1996

The Effects of Botulinum Toxin Injections on Function in Patients with Spasticity

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THE EFFECTS OF BOTULINUM TOXIN INJECTIONS ON FUNCTION IN PATIENTS WITH SPASTICITY

by

Leann Pippen
Bachelor of Science in Physical Therapy
University of North Dakota, 1995

An Independent Study
Submitted to the Graduate Faculty of the
Department of Physical Therapy
School of Medicine
University of North Dakota
in partial fulfillment of the requirements
for the degree of
Master of Physical Therapy

Grand Forks, North Dakota
May 1996
This Independent Study, submitted by Leann Pippen in partial fulfillment of the requirements for the Degree of Master of Physical Therapy from the University of North Dakota, has been read by the Faculty Preceptor, Advisor, and Chairperson of Physical Therapy under whom the work has been done and is hereby approved.

[Signatures]

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(Chairperson, Physical Therapy)
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Department Physical Therapy

Degree Masters of Physical Therapy

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ACKNOWLEDGEMENTS

I would sincerely like to thank my parents, David and Sheila Pippen, for their encouragement and support. I would like to thank my father for his help with the graphic illustrations in this paper. Finally, I would like to thank Peggy Mohr for her valuable guidance during this semester.
ABSTRACT

Spasticity can be one of the most challenging problems for patients with neurologic conditions such as cerebral palsy, spinal cord injuries, cerebrovascular accidents, multiple sclerosis, traumatic brain injuries, etc. It can lead to a wide variety of problems including decreased mobility, decreased quality of movement, interference with normal postural reactions, interference with functional activities, and pressure sores. Therefore, the medical community has focused on effective treatments for spasticity which do not produce overwhelming weakness, spasticity, paralysis, fatigue, and/or muscle atrophy. Since the late 1970's, the use of botulinum toxin (BTX-A) injections to decrease spasticity has been investigated.

The purpose of this paper is to review research studies involving the use of BTX-A injections for the management of spasticity arising from central nervous system dysfunction. This review will focus specifically on: (1) the effectiveness of BTX-A in decreasing spasticity, and (2) improvements in functional performance and quality of life due to this decrease in spasticity (including increased mobility, increased quality of movement, and increased independence in activities of daily living).

In the majority of studies reviewed, significant decreases in spasticity upon injection of BTX-A were reported. These decreases in spasticity caused subsequent increases in active
and passive range of motion, and decreases in pain and uncontrolled movements. Improvements in ambulation, transfer skills, hygiene skills, positioning ease, and overall function were less frequently examined, but reported in approximately half of the studies reviewed. Few studies mentioned the changes in quality of life or the increased ability in carrying out role functions in daily life following BTX-A injections. Additional research studies are needed to quantify the effects of BTX-A injections on functional limitations and on quality of life. If research shows that patients obtain improved function following BTX-A injections, physical therapy may be paramount in helping clients recognize their newly found skills. The role of physical therapy following BTX-A injections is an area that warrants additional research.
CHAPTER 1
INTRODUCTION

Spasticity is an intriguing phenomena which spans an array of diagnoses and ages. It can be one of the most challenging problems for patients with neurologic conditions such as cerebral palsy, spinal cord injuries, cerebrovascular accidents, multiple sclerosis, traumatic brain injuries, etc.¹ Glenn and Whyte¹ describe spasticity as a

"...syndrome associated with a persistent increase in the involuntary reflex activity of a muscle in response to stretch. Four specific phenomena may be variably observed in the constellation of spasticity: hypertonia (frequently velocity-dependent and demonstrating the "clasp-knife" phenomenon), hyperactive deep tendon reflexes, clonus, and spread of reflex responses beyond the muscle stimulated."

The primary consequence of spasticity is abnormal postural tone, a phenomena resulting in an exaggerated array of spontaneous motor activity.² Spasticity may ultimately lead to a wide variety of problems including decreased mobility, decreased quality of movement, interference with normal postural reactions, interference with functional activities, and development of pressure sores.³
Experimental studies in animals suggest that the tone increase associated with spasticity may interfere with longitudinal muscle growth and cause sustained reduction of the anatomical muscle length. This may result in the conversion of dynamic contractures to fixed permanent contractures.

Although the characteristics and causes of spasticity differ across various neurologic conditions, the ultimate goal for rehabilitation professionals is to maximize overall functional performance for individuals with abnormal postural tone. Abnormal postural tone refers to the "abnormal reflexes and neuromuscular signs associated with impaired movement." To maximize function, Perry contended that rehabilitation must emphasize the following areas: (1) contracture minimalization, (2) realistic planning, (3) muscle-strength preservation and restoration, (4) enhancement of returning control, (5) substitution for permanent functional loss. Therapeutic approaches include casting, splinting, positioning, physical modalities, motor learning/relearning, orthopaedic procedures, etc.

Physicians focus on the development of effective treatments for spasticity. Active function will assumingly increase with reduction of spasticity, as long as the treatment does not produce overwhelming weakness, paralysis, fatigue and/or muscle atrophy. With effective management of spasticity, soft tissue contractures can also be prevented. Existing procedures utilized by physicians include pharmacological management (oral baclofen, diazepam, benzodiazepine, sodium dantrolene, phenothiazine), neurosurgical procedures (anterior and posterior rhizotomy, selective posterior rhizotomy, cordotomy, intrathecal chemotherapy),
phenol or baclofen injections, and nerve blocks.\textsuperscript{1,3}

It has been argued that the treatment procedures currently being employed are unsatisfactory in the successful management of spasticity. Medications often produce harmful side effects such as sedation and generalized weakness, and cannot be used to selectively reduce harmful spasticity in one muscular area while preserving useful spasticity in another.\textsuperscript{6-9} Neurosurgical procedures and nerve blocks are invasive, non-selective, irreversible, and there is a chance that the spasticity will re-occur. Intrathecal phenol injections are non-selective, and complications may include incontinence, paresthesia, excessive weakness, and even death.\textsuperscript{10} The conservative techniques utilized in physiotherapy to control spasticity are often unsuccessful and temporary.

