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A Pilot Trial Comparing the Effects of Onabotulinumtoxina and Standard Oxybutynin Therapy as First Line Treatment for the Poorly Compliant Pediatric Neurogenic Bladder

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Graduate Program in Epidemiology and Biostatistics
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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A PILOT TRIAL COMPARING THE EFFECTS OF ONABOTULINUMTOXINA AND STANDARD OXYBUTYNIN THERAPY AS FIRST LINE TREATMENT FOR THE POORLY COMPLIANT PEDIATRIC NEUROGENIC BLADDER

(Spine title: Botulinum toxin versus oxybutynin in neurogenic bladder)

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A thesis submitted in partial fulfillment of the requirements for the degree of Master in Science

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The thesis by

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entitled:

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is accepted in partial fulfilment of the requirements for the degree of Master in Science

Date______________________________

Chair of the Thesis Examination Board
Abstract

Research question
Is it feasible to conduct a phase III RCT to compare OnabotulinumtoxinA injections to oxybutynin as primary therapy in pediatric neurogenic bladder?

Methods
Patients on a stable oxybutynin regimen were recruited for a pilot RCT and underwent randomization to either OnabotulinumtoxinA or continuation of oxybutynin. Primary outcomes included an a priori defined feasibility and acceptability assessment. Secondary outcomes included continence, urodynamic parameters, side effects and QOL.

Results
The study enrolled 8 subjects in the OnabotulinumtoxinA group and 6 in the oxybutynin group. The recruitment rate was 75% and the dropout rate was 6.6%. There were 2 minor protocol deviations. There were no side effects in the botulinum group compared to 66.7% in the oxybutynin group (p=0.02). The clinical and QOL outcomes were comparable.

Conclusion
It is feasible and safe to conduct a phase III trial to investigate the efficacy of primary OnabotulinumtoxinA compared to oxybutynin therapy.

Keywords: pilot studies, urodynamics, neurogenic bladder, oxybutynin, spina bifida
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LIST OF ABBREVIATIONS

SB: Spina bifida
DSD: Detrusor sphincter dyssynergia
DLPP: Detrusor leak point pressure
NDO: Neurogenic detrusor overactivity
NB: Neurogenic bladder
EBC: Expected bladder capacity
MCC: Maximum cystometric capacity
CIC: Clean intermittent catheterization
HRQOL: Health related quality of life
QOL: Quality of life
BTX: Botulinum toxins
BTX-A: Botulinum toxin A
RV: Reflex volume
MDP: Maximum detrusor pressure
U: Unit
BTX-B: Botulinum toxin B
RCT: Randomized controlled trial
PX2: Purinergic receptor
TRPV1: Transient receptor potential cation channel subfamily V member
P2X3: Purinoceptor 3
ATP: Adenosine triphosphate
CGRP: Calcitonin gene-related peptide
NGF: Nerve growth factor
UTI: Urinary tract infection
LUTS: Lower urinary tract symptoms
NNT: Number needed to treat
ICCS: International Children’s Continence Society
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Chapter 1

Introduction

1.1 OVERVIEW

Spina bifida (SB) is the commonest congenital disabling anomaly and its incidence ranges between 1.6- 4 per 1000 births in Canada [1]. Periconceptual maternal folic acid intake and earlier antenatal diagnosis leading to termination of pregnancy has led to a declining incidence of this congenital anomaly. Children with SB experience considerable medical and psychosocial problems related to their neurogenic bladder and bowel including urinary and fecal incontinence, constipation, recurrent urinary tract infections, risk of renal damage and scarring and need for multiple surgical interventions [2,3].

The primary urological abnormalities in children with SB include impaired bladder storage and emptying function and its detrimental effects on the upper renal tracts and achievement of urinary continence. The bladder pressure at which urethral leakage occurred during artificial filling of the bladder (cystometry), defined as the detrusor leak point pressure (DLPP), was described by McGuire et al as a useful predictor of renal damage on follow-up [4]. DLPP is now accepted as one of the important urodynamic parameters to characterize and prognosticate bladder function and its impact on upper urinary tract function. When DLPP exceeds 40 cm H₂O, glomerular filtration rate decreases and pyelocaliceal and ureteric drainage deteriorates leading to hydronephrosis and/or vesicoureteric reflux. One of the mechanisms of raised DLPP is detrusor sphincter dyssynergia (DSD), which leads to a functional outlet obstruction and raises the leak point pressure causing secondary renal damage [5]. Approximately 50 % of children with open SB will demonstrate DSD on urodynamic studies, which is strongly correlated with
presence of vesicoureteric reflux (VUR), a factor associated with recurrent urinary tract infections and a risk factor for renal damage [6]. Moreover persisting DSD can alter detrusor morphology and function over time leading to hypertrophy of the detrusor muscle and increased collagen deposition adversely affecting bladder storage pressures. These pathophysiologic changes affect the viscoelastic properties of the bladder leading to a small capacity non-compliant bladder with elevated filling pressures. These landmark studies led to the establishment of urodynamic studies in children to characterize bladder function in SB early and proactively to allow individualized therapy in high-risk patients [7-9].

The goals of urological management of SB associated neurogenic bladder (NB) include the maintenance of bladder filling pressures under 40 cm H₂O, ensuring complete and low pressure bladder emptying and achieving adequate bladder outlet resistance [9-10]. This will translate to preserved renal function, decrease the risk of VUR and urinary tract infections and achieve socially acceptable urinary continence.

Currently the standard urological care involves early urodynamic monitoring of bladder function with institution of anticholinergic therapy and clean intermittent catheterization (CIC). Oxybutynin is the standard anticholinergic medication used prescribed as an oral formulation or as transdermal patches in children with SB associated NB [11-15]. Oxybutynin acts by a direct spasmolytic action and anticholinergic (M3 selective receptor antagonism) action on smooth muscles of the bladder and intestine [12, 15]. Though the drug is safe and effective, it is associated with significant side effects like constipation and dry mouth. Children with SB and a neurogenic bowel are already predisposed to constipation, which in turn impacts bladder function and predisposes them to recurrent urinary tract infections. These side effects can significantly impact compliance to therapy and this in turn may be detrimental to renal function preservation in the long-term. In addition, the effects of oxybutynin may wean over time as the bladder deteriorates necessitating more invasive surgical options to maintain low bladder pressures.

Surgical interventions to achieve lower bladder storage pressures and continence include
intra-detrusor botulinum toxin injections, bladder augmentation and or bladder outlet procedures [10, 16-19]. Bladder augmentation, which involves using a patch of bowel to increase bladder capacity and lower filling pressures, is an effective surgical option. The ileum is the preferred bowel segment used but colon, stomach and demucosalized segments have been the other alternatives. Unfortunately, the exposure of urine to the bowel patch’s absorptive surface adds a new set of possible complications and morbidities like electrolyte and acid base balance disturbances, urinary tract infections, stone formation, risk of bladder perforation and malignancy [20]. Following adult studies, Schulte-Baukloh et al demonstrated the safety and efficacy of intravesical botulinum toxin injection in pediatric patients with NB [21]. Since then, several observational studies have confirmed the significant and impressive response of botulinum toxin injections in the NB population [22-34]. The current status of this mode of therapy is primarily limited to end stage bladders as an option to delay bladder augmentation.

This study proposes use of botulinum toxin intra-vesical injection as an alternate to standard oxybutynin therapy before this end stage bladder is reached. The rationale for this study is based on the safety and efficacy of botulinum toxin combined with the lack of anticholinergic side effects and the better urodynamic response plausible with a less fibrosed bladder. In addition, since the treating physician will be performing the botulinum toxin injection, compliance is ensured and the long-term deleterious effects of high bladder pressure on renal damage is prevented.

There are no pediatric randomized controlled trials (RCT’s), which have explored the clinical advantage of primary botulinum toxin A injections in neurogenic bladder patients and compared the urodynamic results and side effect profile with standard oxybutynin therapy. Given the expense and ethical considerations of a RCT, a pilot trial assessing feasibility and acceptance of a proposed protocol exploring this hypothesis is beneficial in planning a phase III study. In addition, due to the unavailability of effect sizes for a new indication for an existing intervention, the pilot trial provides an opportunity for sample size calculations, albeit with some caution.
1.2 HYPOTHESIS

It is feasible and safe to conduct a phase III trial to compare the efficacy of OnabotulinumtoxinA bladder injections as first line therapy to standard oxybutynin therapy for spina bifida associated neurogenic bladders.

It is further hypothesized that this phase II pilot trial will demonstrate that patient recruitment and retention goals, randomization, treatment and follow-up protocols and blinding of the assessor are feasible in a phase III trial. In addition, the trial will demonstrate the safety of using Botulinum toxin A injections in this population.

1.3 OBJECTIVES

Primary Objectives

The primary goals of this study are to assess the feasibility and acceptability of the study design and planned interventions for a subsequent RCT to compare primary botulinum toxin A intra-detrusor injections in pediatric neurogenic bladder patients to standard oxybutynin therapy.

Feasibility:

1. To report accrual rates (percentage of eligible patients consenting to participate in trial)
2. To assess feasibility of inclusion and exclusion criteria in selecting participants for the trial. Are patients excluded based on these criteria and are these criteria easy to assess?
3. To document reasons for refusal to participate and assess whether presence of clinical equipoise of the proposed intervention is a factor for refusal.
4. To assess feasibility of obtaining the proposed urodynamic end points and propose a single clinically important variable based on ease and reliability of measurement.
5. To report unexpected outcomes related to study design and redefine, if warranted, the time points for obtaining outcome data and length of follow up.

6. To measure the feasibility of administering the HRQOL questionnaire and the response rate achieved.

7. To assess the randomization process, allocation concealment and the effectiveness of blinding of the outcome assessor and provide an estimation of the number of personnel required per site to conduct this trial.

8. To calculate dropout rates and crossovers if any between proposed groups.

Acceptability:

1. To assess acceptability of patients and caregivers to general anesthesia for OnabotulinumtoxinA injection and their preference.

2. To assess acceptability of data collection procedures and proposed follow up protocol.

Determining effect sizes:

1. To estimate outcome variance and propose sample size for a phase III trial and the limitations thereof.

Secondary Objectives

The secondary objective of this study is to gather preliminary data comparing the clinical and urodynamic effects of intravesical OnabotulinumtoxinA injection to standard oral oxybutinin therapy.

1. To compare bladder storage parameters (maximal end fill detrusor pressure or detrusor leak point pressures, maximal cystometric capacity, reflex volume, pressure specific bladder volumes and safe volumes) achieved at 3 and 6 months following injection with OnabotulinumtoxinA injection and standard maximal tolerated dose of oral oxybutinin.
2. To compare the QOL scores between the two treatment arms using the validated HRQOL for children with spina bifida [35].

3. To document and compare the side effects of each approach.

4. To assess presence and grade of vesicoureteric reflux (VUR), degree of bladder trabeculation and morphology of bladder neck using videocystometry.

5. To compare the 48-hour CIC diaries to note the continence status and average volume at CIC.
Chapter 2

Literature review

2.1 STANDARD THERAPY FOR NEUROGENIC BLADDER

Clean intermittent catheterization (CIC) in combination with anticholinergic medications is the standard therapy for children with neurogenic bladder dysfunction associated with neurogenic detrusor overactivity (NDO), poor bladder compliance and/or DSD [8, 9]. Anti-cholinergic medications eliminate NDO and lower bladder storage pressures while CIC ensures complete bladder emptying and lowers voiding pressures generated secondary to DSD. Oxybutinin is used as the standard anticholinergic medication in children with a hyperreflexic, poorly compliant NB since the late 1970’s [11].

Oxybutinin is a synthetic tertiary amine, which exerts a direct spasmolytic (papaverine-like) action and an anticholinergic (M3 selective receptor antagonism) action on smooth muscles [12, 15]. The spasmolytic effect of the drug has been demonstrated on the detrusor muscle of the bladder, the small intestine, and the colon in several animal studies. In addition oxybutinin has a local anesthetic and calcium channel blocking activity. The usual dose of oral oxybutinin is 0.2-0.6 mg/kg/day in 3-4 divided doses [14]. Cystometric studies in patients with neurogenic bladders indicate that oxybutynin increases urinary bladder capacity, diminishes the frequency and amplitude of NDO and delays the initial desire to void. This translates to an improvement in storage pressures, thus preserving upper renal tracts and improving continence. Based on animal studies, oxybutynin appears to be rapidly and well absorbed from the gastrointestinal tract following oral administration. In rats, studies using radio labeled drug indicated that peak radioactivity occurred in plasma approximately 2 hours following oral administration of the drug, and radioactivity was no longer detectable in the plasma 72 hours after
administration. The onset of action of oxybutynin occurs within 30-60 minutes, and peak effects occur within 3-6 hours after administration. The antispasmodic action may last 6-10 hours. Studies using radio labeled oxybutynin indicate that the drug undergoes some enterohepatic circulation and is excreted in urine and feces.

Adverse effects of oxybutynin are typical of those produced by antimuscarinic agents and are occasionally severe enough to require discontinuation of the drug [11-14]. This may include dry mouth, decreased sweating, urinary hesitancy and/or retention, hot flushes, fever, tachycardia, palpitation, vasodilation, amblyopia, transient blurred vision, mydriasis, cycloplegia, decreased lacrimation and increased ocular tension. Other adverse effects reported include drowsiness, weakness, dizziness, asthenia, hallucinations, restlessness, insomnia, nausea, vomiting, decreased GI motility, constipation, a bloated feeling, impotence and/or suppression of lactation. Severe allergic reactions including rash, urticaria, and other dermatologic reactions have occurred with other antimuscarinic agents and presumably might occur in susceptible individuals following oxybutynin administration. Antimuscarinic agents may also produce signs of CNS stimulation when administered in high doses. Patients on oxybutynin therapy should be cautioned that the drug might impair their ability to perform activities requiring mental alertness or physical coordination.

