.5 years ($p = 0.05$). In accordance with all of the included studies' results, the BTX-A injection, in combination with physiotherapy approaches, could provide better spasticity reduction in children with CP than only physiotherapy treatment.

Two^(36, 37) of of the studies included investigated the efficacy of BTX-A injections in combination with physiotherapy on passive ROM. Both of the studies used to

goniometer as a measurement tool. Xu *et al.*⁽³⁶⁾ evaluated the passive ROM of the dorsiflexion of the ankle joint, measured by a blinded physiotherapist, whilst the participants maintained the knee-extended position. The participants treated with BTX-A injection combined with physiotherapy showed greater improvement in PROM at ankle joint than the participants only treated with physiotherapy at the end of a three-month follow-up period. However, the researchers did not provide a justification as to whether or not such an improvement of ankle joint PROM was clinically meaningful. Tedroff *et al.*⁽³⁷⁾ reported the effectiveness of BTX-A injection in toddlers with CP on ROM at two joint (ankle, knee), and reported a significant increase at knee joint in participants with treated with BTX-A and physiotherapy from baseline at 1 year (mean -2° 95% CI -22° to -4° , $p = 0.009$). Their results also reported significant differences between intervention and comparison groups in popliteal angle from baseline, both at 1 year ($p = 0.017$, ES =1.82) and at 3.5 years ($p = 0.016$, ES =0.88). In addition to these two studies, the study of Liu *et al.*⁽³⁸⁾ was evaluated in terms of the extension of the angle of hip joints in gait cycle via digital imaging technology. Their results demonstrated that the flexion posture at hip joint of two groups (BTX-A or PT) has decreased compared before therapy (Table IV), with the decrease of range in the BTX-A group greater than in the physiotherapy group ($p < 0.01$). To sum up, the BTX-A injections, in combination with physiotherapy approaches, could provide improved joint mobility in children with CP (GMFCS levels I–III) when compared with treatment, including only physiotherapy approaches.

Two^(36, 37) of the studies included evaluated the effectiveness of BTX-A lower limb injections on gait parameters in children with CP. Xu *et al.*⁽³⁶⁾ stated that walking velocity, as measured through 3-metre walking test, significantly improved in all participants ($p = 0.01$); however, no significant difference was detected amongst the BTX-A plus physiotherapy and physiotherapy alone groups throughout the period of the three months obtained with multiple analysis of variances ($p > 0.05$). In another study, Tedroff *et al.*⁽³⁷⁾ evaluated walking ability as measured with GGI. The results of their study did not find any significant changes at 5 years. However, there were some flaws identified in the study's results. First, the study had a sample size of 15; however, the final gait assessment was performed on only 13 participants, which could include performance bias. Second, some of the participants (N=5) in the control group (only physiotherapy treatment) began receiving BTX-A treatment before the final assessment, which could cause bias. Therefore, studies with a rigorous study design are needed in order to verify the effectiveness of BTX-A injection on gait parameters for children with CP (GMFCS levels I–III).

2.4.1. Limitation of this Review and Future Research

Various studies have examined the efficiency of BTX-A on a group of children with CP in different levels of GMFCS. In a number of the works, it was not possible to categorise the children in line with their GMFCS level or otherwise to separate the data in GMFCS levels I–III. Accordingly, this review might not provide a wide-ranging view of clinical indicators for BTX-A use across this group when considering that the relevant information in such works centred on the subjects in GMFCS levels I–III has

not been included, which could mean there is the presence of selection bias. Moreover, this research comprised only those trials documented in English, meaning there is an abundance of other works in this field carried out in other languages, where consideration to such could have induced different findings (Figure 1). Nonetheless, we hold the view that the literature review is thorough, and we have ensured the careful classification of research subjects in line with GMFCS levels, encompassing all relevant information disclosed in the documentation, along with any reference to researches that have analysed the effects of BTX-A in this group. One further limitation associated with this review is the small volume of works that fulfilled the inclusion criteria and the bias risk of the studies included, which causes various problems in making clear conclusions in relation to the overall efficiency of BTX-A for this particular group of individuals. The results of this review therefore need to be interpreted in line with these findings.