Physicians and therapists question whether the reduction of spasticity automatically results in improved functional performance.\textsuperscript{2} For example, many children with cerebral palsy continue to move using irregular movement synergies even after they have undergone selective posterior rhizotomies. If a treatment is successful at reducing spasticity but does not increase functional performance, critics question its legitimacy. An easily administered treatment which successfully controls spasticity \textit{and} increases functional performance is desired.

Since the late 1970's, the use of botulinum toxin (BTX-A) injections to decrease spasticity has been investigated.\textsuperscript{11} It was originally proposed for the correction of strabismus, and is now considered the drug of choice for treatment of the following conditions: hemifacial spasm, torticollis, essential blepharospasm, and spastic
dysphonia. Additional pathologies that are managed with BTX-A injections include spastic torticollis, postural tremors, focal dystonias, and other limb dystonias. Possible advantages of intramuscular BTX-A injections for the management of spasticity include the lack of sensory effects, ability to target specific muscle groups, ability to weaken muscles in a graded fashion, and absence of caustic chemicals.

The purpose of this paper is to review research studies involving the use of botulinum toxin injections for the management of spasticity arising from central nervous system dysfunction. This will enable the researcher to address the following issues: (1) the effectiveness of BTX-A in decreasing spasticity, and (2) improvements in functional performance due to this decrease. Functional performance includes, but is not limited to, increased mobility, increased quality of movement and increased independence in activities of daily living.

This study closely follows the format utilized by Campbell et al, regarding the effects of intrathecally administered baclofen on function in patients with spasticity. Campbell et al utilized a model developed at the National Center for Medical Rehabilitation Research (NCMRR) to determine the functional effects of intrathecally administered baclofen. The dimensions of the NCMRR model include: (1) pathophysiology, (2) impairments, (3) functional limitations, (4) disabilities. The effects of BTX-A will be examined utilizing these four dimensions of the NCMRR model. A review of the literature on BTX-A injections will be conducted and arranged according to the four dimensions developed by the NCMRR.
CHAPTER 2

PATHOPHYSIOLOGY

Pathophysiology of Spasticity

The NCMRR model describes pathophysiology as the "cellular and molecular process of injury or disease pertinent to a particular condition". The pathophysiology of spasticity is complex and varies among neurological conditions. Spasticity is a distinct type of hypertonia in which there is a velocity-dependent opposition to the passive movement of muscles. The faster the muscle is stretched, the more resistance is encountered. Spasticity results from the reorganization of spinal cord reflexes released from the brainstem or cortex, and is due to disease and/or injury to the central nervous system. In the individual without spasticity, the nervous structures within the pyramidal tract exert monosynaptic control over anterior horn cells for refined movements, and influence tone through actions on brainstem nuclei. Thus, the brainstem, which is primarily responsible for unrestrained, primitive reflexes, is controlled through the intricate actions of the motor cortex, basal ganglia, and cerebellum. These areas are no longer in control in the individual with spasticity, resulting in partial or entire brainstem dominance.
If brainstem dominance occurs, and primitive reflexes are uninhibited, the stretch reflex arc becomes deprived of its normal supraspinal modulation.6,13 This results in pathological overactivity in stretch reflex circuits (i.e. exaggerated stretch reflexes). For reasons not completely understood, sensory inputs and lack of supraspinal control result in excessive activation of alpha motoneurons controlling muscle contraction.2 Hypertonic muscles are the result of this activation.

Theoretically, drugs which can be used to interfere with the abnormal reflex arc and depress excessive activity of the muscle fibers are desirable.13 However, side effects and long-term effects must be taken into careful consideration.13 Functional performance can be hindered by those antispasticity drugs producing weakness, paralysis, fatigue and/or muscle atrophy.

Characteristics and Actions of Botulinum Toxin Type-A (BTX-A)

Ingested orally, botulinum toxin causes fatal neuromuscular paralysis and is one of the most potent biological poisons known.15 The botulinum toxin utilized commercially, Oculinum, is derived from the type A strain of Clostridium Botulinum.16 These gram-positive, rod-shaped, spore-forming, anaerobic bacteria are a family of serologically related neurotoxins including A, B, C1, D, E, F, and G.17 Clinically, the unit dose of BTX-A is based on a mouse LD50 equivalent, that is, the amount of toxin which kills 50 percent of a group of 18-20 mice.17,18 Each vial of BTX-A contains 100 mouse units (MU) which is the median lethal dose for a 20 gram Swiss Webster mouse. On the basis of data obtained in monkeys, it has been
estimated that the lethal dose for humans is 625 to 6,250 MU for an adult weighing 110 lbs. There have been no reported instances of systemic toxicity resulting from injections of botulinum toxin.

During the 1970's, extensive research was conducted on botulinum toxin leading scientists to a better understanding of its mechanism of action. It was recognized that the type A toxin could be utilized clinically to selectively paralyze muscles. In fact, scientists discovered it produced a long-term blockade that was very similar to surgical denervation, causing muscle paralysis, atrophy, and electromyographic abnormalities.

Early studies conducted by Drachman and Price focused on quantifying the mechanism of action of botulinum toxin. They discovered that "the action of botulinum toxin is not due to deficient storage of acetylcholine in vesicles or blockade of calcium entry into nerve terminal. Studies suggest that the toxin interferes with the acetylcholine process itself, possibly by blocking exocytosis at the release sites." It is now known that BTX-A acts by inhibiting presynaptic acetylcholine release at the cholinergic nerve terminals without destroying nerve endings, nerve terminals, or neuromuscular junctions.