Administration of oxybutynin during hot weather can cause heat prostration due to suppression of sweating. Oxybutynin should be used with caution in patients with reflux esophagitis, since antimuscarinic agents may aggravate this condition. The possibility that large doses of oxybutynin could precipitate adynamic ileus or toxic megacolon in patients with ulcerative colitis should be considered. Oxybutynin is contraindicated in patients with increased intraocular pressure associated with angle-closure glaucoma. The drug is also contraindicated in patients with myasthenia gravis, partial or complete obstruction of the GI tract, adynamic ileus, megacolon, severe colitis, or ulcerative colitis when toxic megacolon is present. Oxybutynin is contraindicated in patients hypersensitive to the drug or any ingredient in the formulation. Appropriate and sufficient studies have not been performed in children with oxybutynin chloride; therefore, the drug
should not be routinely administered to children younger than 5 years of age. However, clinical use of this drug is accepted in neonates as well as children younger than 5 years of age given its therapeutic potential for clinical benefit.

2.2 BOTULINUM TOXIN

Botulinum toxins (BTX) are neurotoxins produced by the facultative gram-positive anaerobic bacteria Clostridium botulinum and were first isolated by van Ermengem in 1897. The toxins disrupt different parts of the SNARE receptor with botulinum toxin A blocking the release of acetylcholine into the synaptic gap of the neuromuscular junction by acting against synaptosomal-associated protein, SNAP 25 [36-38]. This causes a selective and temporary flaccid paralysis of the target organ. In smooth muscles, it has been proved to trigger the release of nitric oxide that diffuses out of the endothelial cell and causes relaxation of the smooth muscle.

The USA Food and Drug Administration first approved botulinum toxin A (BTX-A) in 1989 for use in patients with strabismus and blepharospasm. Since then, its use has been extended to cervical dystonia, cosmesis, hypersecretory disorders and overactive muscle disorders. There are 7 distinct serotypes of BTX (A-G), of which types A and B have been used clinically. BTX-A was first licensed under the brand name Botox® and has been the most commonly used clinically [38-40]. However, another brand of BTX-A, called Dysport®, is also available but has not been studied as widely in urological conditions. Although both these products are the same serotype, they have different doses, efficacy and safety profiles. It is generally accepted that 1U of Botox® is equivalent to 3 U Dysport®. In addition, the recently licensed BTX-B (Myobloc®) also has a different efficacy, duration, diffusion, and immunogenicity profile and hence must not be considered as clinically equivalent. It has been reported that 1 U BTX-A is approximately equal to 50 or 100 U BTX-B. Additionally, BTX-B is reported to have more systemic side effects. To prevent interchangeability and prevent drug errors, the FDA has enforced a new nomenclature system. Botox® is called OnabotulinumtoxinA,
Dysport® is AbobotulinumtoxinA and Xeomin® is called IncobotulinumtoxinA [41].

OnabotulinumtoxinA blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals and inhibiting the release of acetylcholine. The acceptor molecule responsible for toxin binding and internalization has been identified as the synaptic vesicle protein 2 (SV2) receptor [37, 38]. After internalization, the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, it produces partial chemical denervation of the muscles resulting in localized reduction in muscle activity and possible muscle atrophy. When chemically denervated, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle denervation produced by localized injection of botulinum toxin.

Recent evidence points at another possible mechanism of action for BTX, which suggests that BTX affects afferent pathways suggesting a dual mechanism of action [42-47]. The bladder afferent neuronal receptors implicated include vanilloid, purinergic (P2X), and neurokininin receptors for nerve growth factor [43, 46]. The neurotransmitters acting at these receptors include ATP, substance P, neurokinin A, nitric oxide and calcitonin gene-related peptide (CGRP) which modulate the sensory afferent nerves in the detrusor muscle, especially in the diseased neurogenic bladders with NDO. The role of the suburothelial myofibroblast cells acting as a sensory organ in regulating bladder overactivity and the effect of BTX is being recognized [48].

In a rat model of chronic spinal cord injury and NDO, BTX-A significantly reduced the evoked release of CGRP in isolated rat bladders compared with controls. As evidence of this alternate mechanism of action, in a rat bladder pain model induced by acetic acid instillation, a significant improvement (mediated by decreased CGRP release) was observed in the interval between detrusor contractions in those who had received BTX-A. The toxin has also been shown to reduce ATP and capsaicin-induced DO in a rat model.
Apostolidis et al. have proposed that the primary peripheral effect of BTX-A involves the inhibition of acetylcholine, ATP, and substance P release, as well as the down-regulation of expression of vanilloid and P2X receptors [47]. Studies of bladder biopsies taken at 4 and 16 weeks following BTX-A injections have shown a reduced expression of TRPV1 and P2X3 in the suburothelium of patients with neurogenic or idiopathic DO. In particular, the reduced expression of P2X3 correlates well with the reduction in urinary urgency observed clinically. Further evidence in support of the afferent mechanism of action of BTX-A comes from a proposed anti-nociceptive effect separate from its neuromuscular action. Studies have demonstrated that BTX inhibits the release of radioactive-labeled glutamate from rat dorsal root ganglia. Potentially, this reduction in release of peripheral pain mediators such as glutamate could block peripheral sensitization, indirectly resulting in reduced central sensitization. Jankovic and Schwartz provided additional supporting clinical evidence in patients with cervical dystonia [49]. They documented that pain improved soon after injection of BTX but before a reduction in muscle spasm could be detected. This implies that a mechanism other than flaccid paralysis of the muscle, caused by the toxin, is involved.

If afferent mechanisms are important in ameliorating NDO, the excellent therapeutic efficacy of BTX might be due to its dual mechanism of action [50, 51]. Preliminary reports from small studies using BTX for interstitial cystitis and sensory urgency have been published, but the data need to be validated in larger clinical trials. Further research with BTX might lead to a better understanding of the physiological involvement of the urothelium and suburothelium in afferent mechanisms. This dual mode of action can also explain the more prominent effect of BTX on NDO as compared to bladder compliance, which is not affected by this sensory afferent mechanism unlike NDO.

2.3 SIDE EFFECTS AND PRECAUTIONS WITH ONABOTULINUMTOXINA

It has been documented that little systemic distribution occurs with therapeutic doses of BTX-A. The drug is not present in the peripheral blood at measurable levels following intramuscular or intradermal injection at recommended doses [36]. The recommended
quantities of neurotoxin administered at each treatment session are not expected to result in systemic effects in patients without associated significant neuromuscular dysfunction. However, clinical studies using single fiber electromyography techniques have shown subtle electrophysiological findings consistent with neuromuscular inhibition in muscles distant to the injection site, but these were unaccompanied by any clinical signs or symptoms.

In treating pediatric patients, the maximum cumulative dose recommended for Botox should generally not exceed 10 units/kg, up to a maximum of 300 units, in a 3-month interval [33-34]. There have been rare reports of death associated with aspiration in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BTX has not been clearly established in these cases. Reports of possible distant spread of toxin have been rarely reported in pediatric patients with co-morbidities like cerebral palsy, who received > 8 U/kg. Therefore, extreme caution should be exercised when treating pediatric patients who have significant neurologic disabilities, dysphagia, or have a recent history of aspiration pneumonia or lung disease. In general, adverse reactions occur within the first few days following injection and are generally transient. Botulinum toxin type A is contraindicated in the presence of infection at the proposed injection site and myasthenia gravis.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported [52, 53]. Muscle weakness remote to the site of injection and other serious adverse effects (e.g. dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, some associated with a fatal outcome. As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection.
2.4 INTRAVESICAL ONABOTULINUMTOXINA: INJECTION SITES AND DOSAGE

Intra-detrusor injections should be performed when the bladder is moderately full; excessive bladder filling may prevent backflow of toxin into the detrusor muscle. The number, depth, volume of each injection and whether the bladder trigone should be included or excluded continue to elicit debate among urologists [33, 40]. In the standard injection technique, 30-40 injections of approximately 0.5 ml-diluted toxin is injected into the bladder muscle under cystoscopic guidance, avoiding the trigone.

Karsenty et al. presented data comparing regimens of 30 versus 10 injections of 300 U BTX-A in a population with NDO and concluded that the lower number of injections did not affect efficacy or safety [54]. The exact location of the toxin following injection was a potential concern and a recent study utilizing MRI localization of the toxin study found that approximately 13% of the injected volume was located in the extraperitoneal fat outside the bladder. In addition only one-quarter or one-third of the total bladder wall surface was covered following 10 or 30 injections of the toxin, respectively. Since afferent mechanisms might have an important role in the action of BTX, targeted injections in to the suburothelium might be beneficial. This injection technique raises a suburothelial bleb, which can act on the myofibroblasts. However, most clinicians experienced with BTX-A injections believe that the depth of the injection and whether blebs are formed does not alter the efficacy of the therapy.

Controversy remains regarding the safety and usefulness of injecting the trigone. Proponents of trigonal injections believe that the greater nerve density in this region will lead to a better clinical response, but there is currently no evidence to support this. Opponents argue that trigonal injection could induce a distal ureteric paralysis and VUR. Conversely, the antinociceptive properties of BTX may enhance the effect by inclusion of the trigone. Manecksha et al conducted a RCT to compare trigonal sparing and trigonal included injections and noted better response on an overactive bladder scoring system without onset of VUR in the group receiving trigonal injections [55]. Smith and
colleagues advocate injecting the trigone and bladder base and found this technique useful in preventing elevated post-void residual urine volume following therapy [56]. In sensate non-neurogenic patients trigonal injections may be perceived as painful especially under local anesthetic.

Alternative modes of BTX delivery, such as intravesical instillation or long acting preparations, are currently under investigation. Botox-saline solution instillation has been attempted in animal and humans with limited success on detrusor storage pressures despite using carriers like DMSO or bladder pretreatment with protamine sulfate to enhance absorption [57]. These studies have demonstrated suppression of afferent signaling (CGRP, substance P, ATP and NGF), which reduces detrusor muscle overactivity. This is because the bladder urothelium is watertight at the umbrella cell level, augmented by glycosaminoglycans and uroplakins and does not allow the translocation of a large molecular weight OnabotulinumtoxinA (900 kDa) molecule to passively diffuse across the urothelium. Direct bladder instillation, therefore, is an ineffective method with current delivery modes to alter detrusor storage function. Chuang et al used liposomes to deliver BTX intravesically and showed a decrease in overactivity and SNAP-25 expression [58]. In another study, electromotive transport of instilled BTX was shown to be effective in improving bladder dynamics [59]. This option, though promising still involves a hospital visit and procedure related complications like erythema at the site of electrode application. The search for the ideal carrier, which will allow BTX penetration through the urothelium into the bladder muscle, is therefore ongoing.

2.5 ADULT STUDIES ON BOTULINUM TOXIN USE IN NB

Schurch et al were the first to report the effects of injecting BTX-A into the detrusor muscle in patients with spinal cord injury in a non-randomized prospective study in 2000 [60]. The hypothesis of this trial was based on the response achieved in other parasympathetic autonomic nervous system disorders such as achalasia and hyperhydrosis, which had been successfully treated with BTX-A injections. In this study,
patients with spinal cord injury on CIC who had severe NDO resistant to anticholinergic drugs were selected to receive 200-400 U of botulinum toxin A injected into the detrusor muscle, sparing the trigone. Nineteen patients were regularly followed over 9 months by clinical and urodynamic evaluations. At 6-week follow up after injections, there was a significant increase in the reflex volume (RV) and maximum cystometric bladder capacity (MCC) along with a significant decrease in the maximum detrusor voiding pressure. Anticholinergic medication use was reduced or discontinued and continence was achieved in all but two patients. Patient satisfaction was high with significant improvements in RV, MCC and compliance by 93%, 62.5% and 94% respectively and the reported effects lasted 9 months.

In 2005, Schurch et al. compared two different doses of BTX-A in a double-blind multicenter, randomized placebo-controlled study on 59 patients on CIC with refractory NDO [61]. Patients were randomized to receive 200 U or 300 U OnabotulinumtoxinA or placebo. Follow up evaluations were done at 2, 6, 12, 18 and 24 weeks. The number of incontinence episodes per day decreased significantly from baseline (by approximately 50%) at all time points (p<0.05) except at 12 and 18 weeks in the 200 U group. When compared with the placebo group, improvements reached significance in the 300 U group at 2 weeks (p=0.015) and 6 weeks (p=0.047) and in the 200 U group at 24 weeks (p=0.019). Urodynamic parameters were improved in the BTX-A treated patients with 55% not experiencing NDO compared with 10% in the placebo group. Patients receiving BTX-A at either dose showed significant improvements (p ≤0.002) in quality of life assessed by the Incontinence Quality of Life (I-QOL) questionnaire. The most commonly reported side effect was urinary tract infection (UTI) in 22% of patients. The authors concluded that treatment with 200 U and 300 U of the BTX-A was equally efficacious, though the small sample size may be a limitation of this study.

The results were confirmed in another trial, which recruited 34 patients with idiopathic DO who were refractory to anticholinergic medications [62]. Patients were randomized to receive either 200 U of botulinum toxin A or placebo. Significant benefits with regards to urodynamic parameters and QOL were observed in favor of BTX, and this effect was
sustained for at least 6 months. In a study including 66 patients with NDO, Grosse et al examined the clinical and urodynamic effects of repeated detrusor injections of BTX-A [63]. After each injection, MCC and RV increased significantly from baseline. The authors concluded that repeat injections are as effective as the first one, indicating no evidence of drug resistance.