The injection method of BTX-A was defined in three of the studies included, whilst one of them did not clearly describe the injection method. The further studies need to investigate the optimal BTX-A injection methods for children with CP. This study also did not limit the BTX-A dosage, meaning the dosages of injection showed variation in the studies considered (Table II). A future study could investigate the overall efficacy of standard dosage of BTX-A in children with CP, which should be done by carrying out investigations in line with specific ages and GMFM levels, etc. In addition to this, further research is needed in order to evaluate the efficacy of BTX-A in combination with physiotherapy on specific muscles, such as hamstring and gastrocnemius.

2.5. CONCLUSION

Four studies were included in this review, comparing the use of BTX-A in combination with physiotherapy approaches and physiotherapy alone in terms of improvement in gross motor functions, spasticity, ROM and gait in children with CP equivalent to GMFM levels from I to III. Almost all of the included studies' results reported the positive improvement for BTX-A injections in addition to physiotherapy approaches on spasticity and ROM when compared with physiotherapy application alone. However, the question of whether the treatment of BTX-A plus physiotherapy has a greater improvement on functional capacity, such as gross motor function or gait parameter than only physiotherapy treatments, was inconclusive. Therefore, we cannot firmly recommend the use of BTX-A in combination with physiotherapy approaches in children in GMFCS levels I, II and III. Future studies with rigorous methodological quality are required in order to evaluate evidence for the use of BTX-A in children with CP in GMFCS levels from I to III.

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3. CHAPTER III

CRITICAL REFLECTION

3.1.INTRODUCTION

This part of the study demonstrates the skill and learning statement that reflect the implications of the research experience on my personal and professional development. This chapter also allows the exploration of the knowledge, assumptions and beliefs in the area of study, and how the results identify new meaning, suggesting how this experience can impact and inform future study. The Gibb's reflection cycle was followed in an effort to explain the reflections process during the dissertation process (Gibbs, 1988).

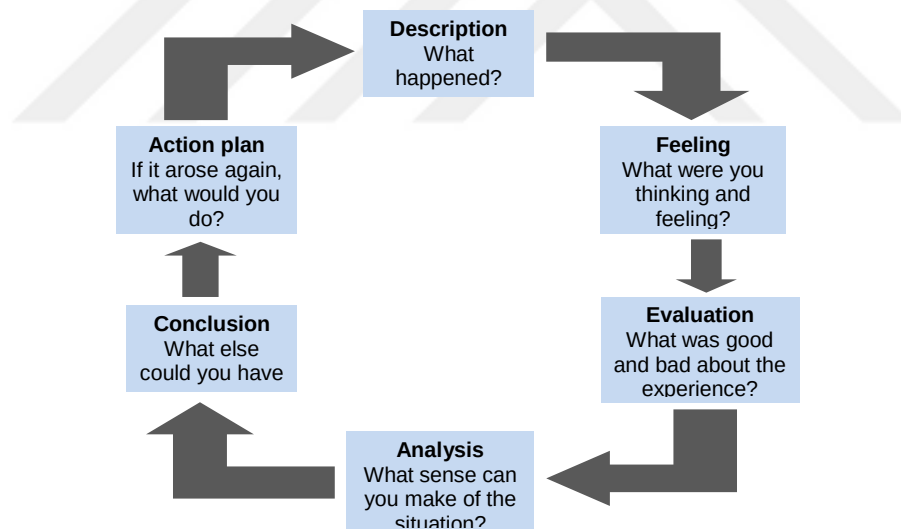


Figure 3 Reflection cycle (adapted from Gibbs 1988)