To thoroughly explain how BTX-A produces its paralyzing effects, it is necessary to review normal neuromuscular conduction. Normal neuromuscular conduction involves the following steps (see Fig. 1): (1) depolarization of the alpha motoneuron causing propagation of an action potential down the nerve axon, (2) conduction of the action potential to the nerve telodendria, which has vesicles
Fig. 1 - "Normal" nerve conduction (adapted from Mohr\textsuperscript{19}). A, shows depolarization of the alpha motoneuron causing propagation of an action potential (AP) down the nerve axon; B, conduction of the AP to the nerve telodendria, which has vesicles storing the acetylcholine (ACh) neurotransmitter; C, influx of calcium into the telodendria causing binding of vesicles to the presynaptic membrane; D, ACh release into the synaptic cleft which binds to receptors on the motor end plate membrane. This causes a motor end plate potential and a muscle AP is generated.
storing the acetylcholine neurotransmitter, (3) influx of calcium into the telodendria causing binding of vesicles to the presynaptic membrane, (4) release of acetylcholine into the synaptic cleft, which binds to receptors on the motor end plate and causes a motor end plate potential, and (5) generation of a muscle action potential with ultimate contraction of the muscle. The inhibitory action of botulinum toxin is believed to occur in three steps (see Fig. 2): (1) irreversible and rapid binding of the toxin to specific presynaptic receptors on the peripheral cholinergic synapses, (2) internalization of the toxin-receptor complex across the presynaptic membrane, and (3) inhibition of acetylcholine release by disrupting the calcium ion-mediated release of acetylcholine. Consequently, BTX-A effectively reduces hyperactivity, producing a functionally denervated muscle, and decreases the excessive alpha motoneuron activity which is responsible for spasticity.

The results of a study conducted by Shaari and Sanders provided evidence that injecting BTX-A at or near the motor end plate region of the muscle produces the most effective paralysis. Maximal paralysis of the spastic muscle occurs several days after injection. The resulting paralysis is dose-dependent and reversible over time, thus, repeat injections are required. The action of botulinum toxin persists for approximately three months in most conditions, with some reported effects lasting up to one year. It is believed that muscle recovery is due to intramuscular collateral axon sprouting, which plays a major role in re-establishing the integrity of neuromuscular transmission. Botulinum toxin binds rapidly to the receptors at the neuromuscular junctions of the target muscles, therefore, little or no systemic
Fig. 2 - Mechanism of action of botulinum toxin (adapted from Koman16); A shows irreversible binding of botulinum toxin (BTX-A) to specific presynaptic receptors on the peripheral cholinergic synapses; B, internalization of the toxin-receptor complex across the presynaptic membrane; C, the inhibition of ACh release by disruption the calcium ion-mediated release of ACh.
absorption of the toxin occurs.\textsuperscript{18}

Scott\textsuperscript{21} was the first to utilize BTX-A therapeutically. After conducting initial experiments on non-human primates, he successfully employed BTX-A injections in the nonoperative management of strabismus.

The National Institute of Neurological Disorders and Stroke, and the Office of Medical Applications of Research of the National Institutes of Health, convened a consensus development conference to officially evaluate the clinical uses of BTX-A therapy in November 1990.\textsuperscript{22} After presentations and discussions by experts in the field of botulinum toxin therapy, the panel issued a statement which covered the following areas: mechanisms of action, indications and contraindications, safe and effective uses, side effects and complications, and further research needs. The panel emphasized that botulinum toxin therapy is an invasive, potent, irreversible treatment, and should only be administered by licensed, experienced physicians. Contraindications to its use include allergy to the drug or infection/inflammation at the injection site(s). Side effects to BTX-A are usually transitory, well tolerated, and treatable.
CHAPTER 3
RESEARCH CONDUCTED ON BOTULINUM TOXIN'S EFFECTS ON IMPAIRMENTS

The NCMRR model described impairments as "derangements of organs and organ system functions that directly result from the injury or disease process." Most of the studies conducted on botulinum toxin described its effects on the musculoskeletal system, specifically, its effects on abnormal postural tone. This included spasticity, pain as a result of spasticity, range of motion, strength, uncontrolled and abnormal movements, spasms, and extremity positioning.

Botulinum Toxin's Effects on Spasticity, Spasms, Pain, and Uncontrolled Movements

Das and Park were the first to study the effects of botulinum toxin injections on spasticity. The Oswestry scale (see Table) was utilized to determine whether eight patients with post-stroke spastic hemiplegia had decreased upper extremity spasticity after injection of BTX-A into the following muscles: biceps, flexor digitorum profundus and flexor carpi ulnaris. The Oswestry scale was designed to be administered by experienced physical therapists. The patients responded well to
Clinical Rating Scales

Oswestry Scale
0 - solely spasticity, no willed movement possible
1 - very severe spasticity, movement very poor
2 - severe spasticity, movement poor
3 - moderate spasticity, movement fair
4 - mild spasticity, movement good
5 - no spasticity, movement normal

The Degree of Adductor Tone
0 - no increase in tone
1 - increased tone, hips easily abducted to 45 degrees by one person
2 - hips abducted to 45 degrees with mild effort
3 - hips abducted to 45 degrees by one person with major effort
4 - two people required to abduct the hips to 45 degrees

Modified Ashworth Scale
0 - no increase in tone
1 - slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion and extension
1+ - slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM.
2 - more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
3 - considerable increase in muscle tone, passive movement difficult
4 - limb rigid in flexion or extension

Spasm Frequency Scale
0 - no spasms
1 - 1 or fewer spasms per day
2 - between 1 and 5 spasms per day
3 - 5 to less than 10 spasms per day
4 - 10 or more spasms per day, or continuous contraction
the injections, and were affected most noticeably at the flexor digitorum profundus. One patient increased from a score of "1" on the Oswestry scale to a score of "4". Another patient increased from a score of "2" to a score of "5".