Several studies have documented the positive impact of BTX-A injection on QOL outcomes in patients with urinary incontinence associated with DO [64-66]. Kalsi et al assessed 48 patients with urodynamically proven intractable DO for changes in QOL 4 and 16 weeks after treatment with intra-detrusor BTX-A injections using the short forms of the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) [64]. Percent changes in total QOL score were correlated to respective changes in clinical parameters recorded by bladder diaries and voiding cystometry. Highly significant decreases (p<0.0001) in QOL scores at 4 weeks follow-up were maintained at 16 weeks for both the neurogenic and non-neurogenic groups. In contrast to the urodynamic parameters, changes in lower urinary tract symptoms (LUTS) appeared to be the major determinant of improvements in the patients’ QOL. Kuo demonstrated similar improvements in QOL among patients with DSD secondary to spinal cord injury and noted that decrease in urinary urgency and incontinence directly contributed to improved QOL scores [65].

The cost consequence of using botulinum toxin to standard therapy or augmentation cystoplasty has been analyzed [67, 68]. Kalsi et al calculated the cost consequence of BTX-A therapy relative to continued standard care in a UK secondary care setting [67]. Although BTX-A may avoid or postpone the need for surgery in some patients, such savings were assumed to fall outside the timeframe of this analysis. All unit costs were based on 2003/4 UK prices with no discounting. 101 patients with urodynamically-proven detrusor overactivity of either neurogenic (n=63) or idiopathic (n=38) origin received intra-detrusor injections of 200-300 units of BTX-A. In an intent-to-treat analysis, 82% of patients showed a 25% or greater improvement in at least two of five parameters (urinary frequency, urgency, urgency incontinence episodes, maximum detrusor pressure) at 4
weeks follow up which reduced to 65% after 16 weeks. There were no significant differences between idiopathic DO and NDO patients. Therapy costs were £826 per patient, with a cost-effectiveness ratio of £617 per patient-year with \( \geq 25\% \) clinical improvement. Based on the 25% cut off, BTX-A costs £617 per improved patient-year, £1005 per initial response and £1264 per sustained response relative to standard care. Although treatment of NDO was more costly than idiopathic DO due to the higher dose required, the greater response rate meant that treatment of NDO patients was associated with a lower cost in those with a sustained response. Padmanabhan et al compared the costs of BTX-A therapy and augmentation cystoplasty over a cumulative 5-year period [68]. BTX-A was more cost effective than augmentation cystoplasty if the effect of injection lasted > 5.1 months per injection assuming a 40% complication rate in the augmentation group. Augmentation cystoplasty was found to be more cost effective if BTX costs increased or the complication rate of augmentation cystoplasty was < 14% over 5 years.

Karsenty et al performed a systematic review of 698 patients with NDO treated with BTX-A [40]. Clinically significant improvements in urodynamic parameters were noted along with improvements in continence, QOL and urinary frequency. The maximal cystometric capacity (MCC) and the reflex volume (RV) increased, thereby improving bladder storage without urinary leakage. Cessation of DO following treatment ameliorates urgency and frequency and improves urinary continence. The maximal detrusor pressure (MDP) on voiding is also decreased and this may protect upper renal tracts, particularly in those with a poorly compliant bladder. Treatment benefit usually lasts between 3 to 14 months and mild, injection related adverse events were reported. The experience of the European group studying BTX-A in NB describes the positive clinical and urodynamic results in more than 200 treated patients [69]. Currently the areas of research focus include the use of newer serotypes, assessing long-term effects and efficacy of repeat injections in relation to tachyphylaxis or antigenicity.
2.6 PEDIATRIC STUDIES ON BOTULINUM TOXIN USE IN NB

The first urologic use of botulinum toxin in the pediatric age group was reported in a 7 year old girl with dysfunctional voiding where the toxin was injected into the external sphincter to improve voiding and prevent recurrent infections [70]. Since then, several prospective and retrospective cohort studies have documented the safety and efficacy of BTX-A intravesical injections in salvage treatment of NB (Table 2.1). The primary indication of BTX-A therapy has been in patients with end stage bladders where anticholinergic medications have failed or cannot be tolerated due to side effects.

Schulte-Baukloh et al replicated the results of adult studies with OnabotulinumtoxinA intravesical injection in children with a hyperreflexic upper motor neuron type NB [21]. Their initial paper showed significant 4-week post injection increase in mean reflex volume (RV increased by 112 %), maximal bladder capacity (MCC increased by 56.5%), maximal detrusor pressure (decreased by 32.6%) and compliance (increase by 121.6%). In a subsequent follow up study in 20 children, the authors showed a significant improvement in the mean RV, MCC and maximal detrusor pressure at 3 months follow up [22]. However by 6 months the positive effects were maintained only with MCC and the other improvements did not reach statistical significance. No side effects were observed in the study barring 4 episodes of UTI. The authors presented their experience with repeat injections (3 or more injections) in 10 children and showed the persistence of beneficial urodynamic effects in all without any untoward effects. In fact the improvement in the parameters appeared to be progressively increased with each injection and the effects lasted longer (up to 9 months) as compared to the 6 months with initial injections.

Riccabona et al demonstrated a similar positive effect on bladder storage function in 15 children prospectively treated with 10 U/kg of botulinum toxin [23]. After the first injection treatment mean RV increased from 72 ± 28.1 ml to 298 ± 32.4 ml (p < 0.001) and maximum detrusor pressure (MDP) decreased from 78 ± 23.1 cm H₂O to 42 ± 24.3 cm H₂O (p < 0.001). MCC increased from 136 ± 45.7 ml to 297 ± 87.1 ml (p < 0.001).
Detrusor compliance increased from $18 \pm 27.1 \text{ ml/cm H}_2\text{O}$ to $51 \pm 38.1 \text{ ml/cm H}_2\text{O}$ ($p < 0.001$). Of the 15 patients, 13 became completely dry with CIC and the remaining 2 patients improved. Results after 9 months were similar to those obtained after 3 months. Mean durability of the effect of the drug was 10.5 months.

Neel et al combined botulinum toxin injections with dextranomer-hyaluronic acid subureteric injection procedures in 10 patients with a mean age of $5.9 \pm 3.6$ years with SB who had associated VUR [30]. All patients were fully compliant to CIC and had failed to gain continence and/or showed continued poor compliance to the maximum tolerable dose of anticholinergic medication. Patients received intra-detrusor injection of 12 U/kg (maximum 300 U) of BTX-A in an infection-free bladder with simultaneous Dextranomer-hyaluronic acid injection for VUR. The grade of reflux was III, IV and V in three, seven and six ureters, respectively. The MCC increased significantly ($p<0.022$) and the MDP ($p< 0.001$) decreased significantly from pre injection values. Five of the six incontinent patients were rendered dry and all but one had VUR resolution. The effect of BTX-A on reducing bladder pressures, which can lead to VUR resolution, was an obvious confounding factor in this study.

Altaweel et al conducted a prospective study to evaluate the effect of repeat BTX-A injections in children with neuropathic bladder dysfunction [31]. A total of 20 patients (average 13 years) received BTX-A injections. Of the patients, 13 (65%) became continent after the first injection. MCC increased from $215.6 \pm 58.8 \text{ cc}$ to $338.3 \pm 98.4 \text{ cc}$ ($p <0.01$), MDP decreased from $43 \pm 13.7 \text{ cm H}_2\text{O}$ to $21.6 \pm 10.5 \text{ cm H}_2\text{O}$ ($p < 0.01$) and compliance increased from $5.2 \pm 2.6 \text{ ml/cm H}_2\text{O}$ to $13 \pm 6.9 \text{ ml/cm H}_2\text{O}$ ($p < 0.01$). At an average of 8.1 months after the first injection all 13 responders received a second injection, which led to similar improvement in urodynamic parameters. Among the responders 3 received 3 injections and 1 received 4 injections, all of who exhibited similar improvement as seen initially. Interestingly, out of the initial cohort of 20 patients, 7 failed to improve initially and 6 of these failed to improve after a second injection. Augmentation cystoplasty was performed as a salvage procedure in these patients. In this study, like others reported, patients were selected after all conservative
measures and maximal dose of anticholinergic medications had failed. The authors concluded that BTX-A therapy could delay the need for augmentation cystoplasty in patients with a non-compliant high-pressure bladder.
<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>N</th>
<th>Study</th>
<th>Inclusion criteria</th>
<th>End points</th>
<th>Dose</th>
<th>Follow up</th>
<th>Statistical analysis</th>
<th>Results</th>
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</thead>
</table>
| Schulte-Baukloh (22) | 20 | Prospective cohort | UMN lesion with DSD Non responsive to AC | 1. Reflex volume  
2. No. of NDO  
3. Max. detrusor pressure  
4. Bladder capacity  
5. Compliance | 12U/kgmax 300 U | 6 mo. | Wilcoxon pair difference (1-sided), p< 0.01 | Significant increase at 3 mos.  
Significant increase in 4 at 6 mo. |
| Riccabona (23) | 15 | Prospective cohort | UMN lesion with DSD Non responsive to AC | 1. Reflex volume  
2. Max detrusor pressure  
3. Continence  
4. Bladder capacity  
5. Compliance | 10 U/kg max. 360 U | 12-30 mo. | Wilcoxon pair difference (1-sided), p< 0.01 | Significant increase at 3 mos.  
Significant increase in 4 at 6  
Mean durability 10.5 mo. |
| Neel (27) | 10 | Prospective cohort | NB with VUR Non responsive to AC | 1. Max detrusor pressure  
2. Continence  
3. Bladder capacity | 12U/kg Max 300U | 6 mo. | Not mentioned | Significant decrease in MDP  
Increase in MCC at 1 and 6 months  
5/6 continent  
No side effects |
| Altaweel (31) | 20 | Prospective cohort | NB with VUR Non responsive to AC | 1. Max detrusor pressure  
2. Compliance  
3. Continence  
4. Bladder capacity | 5U/kg Max 300U | 17 mo. | Students t test | 13 received 1 reinjection,  
3 had 2 and 1 had 3 reinjections  
7/20: no initial response  
No adverse events |
| Kajbafzadeh (25) | 26 | Prospective cohort | NB with VUR Non responsive to AC | 1. Max detrusor pressure  
2. Compliance  
3. Continence  
4. Bladder capacity  
5. Fecal incontinence | 10U/kg Max 300U | 4 mo. | Students t test Wilcoxon pair difference (1-sided), p< 0.01 | Significant improvement in MDP, MCC  
Decrease of VUR grade in 73%  
Bowel function improved in 66%  
No adverse events |
| Akbar (26) | 44 | Prospective cohort | NB with VUR Non responsive to AC | 1. Max detrusor pressure  
2. Compliance  
3. Continence  
4. Bladder capacity  
5. Fecal incontinence | Dysport 20U/kg, max 400U | Median 4.5 y | Students t test p< 0.05 | Significant improvement in MDP, MCC, compliance  
No adverse events  
No tolerance to rpt injections  
44 had 2 injections, 41 had 3 inj,  
11 had 5 and 1 had 6 inj.  
No changes in compliance after rpt inj |

AC: anticholinergics
Hoebeke et al used BTX-A (dose 100U) therapy in 21 patients with a non-neurogenic overactive bladder [24]. Fifteen patients with a minimum follow up of 6 months represented the study group for long-term evaluation. After 1 injection 9 patients showed full response, 3 had a partial response (50% decrease in urge and incontinence) and 3 remained unchanged. Eight of the 9 full responders were still asymptomatic after 12 months. The side effects reported were temporary urinary retention in 1 girl and signs of VUR with flank pain during voiding in 1 boy. Two girls experienced 1 episode each of symptomatic lower urinary tract infection.

In another prospective study, Kajbafzadeh et al assessed bladder and bowel function after BTX injection [25]. Nineteen of 26 patients (73%) in this study became completely dry between CIC 4 months following injection. The mean MDP was decreased to 83 ± 4.6 cm H$_2$O from a baseline of 139 ± 11.2 (p < 0.01). The average MCC increased from 102 ± 6.3 ml to 270 ± 9.5 ml (p < 0.01). Of the 15 patients with VUR before the procedure, 11 (73%) had decrease in the vesicoureteral reflux grade. Bowel dysfunction in the form of fecal incontinence improved in 10 (66%) of the 15 patients. The same authors compared intra- detrusor injections with or without simultaneous external urethral sphincter injections. The advantage of the intra sphincteric injection is to reverse the DSD, which can potentially cure secondary VUR. The urodynamic results were comparable in both groups, except a lower post void residue in the intra sphincteric injection group. This may not be significant clinically as most of these patients are on CIC.

Further confirmation of the repeated effects of BTX was shown by Akbar et al who reviewed there results after multiple Dysport® injections in neuropathic bladders [26]. Bladder compliance, capacity and MDP improved significantly (p < 0.001) compared to baseline after each BTX injection. There was prolonged efficacy of each BTX administration and all repeated injections over a median follow up of 4.5 years showed no evidence for drug tolerance or changes in the morphological appearance of the bladder.
Early in the treatment program, 3 patients who received a dose of 1000 units Dysport® showed systemic side effects and generalized muscle weakness. These resolved without intervention and did not recur after reducing the adult dose to 750 units (pediatric dose 20 units/kg, not >400 units), which seems to be the optimum for good efficacy with an adequate safety margin. Pascali et al described the use of N-DO endo-injector system with a retractable needle, which allows penetration to predefined depths and has a curved needle for lateral bladder wall injection allowing shorter injection times [71]. This device can aid a faster and more precise and uniform injection into the bladder wall.