The decision was made by the author to enrol in an MSc programme at the University of Nottingham with the aim of broadening knowledge and understanding of practice in physiotherapy science. The author graduated from a Turkish university, in the physiotherapy department, and then has worked in the paediatric

physiotherapy field. Botulinum toxin injections are very popular for spasticity management in children with CP in Turkey, as in many other countries. Having completed some background reading in literature, I established a gap pertaining to the overall effectiveness of BTX-A injection on functional performance in children with CP. In the schedule of master programme, I took the module of Evidence for Health and Social Care, which helped me to create a research question and gain understanding of the researches process in the specific arena of medical science. In this module, therefore, I decided to conduct a research specifically examining the adjunct benefit of BTX-A injections in the population. The decision to carry out a systematic review was closely linked to the author's personal interest.

3.2. REFLECTION ON RESEARCH PROCESS

3.2.1. Personal Development

Turkish physiotherapy education was based on oral presentations, practical and written exams; therefore, this dissertation project is the first long written project I have undertaken in my academic life. In line with the principles of the master programme in physiotherapy department at University of Nottingham, the author was paired up with another master student to work together on independently searching and evaluating the literature for their respective reviews. In addition to this, I worked with a supervisor, who has much experience in the paediatric rehabilitation field.

First, the research process required extensive preparation and planning across each stage of the study, where each stage of the study had to be carried out in an organised manner from time perspectives. The author faced challenges in terms of ensuring the progress of the study according to the timetable, which caused feelings of fear and anxiety, which affected my concentration. In this regard, I had

opportunities to meet with my dissertation supervisor six times and obtained practical support regarding various aspects of the work during these meetings. Our first meeting was mainly dedicated to clarifying our expectations of the research. Furthermore, we devised an action plan for each part of the dissertation. For subsequent meetings, I finished one part of the study and got useful feedback from my supervisor, which helped me to identify flaws in the study. Thus, I could finish the extended literature review part and manuscript part by a designated date. This research experience has contributed to the improvement of my time-management skills, which provides considerable benefits for the author in personal, as well as professional, areas. For my own learning, I have gained a wealth of experience in terms of organising long research projects, which will be helpful in the future.

The second challenge was that I was paired up with another master student who prepared her study on adult neuro-rehabilitation field. In line with the study process rules, the students needed to work independently on the searching and quality assessments processes for each other's studies. However, I did not have enough experience on stroke rehabilitation. I felt like I was on a ragged edge because I did not want to negatively affect my peer's study. In our first meeting, we explained the aims of our studies and we shared the search terms, and included databases and quality assessment tools. In the second meeting, we finished the database search and discussed the findings from databases. . However, we had a disagreement about one of the studies in the thesis: whilst she argued that this study should not be included in the dissertation, I thought that we should include the study due to the study design. In this regard, I carried out some background reading on study inclusion methods for academic discussion. We had a very useful meeting and explained our thoughts about the study. However, we could not reach a consensus

as to whether or not the study should be included in the systematic review. We consulted my supervisor as a third writer, and she explained why this study should be included in the systematic review. When I look back, I realise the importance of academic discussions in research process. Accordingly, my own level of self-confidence in an academic discussion has increased significantly as a result of conducting this research.

3.2.2. Professional Development

The second chapter of this thesis project was carried out as a research paper for a targeted journal. Establishing the most suitable journal is a key parameter for the study. However, I did not have an experience in evaluating journals, which caused difficulties in the process. I did not know enough about journals in English in paediatric physiotherapy rehabilitation. Firstly, I wanted to choose an association of paediatric chartered physiotherapists' journal, which is an online published journal. In this context, I would use Pedro quality assessment tool and Cochrane Handbook for Systematic Reviews of Interventions, which I used in my protocol for Evidence for Health and Social Care module assignment. However, my supervisor directed my attention to the importance of the impact factor for a journal and how it might be useful for my academic career. Since then, I have felt a little stressed owing to the fact I thought this chance would cause time loss. In this context, I began to learn how to decide on a targeted journal. I have looked at many journals, which could be my targeted journal. Due to context of the journals, I eliminated all journals except for two; Developmental Neurorehabilitation journal (impact factor; 2.05) and Developmental Medicine & Child Neurology journal (DMCN) (impact factor; 3.51). Due to the high-impact factor and more suitable context of the journal, I decided to conduct my manuscript for DMCN journal. This journal has different guidelines and