Aside from the research conducted by Das and Park\textsuperscript{23}, few studies focused specifically on the effects of botulinum toxin injections to decrease upper extremity spasticity. Memin et al\textsuperscript{11} injected BTX-A into the upper extremity muscles of eight patients with severe, longstanding spasticity. Although no formal spasticity scale was utilized, all eight of the patients experienced a subjective decrease in spasticity, and reported that this decrease in tone was "beneficial". Utilizing a visual analog scale, five patients reported significant pain relief due to decreased spasticity.

Snow and colleagues\textsuperscript{4} were the first to conduct a double blind study evaluating the effects of BTX-A. The spastic adductor muscles of nine patients with multiple sclerosis were injected. Two physicians independently assessed the patients utilizing the Degree of Adductor Tone Scale devised by the researchers (see Table). The results indicated that BTX-A toxin significantly reduces leg adductor spasticity in multiple sclerosis (p = 0.009). This decrease in spasticity resulted in a significant improvement in the ease of nursing care (p = 0.009). In two patients, one nurse was able to perform care that required two nurses before injection. In another patient, a chronic perineal excoriation became accessible to treatment and was successfully healed.

Benecke\textsuperscript{25} found similar results in his study of 14 patients with multiple sclerosis. The patients had prominent, disabling spasticity of their adductor muscles and were
chair-bound or bed-bound. Following the first BTX-A injections, spasticity, spasms and pain were significantly decreased (p < 0.001). The pain scores, based on a subjective scale ranging between 0 (no pain) and 3 (severe and continuous pain), were profoundly decreased. The global functioning score, calculated by summing patient scores for spasticity, spasms, and pain for all patients, improved significantly following BTX-A injection (p < 0.001).

The majority of researchers studying BTX-A employed the modified Ashworth scale\textsuperscript{26} (see Table) to measure and report patient spasticity scores before and after toxin injection. In a study conducted on 10 patients with spastic drop foot, eight patients had decreased spasticity in the injected calf muscles by one to two points.\textsuperscript{27} Four of these patients who complained of pain became pain-free after the injections. In another study, the soleus, tibialis posterior, and both heads of the gastrocnemius muscles were injected in 12 patients with plantar flexor spasticity.\textsuperscript{28} Eighty-three percent of the patients experienced a reduction of calf muscle spasticity after injection, and six of the subjects had decreased achilles tendon clonus. An ankle foot orthosis was no longer needed by one patient and was used to a lesser degree in four subjects.

The results from a study of 12 patients with upper and lower extremity spasticity indicated that every patient who was injected (eight patients in the lower extremity muscles, four in the upper extremity muscles) demonstrated a "significant reduction of tone" based on the Ashworth scale.\textsuperscript{29} These patients also experienced improvements of movement and posture, and five patients with severe painful
spasms noted a decrease in the number and intensity of the spasms. Konstanzer et al\textsuperscript{30} found similar results; 10 of the 11 patients injected with the toxin showed an increase of at least one point on each of the following: Ashworth scale, pain scale, and hygienic scale (see Table).

Case studies were utilized by two researchers to illustrate the effectiveness of BTX-A. Borg-Stein et al\textsuperscript{3} provided case studies of two patients with chronic progressive multiple sclerosis. Subject one had severe adductor spasms which interfered with sleep and caused scissoring during standing. Oral baclofen and dantrolene sodium provided only limited relief of the patient's spasticity. Two months after BTX-A injection, the patient reported no more spasms at night. The subject's adductor tone, based on the Degree of Adductor Tone Scale, decreased from a "4" to "2" (see Table). The patient's spasm frequency score decreased from a "3" to a "1" (see Table).\textsuperscript{7} Polo and Jabbari\textsuperscript{12} reported a case study involving a patient with "painful cramping" and involuntary movements of the left thigh, which were refractory to a wide range of therapeutic treatments. The patient experienced a complete control of pain, a notable reduction of abnormal leg movements, and a distinct decrease of the burst discharges on the EMG for five months following BTX-A injection into the left quadracep region.

The largest series of cases studied was reported recently by Dunne et al\textsuperscript{31} Forty patients with moderate to severe spasticity of the upper or lower limbs who were unresponsive to conventional physical and medical treatments were injected with BTX-A. Clinical videotape assessments of spasticity were utilized and outcome
measures included Ashworth spasticity and spasm frequency scales (see Table). The mean change in the Ashworth spasticity score and the spasm frequency scale was 1.2 and 2.4 respectively, which indicated a significant decrease in spasticity and muscle spasms ($p < 0.0001$). Pain was reduced in 28 of the 31 patients. Overall, a worthwhile benefit occurred in 85% of the patients, and these patients expressed the desire to receive the treatment again if necessary.

Recently, several research studies have focused on the effectiveness of botulinum toxin injections for children with spastic cerebral palsy.$^{4,32,33}$ Cosgrove et al$^4$ studied 26 subjects with cerebral palsy, and found that tone was clinically decreased in the injected muscles (calves and hamstrings) in all but one patient. One child with athetosis had a marked reduction in uncontrolled movements, and his parents and physiotherapists reported decreased athetosis in his other limbs as well.

Koman et al$^{32}$ divided 27 pediatric patients with cerebral palsy into the following groups: three non-ambulatory patients with painful paraspinal spasticity which interfered with sitting balance, eight non-ambulatory children with lower extremity spasticity which interfered with positioning and hygiene, and 16 ambulatory patients with spastic hemiplegia or diplegia. The two groups of non-ambulatory patients were injected with BTX-A to decrease spasticity in order to reduce pain and to facilitate positioning and hygiene. The last group of patients were injected with the toxin to improve their gait. Caregivers reported that the children with painful paraspinal muscle spasticity "rested more comfortably and could be positioned
more easily after the BTX-A injections." Pain was reduced in all three children. The eight children with lower extremity spasticity exhibited markedly reduced spasticity and improved positioning. One patient who could not tolerate bracing before the injection was successfully braced after the injection.