Gamé et al performed a systematic review of all pediatric studies of Botulinum toxin intra detrusor injection for NB [34]. Six studies, including 108 patients were selected. These were all small open label studies constituting level 3 evidence. Dosage used varied between 5 to12 U/kg up to a maximum of 360 U. Dryness between CIC was achieved in 65-87% of patients. All studies showed a significant impact on reducing detrusor-filling pressures, improving RV and MCC. Onset of action was usually within 2 weeks after injection and the mean time period between injections varied between 6 to 9 months. The most common side effect was procedure related UTI (7-20%). The role of decreasing the number of injection sites in the bladder to 10-15 from 30 is discussed as an option to decrease the risk of fibrosis with repeat injections. The studies by Schulte-Baukloh and Riccabona showed worsening of urodynamic parameters at 3 months of injection [22, 23]. One of the issues with these 6 studies is the poor reporting of simultaneous anticholinergic use after BTX injection. Therefore, it is difficult to separate the effect of anticholinergic medications from BTX. This is especially true if the anticholinergic dose was increasing during the study. It is possible to use both treatments simultaneously to achieve a better response and this may limit the dose of both drugs at a lower level to prevent side effects. However, an unspecified or concomitant use of anticholinergic medication prevents assessment of the true efficacy of BTX-A as sole therapy in NB patients.
2.7 RATIONALE FOR PRIMARY USE OF BOTULINUM THERAPY IN CHILDREN WITH NB

Currently botulinum toxin intra-detrusor injections are used as salvage treatment in patients who have either not responded to anticholinergic therapy (with persisting incontinence and/or risk of upper renal tract damage) or has side effects leading to discontinuation of treatment. The rationale for treatment has been based on the avoidance of augmentation cystoplasty in this group of children. Concerns regarding primary use of botulinum toxin are based on the cost, safety, efficacy and temporary nature of the effects of botulinum toxin necessitating repeat injections when compared with standard anticholinergic medications.

The effects of BTX-A are more pronounced in the NB with NDO when compared with a stiff non-compliant bladder with or without overactivity. Horst et al demonstrated lack of bladder compliance improvement following BTX therapy when the baseline bladder compliance was already severely compromised [32]. The authors suggested that earlier use of botulinum toxin might improve bladder compliance more than end stage bladders. Therefore, it may be a clinical option for using botulinum toxin in the early stages of bladder hyperactivity to prevent the development of a non-compliant bladder subsequently. In addition, the effects of the toxin may already be less prominent in children with SB due to decreased peripheral nerve density in NB as compared to adults with spinal cord injury.

Additional concerns regarding histological change and long-term fibrosis following BTX injections have been addressed in the literature. Haferkamp et al. reported a lack of structural changes following BTX injections in patients with NDO [72]. Contrary to reports of BTX effects on striated muscle, very little axonal sprouting was observed following treatment. Comperat and colleagues showed no difference in inflammation and edema between bladder tissue samples collected at cystectomy from patients who had received BTX injections with in the past year and controls [73]. Interestingly, those who had received BTX had less fibrosis of the bladder wall than those who had not, although
assessment was based on the researchers own grading scale. Similarly, Apostolidis et al showed no difference in signs of inflammation and dysplasia except eosinophil infiltration post BTX injection [74]. Unlike earlier animal experiments, the first injection of BTX-A did not cause apoptosis in the bladder urothelium and sub-urothelium at 4 weeks following injection [75].

However, the long-term effects of repeated injections are still unclear. Schulte-Baukloh et al noted that even though bladder compliance improved as compared to the baseline after each injection, the baseline value showed a negative trend with time [22]. While this loss in compliance can be explained by the natural course of a neurogenic bladder the authors did speculate whether this is a detrimental effect of repeated botulinum injection. Although maintained for some months, the actions of the BTX are naturally reversed by neural regeneration and consequently repeat injections are necessary. Grosse et al showed that repeat injections were as effective as the first injection in those treated with Botox 300 U or Dysport 750 U, with patients receiving up to seven injections [63]. The intervals between treatments remained unchanged and there was no difference between injections when comparing the preparations. No drug resistance was encountered. Karsenty et al assessed re-injections in 17 NB patients who had between three and nine injections each (mean 5.4) [76]. They found that repeat injections were as efficacious as the first injection in improving MCC, MDP, and RV and did not have a negative effect on compliance and there were no side effects secondary to repeat injections. Tolerance or exacerbation of regional symptoms, which may be anticipated if enhancement of pathologic innervation occurs following repeat injections, did not occur. Reitz et al similarly confirmed evidence of maintained efficacy in clinical and urodynamic parameters in 20 patients who underwent at least 4 injections [77].

Due to the antigenicity of BTX, a small number of patients mount an immune response with the formation of neutralizing antibodies, after repeat injections. To minimize the small risk of BTX resistance, most investigators currently recommend waiting at least 3 months between treatments, avoiding the use of booster injections and using the smallest dose that achieves the desired clinical effect. The newer formulation of
OnabotulinumtoxinA used after 1998 is thought to have reduced the occurrence of resistance and currently it is believed that antibody formation is seen in < 1% of patients and is not relevant in clinical practice [78]. There have been a couple of case reports of the development of resistance to BTX-A with continued efficacy with therapy switch to BTX-B. The different target proteins for those toxins may explain the continued efficacy following the development of resistance to one serotype. However, the presence of some cross-reactive antibodies may limit this alternative.

Currently, there is inadequate data to suggest primary use of BTX-A for NB patients. On the other hand, early injections may lead to better improvements in bladder compliance and a longer delay to an end stage bladder thus delaying the need for a bladder augmentation, while maintaining patient safety.

2.8 QOL IN SPINA BIFIDA PATIENTS

Parkin et al developed a validated disease-specific QOL instrument for use with children and adolescents 5-20 years of age with spina bifida [35]. The methodological framework for questionnaire development described by Kirshner and Guyatt was used in development of the questionnaire [79]. This approach formally addresses the issue of item selection and reduction as well as score reproducibility and validity. The intended use of the instrument was as a discriminative measure in children and adolescence with SB. The measurement properties required for discriminative instruments are reproducibility and cross-sectional construct validity.

The investigators identified 10 domains: social; emotional; intellectual; financial; medical; independence; environmental; physical functioning; recreation and vocational. Two investigators independently assigned each of the items to a domain, with 85% agreement. In the remaining 15%, a third investigator arbitrated. Within each domain, items generated were broad enough to ensure that the entire spectrum of QOL was represented. Each question (accompanied by a 5-point Likert scale) was given equal weighting. The final score was obtained by summing individual items. Scoring was
reversed for negative questions. The introductory instructions indicated that the parents of the 5-12 year group should respond from their child’s viewpoint; adolescence in the 13-20 year group were instructed to respond directly, asking for help from their parents if necessary.

Reproducibility was measured by administering the questionnaire at 2-week intervals to the same random sample of children and parents who participated in the validity phase. These children were stable during the 2-week interval. Reproducibility was analyzed using the intra-class correlation coefficient with an a priori intra-class correlation coefficient greater than 0.75 being considered as significant. Subsequently, field-testing of the questionnaire was undertaken in a large random sample. Respondents were asked to complete a questionnaire regarding family socio-demographic characteristics and the child’s current physical functioning, the QOL questionnaire and a global question of well-being (‘How do you think you and your child are doing at present?’). The questionnaire was tested for construct validity in the two age groups (5-12 and 13-20 year). In the 5-12 year age group, the correlation between the HRQOL instrument and the global question of the child’s well-being was $r = 0.57$ ($p=0.01$). The correlation between the HRQOL instrument and the Piers-Harris Children’s Self-Concept Scale was weak and in a positive direction ($r = 0.26, p=0.32$). In the 13-20 year age group, the correlation between the HRQOL instrument and the global question of the child’s well-being was $r = 0.63$ ($p=0.01$). The correlation between the HRQOL instrument and the Piers-Harris Children’s Self-Concept Scale was $r = 0.89$ ($p < 0.001$). From the same sample that completed the validation phase, 14 of the 19 children 5-12 years of age and their parents completed and returned the HRQOL questionnaire 2 weeks after the initial completion. The intra-class correlation coefficient was 0.78. Fourteen of the 16 adolescents completed and returned the HRQOL questionnaire 2 weeks after the initial completion with an intra-class correlation coefficient of 0.96.

The final HRQOL questionnaire consisted of two scales: 44 questions for the 5-12 year age group and 47 questions for the 13-20 year age group. The final score is obtained by summing individual items, and scoring is reversed for negative questions. (Questions 15
and 16 in the 5-12 year old scale and question 19 in the 13-20 year old scale). In the 5-12 year age group, the possible range of scores is 44-220. This instrument was developed from the viewpoint of the children and their parents, rather than from the viewpoint of the health care provider. This instrument has very good reproducibility and validity [80]. In addition, the adolescent instrument is further validated by comparison with the Piers-Harris Children’s Self-Concept Scale. Following field-testing, the final questionnaire demonstrated evidence of good internal consistency and validity in the SB population.

Parekh et al reported QOL outcomes 6 months after reconstructive urologic surgery in pediatric SB patients using the PedsQL 4.0 instrument [81]. This is a validated but generic instrument encompassing all 5 aspects of health. The authors noted that children reported higher scores than parents at baseline and on follow up. Despite excellent surgical results, there was no significant difference between pre and post op scores at 6 months follow up. Similarly, MacNeily et al also failed to show any significant improvement using the HRQOL questionnaire after reconstructive surgery in this population, though individual questions related to continence or independence showed improvement [82]. The possible explanations for the negative results could include the multisystem involvement in spina bifida, where surgery for a single system cannot significantly alter the overall QOL. In addition, the instruments available may not be sensitive enough to measure changes after surgical intervention. If the baseline scores are already high, a ceiling effect may lead to the postoperative scores not being significantly high. Sawin performed a comprehensive review of the various generic and specific validated instruments available for studying QOL in patients with SB and suggested various generic instruments which could be used for specific clinical assessments like constipation, shunt related problems and incontinence [83].

2.9 PILOT STUDIES: ROLE, OUTCOMES, AND SAMPLE SIZE ESTIMATION

A pilot study is an investigation designed to test the feasibility of methods and procedures for later use on a large scale or to search for possible effects and associations.
that may be worth following up in a subsequent larger study [84, 85]. A pilot study, which incorporates a randomization procedure, is called a pilot trial. This is synonymous with a phase II study designed to identify dosing regimens and initial efficacy studies for new interventions. Well-conducted pilot studies are invaluable in designing and funding a formal phase III trial.

Despite being designed exactly like a phase III trial, the research question being answered in a pilot trial is different with the central focus being whether a full scale trial should be conducted or not and if so what modifications should be proposed based on the results of the pilot trial. Van Teijlingen et al provide a summary of the reasons for conducting a pilot study [85]:

1. **Process:** This assesses the feasibility of the study design and includes an evaluation of the recruitment rates, retention rates, refusal rates, compliance rates, suitability of the eligibility criteria to optimize recruitment and improve generalizability, acceptability of the interventions and proposed outcome measurement tools.

2. **Resources:** This aspect of a pilot study deals with the time and resources required to conduct the study. The goal is to determine the budgetary requirements and resource issues which may arise in conducting a future trial both in terms of personnel and the center where the study is being conducted.

3. **Management:** This covers issues related to data collection and entry and the specific challenges related to the role of the study personnel involved.

4. **Scientific:** This deals with the assessment of treatment safety, dose, response, treatment effect and variance of the effect.

More specifically, the objectives of a pilot study are [86, 87]:

1. To assess recruitment potential and assess the presence or absence of clinical equipoise, impact of inclusion/exclusion criteria and acceptability of randomization on recruitment.

2. To assess safety, acceptability and implementation of the proposed intervention.

3. To determine factors which hinder protocol adherence.
4. To test the integrity of the study protocol, data collection forms, questionnaires and outcome measurement appropriateness, timing and mechanisms.

5. To assess the effectiveness and implementation of the randomization procedure.

6. To assess the resources, training and time required for conducting the trial.

7. To test the data collection methods and follow up procedures required and assessing follow up and response rates.

8. To select the most appropriate primary outcome measure or if a surrogate measure is being used the pilot study can justify its clinical relevance. In addition, the pilot study can examine unexpected outcomes or conversely find proposed outcomes lack sensitivity or are unfeasible.

9. To estimate effect size and perform a sample size calculation for a phase III trial. However, given their small sample size, it must be recognized that effect estimates in a pilot trial are unreliable and can lead to over or under estimation of the required sample size.

Arnold et al detail the methodological features of pilot trials and recommend explicit objectives and a testable hypothesis [86]. Primarily, this should involve an a priori set up of threshold criteria, which would assess various aspects of the proposed trial. Failure to achieve these criteria should lead to modifications of the proposed protocol to circumvent the problems encountered. The two inter-related key aspects of a pilot trial are feasibility and acceptability. Feasibility refers to the ease or convenience of execution of a protocol (from a researcher perspective) whereas acceptability is defined as the suitability or favorability of reception of the protocol (from a participant perspective) [84]. An intervention, which is not acceptable will not be feasible and vice versa. The concept of acceptability has to be broad and not restricted to patients alone. Several key groups like health care professionals and resources at a center have to accept the proposed trial for seamless execution. In addition, Feeley et al used the term intervention fidelity to determine the extent to which the intervention can be provided as intended [84]. This specifically addresses the question whether the dose, frequency, timing and methods of delivery are feasible and if the trial physicians are adequately trained to implement the proposed intervention. It is also important to determine if the follow-up tests and visits
are acceptable to the participants. The pilot study should assess the burden of participating in a trial for participants, as this is a key factor for recruitment and ensuring good response and compliance rates. If the response rates are poor, the follow up procedures can be modified and made less cumbersome. The pilot trial should also assess the likelihood and estimate of contamination (participants in either group receive intervention for the other group) or co-intervention (differential exposure to other interventions which can impact outcomes).