quality assessment methods for publishing articles; therefore, I had to change some parts of my study, which caused losses in time. However, from this experience I have learnt to evaluate the context and quality of the journals in my field. In addition to this, I have learnt that determining the target journal is one of the preliminary phases of a research process.

The content and number of databases included is an important phase in the research process when striving to create a high-qualified research paper. Therefore, ensuring an effective searching strategy is a crucial component for database selection. I did not have knowledge on this issue, despite the fact I took an evidence-based module in the course of my master programme before this project. I was concerned about finding more appropriate databases for my study. In this situation, I looked at the current researches published in my targeted journal, and accordingly searched the context of these databases. Therefore, I was able to improve my knowledge on the databases in physiotherapy, as well as my medical research area overall. Thus, I decided to include six appropriate databases for research so as to avoid missing a relevant study for my research question. For this reason, I am confident that I performed an extended databases search, which is one of the key strengths of my study. From a professional perspective, I realise that some of the search engines use the same databases, which meant the searching phase was very time-consuming. Therefore, I will ensure I am aware of this in future studies.

Critical thinking and evaluation of the studies were found to be fundamental for researchers. However, the researcher was unaware of the need for such rigorous methodological quality prior to completing this project. In addition to this, the researcher did not have enough knowledge about the meaning of some terms

commonly used in research area, such as statistical significance or insignificance. There are some symbol letters, such as p -value and t -test that provide data in the research. The author was not familiar with these symbols. Understanding these data and terms was the most difficult challenge of the research process. I shared this challenge with my supervisor, who advised of some studies carried out on this issue. Additionally, I applied to the university librarian and borrowed a book titled *Understanding Clinical Papers* (Bowers et al., 2013) which explained statistical terms in research. Throughout the course of this process, the researcher learnt to realise that statistical knowledge was critical during this process, and the researcher was able to understand and interpret basic statistical terms. From this experience, I have concluded that value is not adequate for detailed analysis when seeking to establish the effectiveness of treatments, whereas the effect size and 95% coincidence intervals provide a better estimate. This will definitely help in future academic life. Consequently, I studied at University of Nottingham as a scholarship student from Turkish government. According to this sponsorship, after graduation from this university, I will work in a Turkish university as a lecturer. In this vein, each phase of this process has helped me to gain new experiences, all of which are important not only to my personal development but also to my academic career.

3.3. CRITICAL REFLECTION ON THE RESULTS OF THE RESEARCH

Since I have been working in paediatric rehabilitation, most of my patients have been diagnosed with CP, which is the most common life-limiting diagnosis in childhood, as explained in Chapter I and Chapter II. Spasticity is commonly seen as a characteristic that causes pain and motor functional inadequacy in this population. Botulinum toxin injections in combination with physiotherapy approaches are extremely popular methods believed to be a 'magic intervention' in spasticity

management. However, the use of botulinum toxin injection was an interrogation point regarding the effectiveness on the gross motor functions in my professional career. The results of the current study demonstrated that botulinum toxin injection could have a positive effect on spasticity and ROM. However, the additional use of this injection, combined with physiotherapy, is still inconclusive when compared with only physiotherapy treatment on gross motor function. Therefore, firm conclusions cannot be drawn as a result of the results of the study, meaning the use of BTX-A injection in children with CP equivalent to GMFM levels from I to III cannot be further supported because there was not enough evidence with high-quality methods and a wide enough sample size. Furthermore, blinding was another challenge in this study due to the various ethical issues.