Calderon-Gonzales et al\textsuperscript{33} utilized the Ashworth scale to quantify the change in spasticity after BTX-A injection. Fifteen children with cerebral palsy were included in the study, and it was found that the post-injection scores of muscle hypertonia were significantly lower (P < 0.01) than the pre-injection spasticity scores. The decrease in hypertonicity persisted for four to six months. The movements most significantly changed were hip adduction and knee flexion. Calderon-Gonzales and colleagues suggested that in a young child, selective BTX-A injection may allow sufficient time to regain muscle length before spasticity returns, thus preventing contractures and deformities.

**Botulinum Toxin's Effects on Passive Movement, Active Movement, and Strength**

Along with a decrease in spasticity, many patients experienced an increased range of motion in muscles injected with BTX-A.\textsuperscript{4,5,23,27,31,33,34} Das and Park\textsuperscript{23} found that all eight of their subjects had increased elbow and wrist active and passive range of motion after injection. One patient gained an additional 110 degrees of active and 160 degrees of passive motion at the elbow joint. Wall et al\textsuperscript{34} also studied the effect of BTX-A on upper extremity range of motion. Specifically, the potential of BTX-A for the treatment of the thumb-in-palm deformity in patients with cerebral
palsy was studied. Silhouette tracings were utilized to show that increased hand range of motion after injection improved the hand positions in all five patients. Although these patients had decreased grip strengths initially after the injection, their grip dynamometry scores actually surpassed baseline levels by day 112.

Increased passive mobility has been anecdotally reported following injection of botulinum toxin in two studies involving children with cerebral palsy. Following BTX-A injection into the calf muscles of 23 children, Cosgrove et al determined that 74% of their patients had increased passive ankle dorsiflexion, with younger patients displaying a greater increase than the older patients. In the same study, 21 hamstring muscles of 14 patients were injected with BTX-A and, on average, an extra 20 degrees of passive extension was gained at the knee (p < 0.01). Calderone-Gonzalez and colleagues found similar significant increases of passive range of motion (p < 0.001) in their patients after BTX-A injections.

Dunne and colleagues used goniometer measurements and blinded videotape assessments to determine increases of passive and active lower extremity range of motion after BTX-A injection. Goniometer measurements showed a significant increase in passive range of joint motion (p < 0.0001), with an average gain of 28 degrees. Blinded videotape assessments were based on a zero to four point scale (zero = limb rigid in flexion; four = normal), and indicated significant improvements in both passive range of motion (p < 0.0001) and active range of motion (p < 0.0002). Seventy-five percent of the patients showed at least a one grade improvement in passive range of joint motion. Improved active movement
scores in the lower limbs influenced personal hygiene, transfers, walking, and allowed for more comfortable limb positioning.

Researchers have hypothesized that resolving lower extremity spasticity will consequentially increase voluntary range of motion and have a variety of positive results, however, few studies have systematically evaluated the effects of botulinum toxin on active voluntary movement.² Cosgrove and colleagues⁴ utilized gait analysis to determine the effect of BTX-A on active movement. Following injection of BTX-A into spastic calf muscles, there was an average increase of 11 degrees of active dorsiflexion (p < 0.05). This improvement of active dorsiflexion allowed better ground clearance and more normal patterns of ankle kinematics during gait. Following injection of BTX-A into 21 spastic hamstring muscles, patients were able to fully extend their knees during late stance. The differences between active knee extension before and after injection proved significant (p < 0.01), and there was a mean 22 degree gain in knee extension.

Dengler et al²⁷ also evaluated the effects of BTX-A injections on active voluntary movement. Ten patients with spastic drop foot were treated, and passive and active range of motion values were taken before and after the injection using a goniometer. Seven patients showed an improvement of the drop foot position at rest and an increase in passive dorsiflexion. Of the patients who were assessed for freedom of active range of motion, four revealed an increase of active movement by an average of eight degrees. Four patients showed an improvement of resting supination position and nine showed an improvement of passive pronation in the
lower ankle joint. Four patients showed increased active pronation by an average of 11 degrees, and three patients had an increased range of active movement (supination-pronation) by an average of 10 degrees. Active supination was weakened by the toxin in the remaining three subjects.
CHAPTER 4
RESEARCH CONDUCTED ON BOTULINUM

TOXIN'S EFFECTS ON FUNCTIONAL LIMITATIONS

Functional limitations are defined as "problems with activities of the total body or body segments as a result of impairments; they may or may not be permanent, depending on the course or resolution of the inciting process." Numerous researchers have included anecdotal reports of changes in functional limitations as a result of BTX-A injection, including positive changes in gait, mobility and function, efficiency of transfers and positioning, and ease and efficiency of hygiene skills.

Botulinum Toxin's Effects on Gait

Several researchers have emphasized the changes in gait as a result of BTX-A injections. Hesse et al. provided the most comprehensive study of changes in gait. Gait analysis was utilized to focus on the following variables: velocity, cadence, stride, stance symmetry, swing symmetry, double support times, and force trajectories under the affected and non-affected foot. Following BTX-A injection, velocity, stride length, stance symmetry, and length of the trajectory under the...
affected foot improved significantly ($p < 0.01$). Cadence, double support times, and the trajectory under the non-affected foot also improved, but did not fulfill the chosen significance level of $p = 0.01$. Seven patients demonstrated better loading and push off of the affected limb, and nine patients demonstrated better initial contact of the affected limb. As a result of a longer stride length due to reduced ankle muscle tone, gait velocity notably improved by a mean of 27% for the patient group. The reduction of plantar-flexor spasticity improved the length of the force trajectories under both feet, and increased the progression of body and stride length during ambulation.