Recruitment rates and reasons for refusal to participate help in modifying time lines and budget for the proposed phase III trial, modifying inclusion/exclusion criteria and changing the protocol to make it more acceptable [84]. If the inclusion/exclusion criteria are too broad or narrow they can be modified accordingly. Similarly, participants may be reluctant to randomization, which may alter a subsequent study design radically to a prospective cohort study or a Zelen design [88]. Reluctance to participate in an RCT may simply be secondary to lack of clinical equipoise regarding the risk-benefit ratio of the proposed intervention. Freedman in 1987 was the first to propose this important concept of clinical equipoise [89]. A pilot study should study the presence or absence of clinical equipoise for a proposed intervention. If there is no clinical equipoise it will be a challenge to conduct the study, as clinicians and participants will not be amenable to conducting or participating in a RCT. The other key aspect of a pilot study is to assess how effectively the allocation concealment, blinding and randomization processes have worked as these are key aspects for the internal validity of an RCT. Blinding can be assessed in a pilot trial by direct questioning of the health care professionals or participants involved in the study. A detailed description of the randomization and concealment process should be incorporated so that future researchers can assess or modify the protocol.

The analysis of a pilot trial should be mainly descriptive and for outcome measures should focus on confidence intervals rather than hypothesis testing [90]. Since no formal power calculations are performed, it is not justified to use underpowered studies to comment on or accept significant clinical results. One potential approach involves setting
up a pre-defined minimal important difference between proposed interventions and seeing if the confidence intervals of the treatment effect are contained in this estimate [86]. On the other hand, lack of significant results should not be a reason enough to stop proceeding to the main study. This decision, especially if the study protocol is feasible, should be based on clinical judgment of the confidence intervals of the outcome measure.

Sample size estimation based on pilot studies has to be interpreted with caution and conservative approaches are recommended [91]. However, with new interventions where the phase III study involves the same protocol as the pilot, pilot studies still serve as the best estimate of sample size. For a pilot study to be relatively adequate at estimating effect size, Browne proposed a general rule of at least 30 patients or greater [92]. Lackey and Wingate suggested a sample size of 10% of the final trial size [93]. Hertzog, on the other hand proposed that at least 10-20 participants per group suffice for most pilot trials [91]. Another option involves using an at least 80% upper one-sided confidence limit rather than the estimate itself for sample size determination.

In RCT’s with normally distributed outcomes and equal variance in the 2 groups, the effect size, which is the standardized mean difference between the treatment and control groups (Cohen $d$) can be used to calculate sample sizes [91]. Cohen proposed that $d$ values of 0.2, 0.5 and 0.8 be considered as small, medium and large effects though this has to be interpreted from a clinical standpoint. Internal pilot studies incorporated into a larger trial are another option, which can be used to modify the sample size based on initial estimates [94]. The key advantage of conducting a pilot trial to estimate sample size for future studies is the possibility of incorporating what a patient considers relevant in the calculation besides a simple clinical significance based on clinician opinion.

Kraemer et al provide a review of the caution needed in using pilot studies to guide power calculations for phase III trials [95]. They highlight the problem of a small pilot study in generating large standard errors of the estimated effect size. This can result in a phase III trial being rejected due to an erroneously low $d$ though the actual effect is clinically significant and conversely can also lead to an underestimation of the sample size required
leading to an underpowered study. Another approach that is more applicable from a clinical standpoint is the number needed to treat (NNT). For example, in this proposed trial let’s assume 50% achieve safe bladder pressures with oxybutynin. The clinical question then is what level of success with BTX-A would make the urologist choose this therapy as an alternative. If we assume that the success rate with BTX-A is 70%, the NNT would be 5. This number is easier to interpret from a patient and physician perspective as it indicates the number you would have to treat with botulinum toxin to achieve 1 more success than achieved with oxybutynin. The acceptability of this NNT will depend on the significance and implications of high bladder pressures, the cost and side effects of both treatments and patient perspective.

Finally, all pilot studies should be publically registered to mitigate publication bias and avoid replication of efforts. Thabane et al provide a checklist of items to include when reporting a pilot study based on the CONSORT statement [87]. Halpern et al question the ethical challenges of conducting underpowered trials unless done for rare diseases or in the early stages of drug/device development [96]. On the other hand, it is unethical to run a phase III trial before ensuring its feasibility. Thabane et al stress an important aspect of ethical consideration in pilot trials [87]. Researchers must disclose the feasibility nature of pilot studies to participants explicitly and inform them of the primary and secondary objectives of the study. Publication of pilot studies is difficult because most trials are not clear in their objectives and editors are affected by the lack of power in the study [97]. This can be addressed by a carefully conducted and well-reported pilot trial, which provides clear and pre specified feasibility and acceptability criteria and the researchers do not over interpret the secondary outcomes and effect sizes.
Chapter 3

Methods

3.1 TRIAL DESIGN

This pilot trial was conducted as a randomized, open label, active comparator parallel group study with two treatment arms and single blinding of the evaluator (Figure 3.1). We aimed to enroll 20 subjects in this pilot study with 10 in each arm. Eligibility was assessed and following documentation of informed assent and consent, the subject was randomized to one of the following treatment arms:

Arm 1 – The subject continued the pre study daily dose of oxybutynin. For study purposes, the participants were asked to return to clinic at 1, 3, and 6 months after being randomized.

Arm 2 – Injection of OnabotulinumtoxinA – A single pediatric urologist performed the injection under general anesthesia using a standard dose of OnabotulinumtoxinA (10 U/kg, maximum 300 U) injected into the detrusor muscle directly using cystoscopy. This study involves a single injection of OnabotulinumtoxinA. Based on the literature, the effect of OnabotulinumtoxinA is expected to last for 6 months, at which point the study was completed and the subject resumed their pre-study dose of oral oxybutynin.

The study was of 6 months duration from the time of randomization for the oxybutynin group and from the time of injection for the OnabotulinumtoxinA group. Pharmacokinetic data on oxybutynin suggest a washout period of 3 days. Since the assessments were done at 1, 3 and 6 months from injection, there was no prescribed washout period for the OnabotulinumtoxinA group. Blinding of the surgeon and the subject were not feasible for
this trial. However, a blinded urologist reviewed the urodynamic studies to assess the urodynamic effects of intravesical OnabotulinumtoxinA injection and standard oral oxybutinin therapy. A research assistant blinded to the treatment received performed data abstraction and entry from the HRQOL questionnaires and CIC diaries.

### 3.2 PARTICIPANTS

Participants were recruited from the Thames Valley Children’s Center Spina Bifida clinic and followed at the pediatric urology clinic at London Health Sciences Centre in London, Ontario. This multi-disciplinary clinic conducted for children and adolescents with SB has approximately 120 patients under active follow up. In addition, approximately 5-8 new SB patients are referred every year to this center.
Spina bifida associated neurogenic bladder
- 5-20 years of age
- On clean intermittent catheterization
- On oxybutinin 0.2-0.4 mg/kg/day for at least 3 months
- No prior bladder surgery
- UMN type bladder demonstrated on last urodynamic study

Consent to participate in trial

Assessment and baseline investigations
- Pediatric urology assessment
- 48-hour CIC diary, continence status
- HRQOL questionnaire
- VideoUrodynamic study
- Ultrasound

Randomization

Continues pre randomization oxybutinin therapy

Intravesical OnabotulinumtoxinA injection

1, 3 and 6 months assessment
- Pediatric urology assessment (1,3,6 mo)
- 48-hour CIC diary, continence status (1,3,6 mo)
- HRQOL questionnaire (1, 6 mo)
- VideoUrodynamic study (3, 6 mo)
- Ultrasound (3, 6 mo)

Figure 3.1: Proposed study protocol
Eligibility Criteria

1. Spina bifida associated neurogenic bladder patients 5-20 years of age.
2. Urodynamic or video urodynamic study done within the last 6 months demonstrating an upper motor type of lesion associated with neurogenic detrusor overactivity and/or poor bladder compliance. Specifically, the study showed either detrusor leak point pressure $>40$ cm H$_2$O or $30$ cm H$_2$O below capacity $<60\%$ of total bladder capacity or $20$ cm H$_2$O capacity $<70\%$ of bladder capacity.
3. No prior augmentation cystoplasty or vesicostomy.
4. Currently performing clean intermittent catheterization at least 4 times a day.
5. All patients were under treatment with oxybutinin at a maximal tolerated dose ranging between 0.2 -0.4 mg/kg/day for at least 3 months duration.
6. Able and willing to complete CIC Diaries and quality of life questionnaires.
7. Consent and assent given to participate in trial.

Exclusion criteria

1. History of lung disease, recurrent aspiration or severe neurological impairment, which may increase risk of OnabotulinumtoxinA toxicity or anesthesia.
2. Positive urine culture with symptoms of a UTI.
3. Known allergy to OnabotulinumtoxinA.
4. Patients with a tethered cord demonstrated on MRI or a recent change in continence status were excluded.

3.3 INTERVENTIONS

The control arm of this study consisted of subjects continuing standard pre randomization oxybutinin therapy at maximal tolerated dose. All subjects included in this trial initiated oxybutynin therapy at least 3 months prior to being enrolled. The dose of oxybutynin was increased gradually to achieve a balance of efficacy and tolerability at the discretion of the treating physician. The experimental arm subjects received intra-detrusor injections of
OnabotulinumtoxinA injection under general anesthesia. Both groups underwent the same follow-up clinic visits and assessments at 1, 3 and 6 months.

**OnabotulinumtoxinA injection**

OnabotulinumtoxinA (BOTOX®, Allergan, Irvine) is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of Hall strain of Clostridium botulinum grown in a medium containing N-Z amine, glucose and yeast extract. It is purified to a crystalline complex consisting of the neurotoxin, a non-toxic protein and four major hemagglutinin proteins. One Allegan unit of Botox corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice, performed in a mouse potency assay. This assay method is specific to Allergan’s product Botox. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD50 assays, units of biological activity of Botox cannot be compared to or converted into units of any other BTX-A activity. The specific activity of Botox is approximately 20 units/nanogram of neurotoxin protein complex.

A single surgeon performed the OnabotulinumtoxinA injection as per a set protocol described below, using standard latex precautions. Two patients with SB associated NB, excluded from this trial with similar urodynamic parameters underwent Botulinum toxin injections prior to study initiation to standardize the procedure and check the availability and adequacy of required instruments.

All subjects randomized to the OnabotulinumtoxinA group underwent a preoperative urine microscopy and culture to rule out an active urinary tract infection. A separate consent was obtained for injection under a general anesthetic. Prophylactic cefazolin at a dose of 25mg/kg (maximum 1 gram) was administered at induction. Botulinum –A toxin (Botox®, Allergan, Irvine CA, USA) was injected cystoscopically at 30-40 sites of the bladder sparing the trigone with a 25 cm 3.7 Fr injection needle (Williams needle, Cook Urological, Spencer, Indiana). The dosage used was 10 Allegan U/kg to a maximum of
300U. The toxin was diluted in 15 to 20 ml of saline with injection volumes varying between 0.3 to 0.5 ml at each site. The bladder was drained at the end of the procedure and subjects resumed their CIC regimen post-surgery and discontinued their oxybutinin therapy 48 hours following injection.

3.4 DEFINITION OF OUTCOMES

**Primary outcomes**

The primary outcomes have been described in the earlier section. The following specific criteria (based on our literature review of pilot studies conducted in other fields) were predefined and used for assessing feasibility of conducting a phase III trial. In addition to the safety assessment and clinical response in the OnabotulinumtoxinA group, proceeding to a phase III trial was determined based on the fulfillment of these objective criteria. We deliberately selected criteria 2 and 3 as these were dependent on direct responses from participants rather than tests performed on follow up visits.

1. At least 60% of potential participants will accept recruitment and the dropout rate should be less than 15%.
2. At least 75% of participants will provide fully completed HRQOL questionnaires at 1 and 6 months.
3. At least 75% of participants will complete the CIC diaries at 1, 3 and 6 months.
4. At least 90% of the participants will complete their proposed urodynamic studies and ultrasounds at 3 and 6 months (± 2 weeks).
5. There will be less than 10% crossover between the 2 arms of the trial. In this trial crossovers are not an issue, as both treatment groups will receive the randomly assigned therapy. There will not be any crossovers permitted from the oxybutynin group.
Secondary outcomes

Video urodynamic evaluations were performed on the Laborie Triton machine using ICCS cystometry guidelines of slow fill cystometrogram at baseline (or within 6 months prior to randomization), at 3 and 6 months follow up [100]. A 7 Fr 2-way catheter was used for bladder filling and recording of the intravesical pressure (pves). Abdominal pressure (pabd) was recorded with a 10 Fr rectal balloon catheter. Simultaneous pelvic floor electromyography was recorded using patch electrodes attached to the perineum. Fluoroscopic images during videocystometry were used to detect the degree of bladder trabeculations, grade VUR if present, assess morphology of the bladder neck and assist in recording the DLPP. Standard slow fill cystometry at 5ml/s was performed using normal saline at 32 degree C. The parameters recorded during videocystometry included:

1. Reflex volume (RV): This is the bladder capacity at the first neurogenic detrusor overactivity (NDO), which leads to EMG overactivity, leakage or is more than 15 cm H$_2$O in amplitude. This value is expressed as a percentage of the maximal cystometric capacity.