On the other hand, this study and research process have provided insight into many different perspectives on the issue of the botulinum injections and CP. Children's age in included studies has varied because the current study did not limit the data according to age. In this context, the efficiency of botulinum toxin injection on specific age groups needs to be investigated in future studies. In addition to age groups, the efficacy of this injection should be defined in specific muscles groups. These are the limitations in the literature, which will form the key questions to future studies and which needs to be taken into account by other researchers.

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APPENDICES

Author Guidelines for target journal

Guidelines for Contributors

Developmental Medicine & Child Neurology

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Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman RA, Nelson NM, editors. *Primary pediatric care*. 2nd ed. St. Louis: Mosby Yearbook, Inc.; 1992. 1367–78.

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Please be aware that the content of the video should not display overt product advertising.

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Please send the video file along with your portrait and an Online Video Broadcast Release Form, by email to DMCN Journal dmcn@editorialoffice.co.uk together with details of the paper to which it refers.

4. Selection and publication

a) Editorial review

Submissions are normally sent to at least two independent referees. Case reports and reviews are assessed by the Editors and one or more independent referees. During the submission process, authors have the opportunity to, and are encouraged to, suggest three suitable independent referees (with their contact details) but the choice of referee rests with the Editors. Most papers also undergo statistical review before acceptance.

Editors and editorial board members are not involved in editorial processes or decisions about their own work.

Reviewers are asked to disclose potential conflicts of interest when they are invited to review a paper and when they submit their review.

Papers thought to have immediate, clinically important consequences may be considered for fast-track publication. The decision to prioritize remains with the Editors.

b) After acceptance

The Editors reserve the right to determine whether accepted papers will be published in the online version of an issue ('E-Papers') or in both the print and the online version. E-Papers are listed in the table of contents of the issue in which they are published, and their abstracts and citation information appear in the print issue.

After acceptance, authors will be able to track the progress of their article through production to publication by registering for Author Services with Wiley Blackwell.

Authors will be sent information about how to register for Author Services once their article has been accepted.

When an accepted paper has been copy-edited, has been approved by the authors, and is ready for publication, it will normally be posted online in the journal's 'EarlyView' section before allocation to an issue. EarlyView articles are in their final form and are fully published and citable.

Authors receive a free PDF of the paper soon after publication. Reprints may be ordered when returning proofs. Please send no payment: an invoice will be sent shortly after you receive the reprints.

c) After publication

If errors affecting the interpretation of data or information are discovered after publication, an erratum will be published in the next available issue of the journal and published online.

5. Style points

Jargon Avoid it strenuously. The journal aims to communicate across disciplines, and many of its readers do not have English as their first language, so plain language is always preferred. The Editors may clarify and shorten manuscripts accepted for publication as necessary.

Abbreviations These should be kept to a minimum and restricted to those that are generally recognised. They must be spelled out in full on first usage in text and again in figure captions and table footnotes. They should be avoided in titles, headings and subheadings.

Participant details Give mean (SD) age in years and months (not decimal years) and sex (*n*, not %). Ensure this information is included in the abstract. In the text, indicate where study and comparison groups are from and how participants were selected.

Measurements Use SI units, except for blood pressure (mmHg); convert imperial units to metric. Do not use percentages for sample sizes below 50; use the symbol ‘%’ in tables. Show standard deviations as (SD), not $\pm$. Abbreviate probability with a lower case italicized *p*.

Numbers In general, use numerals, but spell out numbers at the beginning of sentences. Spell out numbers ‘one’ to ‘nine’ if they refer to nouns that are not units of measurement, e.g. ‘The results from four children confirm the findings’. For ages and

time periods, use years, months, weeks and days, not decimals (e.g. 5 years 3 months, not 5.25 years).

Equipment and drugs Include (in parentheses) the name of the manufacturer, the city, and country of production.