Mezaki et al$^{55}$ reported variable effects on the gait of three patients with spastic paraparesis following BTX-A injection. Two patients had improved gait, however, the effect was shortlived. Mezaki et al$^{55}$ attributed this transient effect to compensation by the non-injected muscles for the muscles which were weakened upon BTX-A injection. In the third patient, BTX-A injection into the quadriceps caused a weakness with exacerbation of gait disturbance. Borg-Stein et al$^{3}$ also found varied results. They discovered that following injection of the adductor muscles in a subject with a "classic" scissored gait pattern, the patient was able to walk between parallel bars without scissoring for the first time in several months. Two months later, however, the patient reported a new inability to walk between parallel bars, which was attributed to knee buckling.

Dunne and colleagues$^{31}$ reported that 10 patients had improved gait pattern and five patients returned to walking following BTX-A injections into lower extremity
musculature. Lindmark's modified motor assessment system\textsuperscript{36}, which assesses active movements, repetitive movements, and mobility of all limbs, was utilized to measure motor function. It was reported that following BTX-A injection, the mobility of 27 patients was significantly increased ($p = .007$). Dengler et al\textsuperscript{27} also noted improvements in gait after injection into the calf musculature of ten patients with spastic drop foot. The changes in stance and gait were evaluated by physiotherapists. Among the six ambulatory patients, three revealed a "remarkable" and two a "moderate" improvement in gait. This improvement in stance and mobility was attributed to the improvement of joint mobility following BTX-A injection.

All of the studies reviewed involving children with cerebral palsy included qualitative measures of gait before and after botulinum toxin injection.\textsuperscript{5,18,32,33} In two separate studies, Koman et al\textsuperscript{18,32} utilized several different measures to assess lower-extremity function including gait analysis, physical therapy evaluation, Biodex evaluation, physician rating scale (PRS), and parent/guardian questionnaire. Preliminary results indicated that all of the patients, except for one child with a fixed contracture, showed changes in tone of injected muscles. The PRS, which measures degree of crouch, degree of equinus foot, position of hindfoot, position of knee, speed of gait, and pattern of gait, increased from an average pretreatment score of 5.0 to an average post-treatment score of 10.3. This proved a significant increase ($p < 0.05$) and was indicative of improved gait dynamics. Koman and associates\textsuperscript{18} utilized a randomized double blind trial for the follow-up study.
Independent physical therapy evaluations of gait analysis films suggested that BTX-A treatment improved gait as compared to placebo injections. Biodex measurement proved to be an inappropriate evaluation tool for children with cerebral palsy. Post-treatment PRS scores showed an improved gait pattern in 83% of the patients, and the parents/guardians of four of the six children receiving toxin reported that their child's gait had improved during the trial.

Cosgrove and colleagues utilized electrogoniometric measurements of sagittal plane kinematics at the hip, knee, and ankle to assess gait in children with cerebral palsy. Nine of the 19 patients who had potential for gait improvements experienced a one to two-level progression in ambulatory status. Three patients who were classified as "non-functional" ambulators became "functional" ambulators. After six months, six patients continued to have a higher ambulatory status than before the toxin injection. Resolution of spasticity with injection into the calf and hamstring musculature allowed for better clearance of the foot during the swing phase of gait and increased extension of the knee during the stance phase of gait. Calderone found similar results in three children who received injections into their gastrocnemius muscles. These patients were able to achieve active heel-strike during gait.

**Botulinum Toxin's Effects on Mobility and Function**

Several research studies included data on the effects of botulinum toxin on mobility and function. Utilizing the Barthel index, which was developed to assess functional independence before and after treatment, Das and
Park\textsuperscript{23} recorded the functional abilities of a sample of ten patients with spasticity associated with stroke-related hemiplegia. The test was given every two weeks post-injection, and repeated measurements showed "some" improvement of functional status. Increased independence in self-care and mobility skills in six patients was also observed. The majority of patients increased their pre-injection Barthel index score by 10 - 15%.

Hesse et al\textsuperscript{28} employed the Rivermead Mobility Index (RMI) to assess leg and trunk motor function pre- and post-botulinum toxin injection. The RMI is an evaluation tool used to measure physical recovery and progress following a stroke. Two weeks after the injection, the Rivermead score increased by one point in three patients and by two points in one patient. One patient was able to tap with the non-affected foot five times while standing on the affected foot. Two patients could achieve dorsiflexion of the ankle with the knee partially flexed and two could achieve this with an extended knee.

Wall and colleagues\textsuperscript{34} utilized comprehensive videotape assessments to determine if BTX-A injections in patients with cerebral palsied hands improved gross and fine motor functions. Function of the affected hand was compared with function of the unaffected hand in the following tasks: tube transfer pronated, barrel opening, card transfer, peg transfer, and overall function. Appearance of the hands was judged from still photographs in five standard positions including: (1) prone, (2) midposition, (3) attempted supination, (4) maximum finger and thumb extension in prone position, and (5) fisted. The overall functional and cosmetic improvement
gained after BTX-A injection was found clinically significant ($p = 0.06$), and persisted throughout the follow-up time of 229 days. "Overall function" and "overall appearance" were increased by as much as 43% and 64% respectively, and were expressed as percentages compared to the function and appearance of the unaffected limb. Parent and teacher reports indicated that the subjects increased the spontaneous use of the affected hand both at "work" and at play. Wall et al concluded that even if re-injection was required on an annual basis to attain constant chemodenervation, BTX-A injection of the adductor pollicis is a safe, appropriate alternative to surgical release.