2. Maximal cystometric capacity (MCC): The bladder capacity at continuous passive bladder leakage. In the absence of leakage, filling is stopped at expected capacity for age given by the formula (age+2) x30 ml. The % of expected bladder capacity for age (%EBC) is the MCC expressed as a percentage of expected bladder capacity for age given by the above formula.

3. Detrusor leak point pressure (DLPP): The detrusor pressure \( p_{\text{det}} = (p_{\text{ves}} - p_{\text{pabd}}) \) at the point of passive bladder leakage as determined on videocystometry.

4. Maximal end fill detrusor pressure (EFP): In participants who did not demonstrate a DLPP, the maximal detrusor pressure (MDP) at expected bladder capacity was recorded and used instead of the DLPP.

5. Pressure specific bladder volume at 20 and 30 cm H$_2$O (20 below and 30 below): The bladder volume expressed as a percentage of the MCC when the passive bladder pressure (pdet) reaches 20 and 30 cm H$_2$O.
6. Safe volume: This is the bladder capacity reached under 40 cm H$_2$O filling pressures (pdet).

In addition to the above urodynamic variables, which were recorded as continuous variables, the presence or absence of NDO and the value of DLPP < or > 40 cm H$_2$O was also recorded as binary variables. The other variables recorded during videocystometry included VUR presence and grading, presence and grading of trabeculations and the morphology of the bladder neck. VUR grading was based on the standardized International VUR grading system. Bladder trabeculation was graded from 0 to 3 based on a previously used non-validated classification system [19]. Bladder neck morphology was classified as open, funneled or closed based on the fluoroscopic images during cystometry.

The validated HRQOL questionnaire developed by Parkin et al was administered at baseline, 1 month and 6 months follow up [35]. This questionnaire consists of two scales: 44 questions for the 5-12 year age group and 47 questions for the 13-20 year age group. The final score is obtained by summing individual items, and scoring is reversed for negative questions. The following 10 domains were assessed: social; emotional; intellectual; financial; medical; independence; environmental; physical functioning; recreation and vocational. Each question (accompanied by a 5-point Likert scale) was given equal weighting. The parents of the 5-12 year participants responded from their child’s viewpoint while adolescents in the 13-20 year age group responded directly, asking for help from their parents if necessary.

3.5 SAMPLE SIZE DETERMINATION

The sample size calculation for this pilot study could be potentially estimated based on several criteria described in the literature [90-94]. In general, an arbitrary sample size of approximately 15- 20 is recommended for a pilot trial, though this approach neglects any estimate of the effect size and its clinical significance, which can vary depending on the research question. The ideal approach for a sample size calculation is to perform a formal
calculation based on the hypothesis using effect sizes of the variable of interest and variances recorded in other trials. However, the patient group being offered the intervention in this pilot trial was different from the previous observational studies conducted. This is the first RCT on SB patients who have received OnabotulinumtoxinA injection as primary therapy. In addition, these patients were different from a clinical and urodynamic perspective and had not reached the point where anticholinergic therapy failed or was not tolerated. None of these patients were deemed to be clinically at a stage, which required a bladder augmentation procedure. This group of patients had moderately affected bladder storage function, which by current standard of care will be treated with anticholinergic therapy.

In patients with a NB, there are several clinically important urodynamic variables, which can be selected for sample size estimation. These include measurements of DLPP or end fill pressures, 20 and 30 cm H\textsubscript{2}O volumes expressed as percentage of MCC and safe volume under 40 cm H\textsubscript{2}O. These are measures of bladder compliance, which is an important determinator of upper urinary tract safety. Other variables like presence or absence of NDO or the bladder volume at onset of NDO (RV) or dryness between CIC can also be used as the primary end point. Since this is a pilot trial assessing feasibility and acceptability criteria, a formal sample size calculation was not performed and a sample size of 20 based on the literature review on pilot trials was used for this study.

3.6 RANDOMIZATION

After completion of the eligibility visit, if the subject met the inclusion and exclusion criteria and consented to participate, randomization was performed to one of two treatment groups. Restricted randomization was used for this study with a 1:1 allocation in a balanced block manner (fixed block sizes of 4 each) with allocation concealment. The sequence was pre-generated using a computer-generated list of random numbers, which were placed in a sealed envelope. Randomization occurred at the physician office by the administrative assistant using this pre-determined randomization sequence with allocation concealment of the recruiting physician. Once randomized, the subject was
followed for 6 months and all outcome events were attributed to the study group to which the subject was originally assigned (intent-to-treat-analysis). Follow-up visits were conducted at 1, 3 and 6 months after trial commencement. Beyond 6 months, follow up continued as per standard clinical practice.

3.7 BLINDING

The study was conducted with single blinding of the outcome adjudicator defined as the individual interpreting the urodynamic studies and performing the statistical analyses. The health care providers and patients were not blinded to the treatment received, as this was not feasible in the surgical care setting [98]. The treating physician performed the recruitment and conducted follow up assessments. Completed CIC diaries and HRQOL questionnaires were collected by a research assistant and entered into a database. The outcome evaluator assessed the urodynamic studies after removal of all patient annotation and assignment of random numbers to each urodynamic study at baseline, 3 and 6 months. After interpretation of the urodynamic study and all data entering, the patient groups were un-blinded and the final analysis was performed. In this trial, except for the QOL assessments, all secondary outcomes are objective measurements. The primary outcomes on trial feasibility were assessed with a predetermined evaluation criterion.

3.8 STATISTICAL METHODS

The primary outcome of assessing trial feasibility involved a descriptive analysis of the proposed outcome measures reported as percentages. Missing values of the proposed urodynamic, clinical and HRQOL questionnaires variables are reported to allow selection of the final variables for the phase III trial.

Analysis of continuous outcome data

SPSS version 20 was used to perform the statistical analysis at the end of 6 months of follow up. No other interim analyses were planned or conducted. An intent- to treat
analysis was performed for all variables irrespective of protocol deviation or crossovers, but excluding any drop-outs. Participants were not excluded from analysis based on missing values of some outcome variable.

Continuous outcomes were analyzed using a 2 sided Student’s unpaired t-test on the post-score and the change scores, assuming unequal variances in the 2 groups. The change scores were the primary focus of the analysis as there is likely to be significant correlation between the pre and post scores. This is because the pre intervention urodynamic variables are indicative of the degree of bladder involvement and the response to the interventions will depend on how severely the bladder is involved (i.e. a less affected bladder will have a presumed better response to therapy in both groups). A Pearson correlation test was performed on the important urodynamic variables to test this hypothesis before using a change score analysis. 95% confidence intervals and p values are reported for all outcome measures, with significance set at $\alpha = 0.05$.

There are 2 assumptions of the t test:
1. The scores are normally distributed. In this study, the small sample size is inadequate despite the robustness of the t test and therefore the Central Limit Theorem cannot be applied.
2. The standard deviations in the 2 intervention groups are homogenous.

Based on these 2 assumptions, the t-test may not be appropriate for our given sample size. Therefore, a more conservative, assumption free non-parametric test was performed on the continuous variables of interest for both the post and change scores. The Mann Whitney U test was the non-parametric test used and the exact significance values instead of the asymptotic significance values are reported.

**Analysis of categorical outcome data**

Since the expected frequencies in a 2X2 table was going to be 5 or less for many
variables, a Fisher’s exact test was used to assess the categorical binary variables in this study. Significance was set at $\alpha = 0.05$.

### 3.9 STUDY VISITS AND ASSESSMENTS

Approval of the University of Western Ontario Research Ethics Board was obtained prior to study initiation (Appendix 2). A screening of all patient charts with a diagnosis of spina bifida associated neurogenic bladder in the study age group was conducted to identify potential subjects based on the eligibility criteria. Potential candidates were invited for a formal assessment by a pediatric urologist after receiving prior mailed information about the proposed trial. Eligibility for study inclusion was reassessed at this visit along with a discussion of the aims and objectives of the study. Parents and children assenting to participate were then formally consented for the study. Table 3.1 lists the schedule of visits and procedures followed for study participants.
Table 3.1: Schedule of visits and procedures

<table>
<thead>
<tr>
<th>Visit windows</th>
<th>Screening and baseline visit</th>
<th>Treatment Day 1</th>
<th>Follow up visit 1 (1 month)</th>
<th>Follow up visit 2 (3 months)</th>
<th>Follow up visit 3 (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment for eligibility</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent/ assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urodynamics</td>
<td>X (if not done within 6 months)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bladder and kidney ultrasound</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis/culture-sensitivity</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CIC diary</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Study BTX-A injection</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<td>HRQOL questionnaire</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse effects monitoring</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Note:
Patients randomized to the oxybutynin arm begin the trial at randomization while patients in the OnabotulinumtoxinA arm begin the trial on Treatment day 1.

The following were obtained at the initial eligibility visit: (1) written informed consent
(2) history of relevant conditions and current medications (3) a physical examination including determination of subject’s height, weight, and body surface area (4) baseline ultrasound of the kidneys and bladder (5) baseline HRQOL questionnaire was provided and asked to be mailed in after filling (7) Videocystometry if not performed within the last 6 months (8) CIC diary was be provided and asked to be mailed in after filling.

Randomization to treatment groups followed a completed eligibility assessment and consent. The Botulinum toxin group was then consented separately for the general anesthetic and the surgical procedure. This group entered the trial on the day of injection; the oxybutynin group entered the study at randomization. The follow-up visits occurred at 4 weeks, 3 and 6 months calculated from the point of entry into the trial (Fig 1). Subjects had access to additional care if needed during the trial period. At each visit a complete urological assessment was performed and details about the side effects of each intervention were recorded. The following additional assessments were performed:

1 month: Participants returned to the urology clinic at 1 month with a completed HRQOL questionnaire and CIC diary. This visit was foregone for those not receiving Botulinum toxin injections provided they mailed in their CIC diary and HRQOL questionnaire.

3 months: Participants returned to clinic 3 months with a completed CIC diary and underwent an urodynamic study and KUB (Kidney, Ureter, and Bladder) ultrasound.

6 months: Participants returned to clinic at 6 months with a completed HRQOL questionnaire and CIC diary and underwent a second follow-up urodynamic study and KUB ultrasound.

3.10 ADVERSE EVENTS AND SAFETY DATA

A Special Event form required completion for every complication associated with OnabotulinumtoxinA injection under anesthesia. Detailed information was collected for the event including diagnosis, time to event and required treatment. The study physician was responsible for the safety of all participants and ensured that the standard of care was maintained throughout and after the completion of the study.
3.11 TERMINOLOGY AND REPORTING

The trial and its reporting used the current ICCS recommended terminology for reporting clinical and urodynamic variables and the CONSORT statement and checklist for reporting of randomized clinical trials [99, 100].
Chapter 4

Results

4.1 PARTICIPANT FLOW

The study was conducted at the pediatric urology clinic at London Health Sciences between May 2011 and April 2012 after obtaining a full board ethics approval from the UWO REB (Appendix 2). The first recruitment and randomization was performed on 29th May 2011 and the last subject was recruited in October 2011. The 6-month follow up for the last recruited patient was completed in April 2012. Based on our a priori recruitment goal of 20, we recruited 15 subjects with 5 of the 20 eligible subjects approached refusing participation (Refusal rate= 25%). The primary reason for refusal was the required follow up visits at 1 and 3 months with the additional urodynamic testing required outside of the standard of care. Patients did suggest that the 50% possibility of being randomized to the oxybutynin arm with no added benefit to them to participate in this trial was another deterrent. Figure 4.1 summarizes the flow of participants in each group. Out of the 15 recruited, 8 were assigned to the botulinum toxin group and 7 to the oxybutynin group. One participant in the oxybutynin group dropped out due to unavailability to attend follow-up visits at 1, 3 and 6 months (dropout rate= 6%). 14 subjects completed the 6- month trial period and were included in the analysis.
Figure 4.1: Participant flow chart

Assessed for eligibility (n= 32)

Excluded (n= 17)
Not meeting inclusion criteria (n= 12)
Declined to participate (n=5)

Randomized (n= 15)

Allocated to OnabotulinumtoxinA (n= 8)
Received allocated intervention (n=8)

Allocated to continuing Oxybutynin therapy (n= 7)
Received allocated intervention (n=7)

Lost to follow up (n= 0)
Protocol deviation- Received oxybutynin after OnabotulinumtoxinA injection (n=1)

Lost to follow up (n= 1)
Discontinued intervention (n=0)

Analyzed (n=8)
Analyzed (n=6)
4.2 PRIMARY OUTCOMES

Feasibility:
Of the 32 patients assessed, 12 were not recruited, as they did not meet eligibility criteria. The primary reason for not meeting eligibility criteria was the lack of a stabilized, maximally tolerated dose of oxybutynin. Some of these patients would be acceptable candidates over a period of follow up once they have reached a maximal tolerated dose and therefore this eligibility criteria is not a hindrance to recruitment. Another reason for not meeting eligibility criteria was the urodynamic inclusion criteria at baseline, which excluded patients with mildly impaired bladder compliance. Based on the results of this pilot trial, we would propose changes to this eligibility criteria and this is discussed later. Our recruitment rate of 75% was achieved in a period of 5 months and highlights the acceptability of the proposed intervention. The primary reasons for refusal to participate were the 3 post randomization visits and the lack of time and resources to attend follow up visits. Since the first visit at 1 month is not clinically relevant for the patients randomized to the oxybutynin arm, an option to mail in the CIC diary was used in our trial. However, despite this, the return rate of completed CIC diary and HRQOL questionnaire was poor and a telephone contact by a research assistant may be appropriate for this group in our proposed final trial design. None of the patients refused participation due to safety concerns of BTX injection or acceptability of the study protocol.