Calderone-Gonzales et al and Cosgrove et al reported the effects of BTX-A injections on functional outcomes in patients with cerebral palsy. Calderone-Gonzalez and associates measured the functional improvements of six patients on the basis of their upright standing positioning. Six children who demonstrated severe scissoring during standing were injected in their adductor muscles. The scissoring tendency during standing "practically disappeared" in all six children. Six children were injected in their knee flexor muscles and were able to straighten their knees fully. Likewise, their body posture improved due to a more upright trunk and reduced hyperflexion of the hip. Two patients improved in their weight bearing ability and were able to initiate unassisted gait. One patient who was injected in the posterior tibial muscle improved in varus deviation by 80%, and another patient who was injected in the wrist flexor muscles was able to place his hand flat on the table with wrist dorsiflexion. This enabled the patient to tolerate a wrist brace for the first time.
Cosgrove and colleagues\textsuperscript{4} provided subjective data to illustrate the functional changes of 26 patients with cerebral palsy. Fourteen children were reported by their parents to have displayed "marked" functional improvement, 10 reported a "moderate" improvement, one reported "no change", and one reported a "moderate deterioration". Based on subjective reports, 92\% of the children experienced a functional gain following BTX-A injection.

Borg-Stein et al\textsuperscript{3} reported a case study describing the functional gains experienced by a patient whose right hamstring musculature was injected with BTX-A. During the eight month interval following injection, her short sitting ability increased from five-and-a-half minutes of static sitting with assistance to more than 30 minutes of sitting while performing dynamic upper extremity activities.

**Botulinum Toxin's Effects on Ease and Efficiency of Transfer Skills, Positioning, and Hygiene Skills**

Following a pilot study conducted on two patients with severe leg adductor spasticity, Snow and colleagues\textsuperscript{7} found that injection of BTX-A is a useful adjunct in overall nursing care. They concluded that botulinum toxin is potentially more beneficial for patients with isolated muscle contractions than "traditional" systemic drug treatment. Potential applications include: treatment for patients with adductor spasticity making care of the perineum difficult, treatment for patients at risk of soft-tissue necrosis between the legs, and treatment for patients with flexion and adduction of the hip causing necrosis over the femoral head.

Konstanzer and colleagues\textsuperscript{30} utilized the hygienic rating scale to determine the
efficacy of botulinum toxin injections. Ninety-one percent of the patients injected experienced an improvement of at least one point in hygienic scales. Memin et al\textsuperscript{11} concluded that "most of the patients reported a benefit in their limb tone and referred to a subjective improvement in the activity of daily life and nursing following injection". Borg-Stein et al\textsuperscript{3} discussed a patient who experienced increased ease of abduction for catheterization, and became independent in cleaning and catheterization.

The effects of BTX-A injections on the ease of positioning and transfers was reported by several researchers.\textsuperscript{3,12,32} Koman and colleagues\textsuperscript{32} found that the three children injected with BTX-A into spastic paraspinal musculature rested more comfortably and could be positioned more easily. The nonambulatory children with spastic lower extremities also experienced improved and more comfortable positioning post-injection. Borg-Stein et al\textsuperscript{3} discussed a patient whose spasms inhibited effective transfers. Eight months following BTX-A injection into the right hamstrings, the patient progressed from use of a Hoyer lift to sliding board transfers with assistance. However, following injection of BTX-A into the bilateral hip adductors, the subject noted increased difficulty with hip flexion in preparation for bridging. Polo and Jabbari\textsuperscript{12} described the effective treatment of an unusual movement disorder with injection of BTX-A. Reduction of the constant movements experienced by a patient with painful limb myoclonus enabled easier extremity positioning and improved rest.
CHAPTER 5

BOTULINUM TOXIN'S EFFECTS ON DISABILITY IN ROLE FUNCTIONS

The NCMRR model defines "disabilities" as "difficulties in fulfilling the typical role functions of daily life in the home, school, workplace, and community." The studies reviewed did not attempt to measure changes in quality of life, or report the decline of disability in carrying out life roles in the home and community. Some studies did, however, provide an anecdotal account of individuals who experienced an increase in ability to participate in daily life role functions.

Das and Park used the Barthel index to assess improvements in self-care independence in eight patients injected in their upper extremity musculature. Six patients experienced greater independence in activities of daily living and self-care, enabling them to more effectively carry out "typical" role functions.

Grazko and colleagues offered two accounts of patients whose daily life role functions changed after receiving BTX-A injections. First, a patient with traumatic paraplegia complained of severe muscle spasms in the lumbar paraspinal region causing reoccurring back pain. The patient was injected between the first and fifth lumbar paraspinous muscles, where increased tone was located. The patient's spasms were reduced significantly, from more than 10 spasms per week, to between two to five spasms per week. Following four injections of BTX-A in a three month
period, the patient demonstrated an "improvement in lifestyle". Second, a bedridden patient with advanced multiple sclerosis had severe spasticity of lower-limb musculature. Based on results from the Degree of Adductor Tone Scale (see Table), BTX-A injections decreased the patient's adductor tone from a "4" to a "2", and enabled her to wear an adductor brace for the first time. The patient could then sit upright in a chair, which had not been previously possible for several years.

Increased independence in life activities was described by several researchers.\textsuperscript{3,4,31} Borg-Stein et al\textsuperscript{3} discussed a patient who became more independent in basic transfers after injection with BTX-A. Dunne et al\textsuperscript{31} reported that treatment with BTX-A enabled five patients to walk again, thus encouraging greater independence. Cosgrove et al\textsuperscript{4} discussed a patient with athetoid cerebral palsy who had particularly satisfying results after injection into the tibialis posterior muscle. Preceding injection, the patient was unable to ambulate because of a dynamic equinovarous deformity with forefoot adduction. Following injection, the patient became able to position his foot plantigrade, producing a stationary foot for weight-bearing and allowing independent ambulation for the first time.
CHAPTER 6
DISCUSSION AND CONCLUSION

Discussion

Clearly, injection of BTX-A into spastic muscles has been demonstrated to decrease spasticity and hypertonia for the majority of individuals with multiple sclerosis, cerebral palsy, spinal cord injury, spastic paraplegia, and spastic hemiplegia. Based on the results obtained from a majority of studies, researchers found significant decreases in spasticity based on qualitative data utilizing measures such as the Oswestry scale, Degree of Adductor Tone Scale, and Ashworth scale. This decrease in spasticity subsequently caused increased active and passive range of motion, and decreased pain and uncontrolled movements in several cases.

To further our understanding of BTX-A and its effects on patients with spasticity, it is necessary to go beyond the impairment dimension and the mere assessment of movement using single-joint analysis. Patients often face the reality of their impairments in the dimensions of functional limitations and disability, which few researchers have considered in their studies. Several studies have attempted to prove statistically that BTX-A injections improve gait and mobility, however, more double-blind, placebo-controlled studies are necessary in these areas to quantify the effects and validate the cost effectiveness of BTX-A treatment.
Two of the studies reviewed utilized intricate gait analysis techniques to quantify the difference in gait dynamics following BTX-A injections.\textsuperscript{4,28} Both studies indicated substantial changes, enabling their patients to have more "normal" gait patterns. Other researchers attempted to quantify changes in gait dynamics utilizing a variety of measures, including the physicians rating scale, Lindmark's motor assessment, Biodex evaluation, and PT evaluation/observation. Many patients appeared to benefit from BTX-A injections, and demonstrated improved gait patterns, "easier" ambulation, decreased scissoring, increased ability to clear the foot during swing phase, increased ability to extend the knee and bear weight, and increased balance.\textsuperscript{3,27,29,31-33} Due to these positive preliminary results, researchers have suggested the need for randomized, controlled clinical trials and detailed documentation to define the proper role of BTX-A muscle injections in individuals with spasticity.

The effects of botulinum toxin on disability in role functions is an area which has been neglected in research studies. Few studies have mentioned the changes in quality of life or the increased ability in carrying out life roles. This is an important area to examine, and may help justify the use of BTX-A injections as a viable, validated treatment. Of significant importance is quantifying the influence of decreased impairment on the dimensions of function and disability. Hence, information from these dimensions can be combined to expand our understanding of the problem of spasticity and the effects of its resolution.\textsuperscript{2}

Critics of BTX-A therapy caution that before it is promoted as a "dramatic
breakthrough for patients with spasticity, larger randomized controlled trials are needed.\textsuperscript{37,38} Bleck\textsuperscript{37} questioned how long patients can be cajoled into accepting repeated injections over a period of a year or more. Neville\textsuperscript{38}, professor of pediatric neurology, wrote recently on the use of botulinum toxin for children with cerebral palsy:

"If (further studies) confirm benefit, then botulinum toxin could find several uses in the treatment of the cerebral palsies. These include the modification of early patterns of axial asymmetry that may influence later development of the spine and hips. It could be used early to modify the effects of spasticity on soft tissue and bone, thereby reducing the extent of later surgery. It could also be used to mimic the effects of possible surgical procedures. It could provide a time window for physical, including orthotic, interventions...and it could be used to treat focal dystonias within the cerebral palsies, for which surgery has gained such a bad reputation...Botulinum toxin is expensive and requires further studies combining careful clinical and biomechanical delineation of specific problems and methodological rigor."

During the consensus development held by The National Institute of Health (NIH), suggestions were made for further areas of research for BTX-A treatment.\textsuperscript{22} These included continued research in the following areas:
"1. Study of the general properties of botulinum toxin including: mechanism of action, metabolism and catabolism, mechanisms of recovery from paralysis, the target receptors, pharmacology of other serotypes, antidotes and blocking techniques, techniques to increase the specificity and duration of action, stability and consistency of pharmaceutical preparations.

2. Study of the indications for botulinum toxin treatment including: efficacy and safety through controlled clinical trials that use reliable outcome measures, optimal measures of clinical benefit, long-term and remote effects, does/response relationships and dose schedules, causes of primary failure, causes of secondary failure, pathophysiology of the diseases treated, physiology of spasm reduction in regional muscles that are not directly injected.


4. Study of the technique of injecting and handling of botulinum toxin including: effects on location, dose, concentration, and volume on response; dose selection based on objective physiologic or anthropometric parameters; the value of EMG for diagnosis, localization of the site(s) of administration, and control of dose.
5. Study of the side effects and complications of botulinum toxin treatment including: antibody formation and its implications, long-term consequences of repeated injection, the variability in sensitivity to injection among different patients and difference muscle groups in an individual patient, the mechanism of undesirable regional effects, valid and reliable parameters for assessment of outcome, systemic effects."

The NIH emphasized that although botulinum toxin may help decrease the negative effects of neurological symptoms (i.e. spasticity, uncontrolled movements, etc.), it is not curative in nature.

**Conclusion**

Preliminary results from numerous studies have paved the road for additional investigations involving BTX-A injections for individuals with spasticity. The data accumulated from current research studies proved that botulinum toxin injections are successful in treating the impairments associated with spasticity. Therefore, research efforts need to be extended to the other dimensions of the NCMRR model such as the effects of BTX-A injections on functional limitations and on disability in role functions.

Research data has suggested that reducing muscle spasticity has the short-term benefit of improving function and the long-term benefit of improving longitudinal muscle growth. Although BTX-A injections may not permanently remove the prospect of surgical intervention, they may delay surgery until the patient is older
and at a lower risk for possible complications and recurrence of deformity. If patients are able to obtain improved function, physical therapy following injection of botulinum toxin may play an important role in helping clients recognize their newly found skills and maximize the use of these abilities. Physical therapy may be the key in helping patients gain benefit from botulinum toxin in the functional and disability dimensions, and is another area that warrants additional research.
REFERENCES