One of the primary motivators highlighted by participants was the option of a medication like OnabotulinumtoxinA, which does not have to be taken daily and is not associated with anti-cholinergic side effects. There was a single drop out in the control arm due to the lack of any clinical benefit for the patient and the difficulty in presenting for the follow up visits. None of the treatment group subjects who received botulinum toxin injections dropped out. There was 1 patient in the OnabotulinumtoxinA arm that restarted oxybutynin therapy at 1 month following injection. This patient received the proposed intervention but did not have adequate response and started oxybutynin at a lower dose than pre BTX-A injection to achieve a greater degree of dryness between catheterizations. This is not a significant protocol deviation because continuing oxybutynin after
botulinum toxin injections may have an added clinical benefit as long as the dose of oxybutynin is tolerated without significant side effects. The urodynamic studies were conducted without any adverse events and all the proposed variables were recorded without procedural difficulties and the missing values were less than 10% for most variables for the 14 patients included in the analysis. The reliability of the urodynamic variables was not assessed in this study as only one filling cycle was performed for the studies. Ideally, it is recommended that at least 2 filling cycles be used for urodynamic studies.

Of our proposed feasibility criteria, the following results were achieved:

1. The recruitment rate was 75% and the dropout rate was 6.6%.
2. The percentage of questionnaires submitted was 65% at 1 month and 80% at 6 months. In addition, several questionnaires missed answers for questions, which made the total score invalid.
3. The percentage of completed CIC diaries was 36% at 1 month, 50% at 3 months and 70% at 6 month.
4. 13 of the 14 patients completed the 2 follow up urodynamic tests at 3 and 6 months (proposed 90% completion rate). This does not include the one patient who dropped out.
5. The crossover rate was 0% (accepted 10% crossover rate) but one patient in the OnabotulinumtoxinA restarted their medication, which constituted a protocol deviation.

Protocol deviations:

1. One patient in the OnabotulinumtoxinA group did not return for their 3-month urodynamic study and had a delayed second urodynamic study at 7 months instead of 6 months.
2. One patient in the OnabotulinumtoxinA group had to restart oxybutynin therapy after injection at 1-month follow-up.

The conduct of the trial was difficult with 3 personnel- the physician who was the
recruiter and evaluator, the research assistant who entered data and the administrative assistant who performed the randomization. The process of allocation concealment and randomization worked effectively. However, the blinding of the evaluator was not ideal as it was the physician recruiting and following up these patients. It can be argued that since the secondary urodynamic outcome measures were objective and reported in a blinded fashion, the results should not be biased. For the proposed phase III trial, each site should have 2 physicians, with one blinded to the treatment assigned who will perform the follow up assessments and interpret the urodynamic tests. Since, the side effects of both treatments are specific; this physician should not assess this variable to preserve the blinding process. In addition, a third party completely detached from the conduct of the trial should evaluate the data and perform the analysis. The randomization process should be done centrally.

Acceptability:

There were no untoward events related to the anesthetic given to the OnabotulinumtoxinA group. 3 of the 8 patients expressed reservations about an anesthesia for injection with its additional risks and recovery period. This will not be an issue for future trials as in insensate SB patients who perform CIC; OnabotulinumtoxinA can be injected without anesthesia in the clinic. In this trial anesthesia was preferred to optimize conditions as the trial has an explanatory rather than a pragmatic approach. The patients assigned to the oxybutynin arm expressed dissatisfaction at not having the opportunity to try this new treatment modality. Based on the results of this trial we are planning to offer Botulinum toxin injection to our control group and recruit them as a partial crossover study after obtaining the necessary ethics approval. The follow up visits and the tests conducted were therefore more onerous for this group as they did not receive any clinical benefit of participating in the trial. In both groups, it was difficult to obtain complete HRQOL questionnaires and CIC diaries. To increase response rates, it would be beneficial to have the participants complete the HRQOL questionnaire at the follow visit rather than have them mail it. A trial nurse can assist with questions, which are difficult to answer or are ambiguous. The CIC diaries are an important component of the outcome as it helps in
assessing the continence over a 48-hour period along with multiple CIC volumes, which provides a more reliable estimate of the functional bladder capacity. A more thorough explanation of its importance with phone calls prior to the follow up visits can improve response rates in this regard.

**Determining effect sizes: Variable selection and sample size calculations**

The final variable selected should meet the following criteria:

1. The variable should be clinically relevant to the patient and the physician
2. The variable should have acceptable validity and be recorded reliably
3. The sample size calculated should be feasible

Table 4.1 and 4.2 illustrate the possible end points for a phase III trial and the sensitivity analysis of the sample size required for conducting a superiority trial. Since the side effect profile of OnabotulinumtoxinA injection is favorable compared to oxybutynin therapy and injections by physicians obviate the risk of non-compliance, it may be feasible to design a rigorous equivalence trial showing equal urodynamic outcomes (with better side effect profile), which will justify the use of OnabotulinumtoxinA compared to standard oxybutynin therapy.

**Formula for comparing 2 means:**

\[ H_0 = \mu_E = \mu_C \]

\[ \sigma = \text{Standard deviation of response variable} \]
\[ \Delta = \text{Smallest difference between } \mu_E \text{ and } \mu_C \text{ of clinical significance} \]
\[ (Z_\alpha + Z_\beta)^2 = \text{Multiplier which depends on level of significance } \alpha \text{ and power } 1-\beta \]
Required number of subjects per group =

\[ N = \frac{(Z_{\alpha} + Z_{\beta})^2 2 \sigma^2}{\Delta^2} \]

Clinically significant change in DLPP in Botulinum toxin group compared to oxybutynin group \((\Delta) = 10 \text{ cm H}_2\text{O}\)

N= 68 per arm

Allowing for 10% drop out rate, total sample size = 150

**Table 4.1: Possible primary end point for the proposed phase III trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| 20 below capacity | - Significant at 3 months  
                   | - Reliable surrogate measure of compliance                           | - Has to be carefully recorded during urodynamics  
                   |                                                                       | - Not well reported in other Botox studies                                               |
| DLPP           | - Well accepted measure prognosticating upper tract damage  
                   | - CI and p value suggested close to significant results               | - Cut off 40 cm H\(_2\)O accepted- should it be used as a binary or continuous variable?  
                   |                                                                       | - Can be missed if not careful during study in insensate patients                      |
| RV             | - Related to NDO which impacts continence  
                   | - Botox has prominent effect on NDO                                   | - Difficult to measure reliably  
                   |                                                                       | - Affected by rate of filling and several other factors                                 |
| MCC or %EBC    | - Prominent effect of Botox  
                   | - Easy and reliable measure  
                   | - Impacts continence                                                  | - Does not directly predict upper tract damage                                            |
| Safe volume    | - Good measure as combines capacity, compliance and DLPP             | - Varies by age                                                       |
                   | - Significant at 6 months                                           |                                                                       |


Table 4.2: Sample size calculations for a superiority trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ</th>
<th>σ</th>
<th>α</th>
<th>Power (1- β)</th>
<th>N per group</th>
<th>Add 10%</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPP (as continuous)</td>
<td>20</td>
<td>20.8</td>
<td>.05</td>
<td>.80</td>
<td>17</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>20.8</td>
<td>.05</td>
<td>.90</td>
<td>23</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>20.8</td>
<td>.05</td>
<td>.80</td>
<td>8</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>20.8</td>
<td>.05</td>
<td>.90</td>
<td>10</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>20.8</td>
<td>.05</td>
<td>.80</td>
<td>68</td>
<td>7</td>
<td>150</td>
</tr>
<tr>
<td>DLPP (as binary)</td>
<td>P_c=0.5</td>
<td>N/A</td>
<td>.05</td>
<td>.80</td>
<td>90</td>
<td>9</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>P_c= 0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 below</td>
<td>30</td>
<td>18.1</td>
<td>.05</td>
<td>.80</td>
<td>6</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>18.1</td>
<td>.05</td>
<td>.90</td>
<td>8</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>18.1</td>
<td>.05</td>
<td>.80</td>
<td>13</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>18.1</td>
<td>.05</td>
<td>.90</td>
<td>18</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>18.1</td>
<td>.05</td>
<td>.80</td>
<td>52</td>
<td>57</td>
<td>114</td>
</tr>
<tr>
<td>MCC</td>
<td>50</td>
<td>143.1</td>
<td>.05</td>
<td>.80</td>
<td>129</td>
<td>133</td>
<td>266</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>143.1</td>
<td>.05</td>
<td>.80</td>
<td>33</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>Safe volume</td>
<td>50</td>
<td>152.2</td>
<td>.05</td>
<td>.80</td>
<td>146</td>
<td>161</td>
<td>322</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>152.2</td>
<td>.05</td>
<td>.80</td>
<td>65</td>
<td>72</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>152.2</td>
<td>.05</td>
<td>.80</td>
<td>37</td>
<td>41</td>
<td>82</td>
</tr>
<tr>
<td>RV</td>
<td>20</td>
<td>24.4</td>
<td>.05</td>
<td>.80</td>
<td>23</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>24.4</td>
<td>.05</td>
<td>.80</td>
<td>11</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

4.3 SECONDARY OUTCOMES

The clinical secondary outcomes were analyzed at 1, 3 and 6 months follow up in 14 patients. The primary analysis was intention to treat and involved all patients who were randomly assigned, except the one early drop out in the oxybutynin group who had no follow up data at 1,3 and 6 months.
Baseline assessment

Tables 4.3-4.5 compare the baseline demographics, clinical and urodynamic characteristics of the 2 groups. Significance tests are not recommended to compare baseline characteristics, as any baseline differences in the 2 groups in a RCT are a result of chance rather than bias [99]. Despite the small sample size in this pilot trial, the 2 groups were similar in baseline characteristics. The groups are comparable with respect to age, gender, ambulatory status, underlying cause of the NB, presence of ventriculoperitoneal shunt and continence status. Nine of the 14 patients (64%) in this trial were wet between CIC at study initiation based on the history and CIC diary. Seven of the 8 patients in the botulinum toxin group and 4 of the 6 in the oxybutynin group reported side effects on current oxybutynin therapy. The 2 frequently reported side effects included dry mouth and constipation. The 2 groups were on similar doses of oxybutynin and CIC frequency. Baseline urodynamic studies revealed comparable bladder capacities and DLPP in the 2 groups. The botulinum toxin group had more affected bladder storage function compared to the oxybutynin group with lower bladder capacity, 20 below capacities and volumes stored at a safe pressure under 40 cm H₂O. The DLPP was above 40 cm H₂O in 6 of the 8 patients (75%) in the OnabotulinumtoxinA arm compared to 2 of 6 (33%) in the oxybutynin arm.

Table 4.3: Baseline demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>15.7 (3.65)</td>
<td>16.2 (3.43)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>MMC= 7 Diastometamyleia=1</td>
<td>MMC= 5 Lipo MMC= 1</td>
</tr>
<tr>
<td>Shunted</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)
Table 4.4: Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continence (wet)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Oxybutynin dose (mg/d)</td>
<td>24 (8.2)</td>
<td>20 (3.2)</td>
</tr>
<tr>
<td>CIC frequency/d</td>
<td>4.3 (0.74)</td>
<td>4.5 (0.83)</td>
</tr>
<tr>
<td>Trabeculations (present)</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Bladder neck (open)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>VUR (present)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Side effects (present)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>HRQOL score</td>
<td>200 (31.9)</td>
<td>190 (31.9)</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

Table 4.5: Baseline urodynamic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>312.2 (142.3)</td>
<td>453.6 (105.6)</td>
</tr>
<tr>
<td>%EBC</td>
<td>66.5 (30.1)</td>
<td>89.5 (9.9)</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>58.3 (24.9)</td>
<td>39.8 (4.9)</td>
</tr>
<tr>
<td>RV (%)</td>
<td>34.3 (29.7)</td>
<td>27.8 (14.3)</td>
</tr>
<tr>
<td>20 Below (%)</td>
<td>36.1 (10.1)</td>
<td>59.2 (18.6)</td>
</tr>
<tr>
<td>30 Below (%)</td>
<td>62.7 (13.7)</td>
<td>77.7 (18.4)</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>241.2 (125.9)</td>
<td>435.6 (110.1)</td>
</tr>
<tr>
<td>NDO (present)</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>DLPP &gt; 40 (yes)</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

NDO: Neurogenic detrusor overactivity, DLPP > 40: Detrusor leak point pressure > 40
Assessment at 1 month
At one month follow up the continence status based on CIC diaries and history; HRQOL response and side effect profile was evaluated. There were no adverse events related to OnabotulinumtoxinA injection. All 8 patients who received botulinum toxin discontinued their oxybutynin after injection. The 4 patients who reported side effects in the oxybutynin group continued to report similar side effects but continued their oxybutynin therapy. The option of mailing in the CIC diaries and HRQOL questionnaire for the oxybutynin group led to a significant non-response rate, which led to several missing values and lack of enough data to perform an analysis. Of the 6 patients wet in the botulinum toxin group, 4 had achieved dryness and 2 continued to be wet. One of the subjects in the OnabotulinumtoxinA group re-initiated oxybutynin therapy as she continued to have ongoing wetness but this additional therapy did not lead to dryness. There was no improvement in the QOL outcome in this group as assessed by the questionnaire.

Assessment at 3 months
QQ plots and Pearson correlation coefficients were calculated for all urodynamic continuous variables to assess linearity and the correlation between baseline, 3 and 6-month scores (Table 4.6). Based on significant correlation shown statistically as well as clinical likelihood of correlation, a change score analysis was also conducted along with post score analysis. Unpaired t tests and the Mann Whitney U tests were performed for all continuous variables and the Fisher exact test was conducted for binary variables. There were no significant differences on post score analysis between the 2 groups at 3 months, except the proportion of patients who reported side effects (Table 4.7, 4.8). None of the botulinum toxin group had side effects, compared to 4 of the 6 in the oxybutynin group (p= 0.01).
Table 4.6: Pearson correlation between continuous urodynamic variables (performed after QQ/PP plots showing linear distribution)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Pearson r</th>
<th>Significance (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC baseline</td>
<td>372.8</td>
<td>0.598</td>
<td>.031</td>
</tr>
<tr>
<td>MCC 3 mo.</td>
<td>390.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCC baseline</td>
<td>372.8</td>
<td>0.672</td>
<td>.008</td>
</tr>
<tr>
<td>MCC 6 mo.</td>
<td>378.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLPP baseline</td>
<td>50.4</td>
<td>.944</td>
<td>.000</td>
</tr>
<tr>
<td>DLPP 3 mo.</td>
<td>40.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLPP baseline</td>
<td>50.4</td>
<td>.673</td>
<td>.008</td>
</tr>
<tr>
<td>DLPP 6 mo.</td>
<td>55.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 below baseline</td>
<td>46.0</td>
<td>.027</td>
<td>.934</td>
</tr>
<tr>
<td>20 below 3 mo.</td>
<td>59.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 below baseline</td>
<td>46.0</td>
<td>.449</td>
<td>.107</td>
</tr>
<tr>
<td>20 below 6 mo.</td>
<td>46.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 below baseline</td>
<td>69.1</td>
<td>.236</td>
<td>.461</td>
</tr>
<tr>
<td>30 below 3 mo.</td>
<td>87.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 below baseline</td>
<td>69.1</td>
<td>.711</td>
<td>.004</td>
</tr>
<tr>
<td>30 below 6 mo.</td>
<td>58.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV baseline</td>
<td>31.8</td>
<td>-.556</td>
<td>.195</td>
</tr>
<tr>
<td>RV 3 mo.</td>
<td>35.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV baseline</td>
<td>31.8</td>
<td>.314</td>
<td>.347</td>
</tr>
<tr>
<td>RV 6 mo.</td>
<td>30.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe volume baseline</td>
<td>324.6</td>
<td>.504</td>
<td>.095</td>
</tr>
<tr>
<td>Safe volume 3 mo.</td>
<td>360.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe volume baseline</td>
<td>324.6</td>
<td>.647</td>
<td>.012</td>
</tr>
<tr>
<td>Safe volume 6 mo.</td>
<td>266.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.7: Urodynamic and clinical variables at 3 months follow up (Post score analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>346.8 (147.3)</td>
<td>440.3 (43.6)</td>
<td>0.153</td>
</tr>
<tr>
<td>%EBC</td>
<td>72.7 (26.5)</td>
<td>87.6 (8.9)</td>
<td>0.201</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>43.2 (23.3)</td>
<td>37 (6.2)</td>
<td>0.556</td>
</tr>
<tr>
<td>RV (%)</td>
<td>30 (22.6)</td>
<td>38.2 (21.4)</td>
<td>0.707</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>66.5 (21.5)</td>
<td>51.6 (18.8)</td>
<td>0.233</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>86.3 (21.8)</td>
<td>88.8 (9.7)</td>
<td>0.805</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>298.3 (161.2)</td>
<td>421.8 (35.7)</td>
<td>0.121</td>
</tr>
<tr>
<td>Trabeculations (present)</td>
<td>7</td>
<td>5</td>
<td>0.476</td>
</tr>
<tr>
<td>DLPP &gt; 40 (yes)</td>
<td>3</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Bladder neck (open)</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>VUR (present)</td>
<td>2</td>
<td>3</td>
<td>0.592</td>
</tr>
<tr>
<td>NDO (present)</td>
<td>2</td>
<td>5</td>
<td>0.103</td>
</tr>
<tr>
<td>Continence (wet)</td>
<td>2</td>
<td>3</td>
<td>0.580</td>
</tr>
<tr>
<td>HRQOL</td>
<td>208 (20.2)</td>
<td>202 (18)</td>
<td>0.713</td>
</tr>
<tr>
<td>Side effects</td>
<td>0</td>
<td>4</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

- *Independent samples t test, equal variances not assumed, 2-tailed
- All categorical variables: Fisher exact tests

Table 4.8: Non parametric tests at 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>0.181</td>
</tr>
<tr>
<td>%EBC (%)</td>
<td>0.366</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>0.818</td>
</tr>
<tr>
<td>RV (%)</td>
<td>0.571</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>0.240</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>0.589</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>0.065</td>
</tr>
<tr>
<td>HRQOL</td>
<td>0.90</td>
</tr>
</tbody>
</table>

- Independent samples Mann-Whitney U test
- Testing distribution in the 2 groups, Exact significance displayed
Table 4.9 and 4.10 shows the change scores in the 2 groups along with 95% confidence intervals of the effect sizes. The botulinum toxin group showed a significant increase in the 20 below capacity at 3 months compared to the oxybutynin group on both the t test and the Mann Whitney U test (p= 0.001 and 0.009 respectively, 95 % CI -62 and -21, Figure 4.2). Interestingly, there was a decrease in mean MCC, 20 below capacity and safe volumes in the oxybutynin group compared to baseline values. There are 2 possible explanations of this finding. One possible explanation is the role of a single outlier in the oxybutynin arm with reduced MCC and safe volumes (Fig. 4.3 & 4.4). The effect of this outlier was not evident for the poor 20 and 30 below (Fig. 4.2, 4.5) capacities seen in this group and this may be explained by either a true deterioration in bladder function or a reflection of poor compliance to therapy secondary to side effects of oxybutynin. There was an impressive increase in the safe volume in the OnabotulinumtoxinA group of 92 ml compared to baseline. Similarly, the reflex volume increased by about 40% compared to 8% in the oxybutynin group (p= 0.089, Figure 4.6). There was no significant difference between the botulinum toxin and oxybutynin group in the reduction in DLPP achieved at 3 months (Fig. 4.7). NDO was seen in all 8 patients (100%) in the OnabotulinumtoxinA arm at baseline but demonstrated in only 2 of the 8 (25%) at 3 months. Despite these results the HRQOL assessment was not significantly different between the 2 groups. There was improvement in the continence status in the botulinum toxin group from 2 patients being dry at baseline to 6 dry at 3 months but this result was not statistically different compared to the oxybutynin group (3 dry at baseline and 3 dry at 3 months).
Table 4.9: Change score analysis: 3 months- baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>45.7 (121.3)</td>
<td>-11.6 (124.1)</td>
<td>0.42</td>
<td>-208.4, 93.7</td>
</tr>
<tr>
<td>%EBC</td>
<td>8.3 (22.3)</td>
<td>-1.8 (10.8)</td>
<td>0.315</td>
<td>-31.6, 11.4</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>-7.8 (5.1)</td>
<td>-2.8 (4.7)</td>
<td>0.092</td>
<td>-9.6, 11.0</td>
</tr>
<tr>
<td>RV (%)</td>
<td>40.8 (29.9)</td>
<td>8.6 (31.6)</td>
<td>0.089</td>
<td>-70.2, 5.8</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>34.3 (16.9)</td>
<td>-7.5 (14.6)</td>
<td><strong>0.001</strong></td>
<td><strong>-62.2, -21.4</strong></td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>24.5 (18.1)</td>
<td>11.2 (22.8)</td>
<td>0.29</td>
<td>-40, 13.3</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>92.8 (155.3)</td>
<td>-13.8 (122.5)</td>
<td>0.218</td>
<td>-287.9, 74.6</td>
</tr>
<tr>
<td>HRQOL</td>
<td>-5.6 (7.2)</td>
<td>12.3 (15.6)</td>
<td>0.05</td>
<td>-0.02, 36.01</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

- *Independent samples t test, equal variances not assumed, 2-tailed

Table 4.10: Non-parametric tests on change scores at 3 and 6 months (compared to baseline) and between 6 and 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value (3months-baseline)</th>
<th>p value (6 months -baseline)</th>
<th>p value (6 months -3months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>0.445</td>
<td><strong>0.008</strong></td>
<td>0.181</td>
</tr>
<tr>
<td>%EBC</td>
<td>0.234</td>
<td><strong>0.029</strong></td>
<td>0.628</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>0.101</td>
<td>0.081</td>
<td><strong>0.032</strong></td>
</tr>
<tr>
<td>RV (%)</td>
<td>0.138</td>
<td>0.181</td>
<td>0.234</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td><strong>0.009</strong></td>
<td>0.108</td>
<td>0.065</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>0.394</td>
<td>0.345</td>
<td>0.485</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>0.180</td>
<td><strong>0.001</strong></td>
<td>NA</td>
</tr>
<tr>
<td>HRQOL</td>
<td>0.167</td>
<td>0.537</td>
<td>NA</td>
</tr>
</tbody>
</table>

Independent samples Mann-Whitney U test

Testing distribution in the 2 groups, Exact significance displayed
Figure 4.2

CHANGE IN % 20 BELOW CAPACITY AT 3 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.3

Change in MCC at 3 mo compared to baseline

TX GROUP
TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.4

CHANGE IN SAFE VOLUME AT 3 MO COMPARED TO BASELINE

TX GROUP
TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX

$0^2$
Figure 4.5

CHANG IN % 30 BELOW CAPACITY AT 3 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX

Figure 4.5
Figure 4.6

CHANGE IN REFLUX VOLUME AT 3 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.7
**Assessment at 6 months**

A change score and post score analysis was conducted at 6 months follow up. Unpaired t tests and the Mann Whitney U tests were performed for all continuous variables and the Fisher exact test was conducted for binary variables.

Tables 4.10-4.13 list the post score and change score analysis at 6 months compared to baseline. Again, like at 3 months follow up, the side effects were significantly higher in the oxybutynin group compared to the botulinum toxin group (p=0.015). There were no other significant differences on post score analysis using parametric or non-parametric statistical analysis. The change score analysis revealed significant improvements in the OnabotulinumtoxinA group in MCC (Fig. 4.8), % EBC and safe volumes (Fig. 4.9) compared to the oxybutynin group (p= 0.01, 0.02, 0.003 respectively). Similar results were obtained with the Mann Whitney U test for these variables (p= 0.008, 0.029 and 0.001 respectively). There was an outlier in the oxybutynin group, which could explain the safe volume difference between the 2 groups but this was not the case for the MCC and % EBC assessments. Figures 4.10-4.13 compares the change in DLPP, RV, 20 and 30 below capacities between the 2 groups.
Table 4.11: Urodynamic and clinical variables at 6 months follow up (post score analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>379.5 (112.8)</td>
<td>376.3 (119.9)</td>
<td>0.961</td>
</tr>
<tr>
<td>%EBC</td>
<td>80.25 (23.9)</td>
<td>80.0 (25.8)</td>
<td>0.986</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>56.5 (23.8)</td>
<td>55.2 (20.9)</td>
<td>0.913</td>
</tr>
<tr>
<td>RV (%)</td>
<td>30.1 (6.2)</td>
<td>30.6 (19.4)</td>
<td>0.964</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>45.7 (29.7)</td>
<td>46.8 (27.2)</td>
<td>0.945</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>55.8 (25.4)</td>
<td>61.2 (33.7)</td>
<td>0.755</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>253.6 (131)</td>
<td>282.8 (144.2)</td>
<td>0.705</td>
</tr>
<tr>
<td>Trabeculations (present)</td>
<td>8</td>
<td>4</td>
<td>0.341</td>
</tr>
<tr>
<td>DLPP &gt; 40 (yes)</td>
<td>6</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Bladder neck (open)</td>
<td>3</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>VUR (present)</td>
<td>2</td>
<td>3</td>
<td>.580</td>
</tr>
<tr>
<td>NDO (present)</td>
<td>6</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Continence (wet)</td>
<td>4</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>HRQOL</td>
<td>194 (24.7)</td>
<td>182.3 (28.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Side effects</td>
<td>0</td>
<td>4</td>
<td>.015</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

- *Independent samples t test, equal variances not assumed, 2-tailed
- All categorical variables: Fisher exact tests

Table 4.12: Non parametric tests at 6 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>0.950</td>
</tr>
<tr>
<td>%EBC (%)</td>
<td>0.950</td>
</tr>
<tr>
<td>DLPP (cm H₂O)</td>
<td>0.852</td>
</tr>
<tr>
<td>RV (%)</td>
<td>1.0</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>0.950</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>0.852</td>
</tr>
<tr>
<td>Safe Volume (ml)</td>
<td>0.755</td>
</tr>
<tr>
<td>HRQOL</td>
<td>0.567</td>
</tr>
</tbody>
</table>

Independent samples Mann-Whitney U test
Testing distribution in the 2 groups, Exact significance displayed
Table 4.13: Change score analysis: 6 months- baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
<th>p value</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>67.2 (72.5)</td>
<td>-77.3 (89.8)</td>
<td>0.01</td>
<td>-245, -44.1</td>
</tr>
<tr>
<td>%EBC</td>
<td>13.7 (16.8)</td>
<td>-9.5 (17.0)</td>
<td>0.028</td>
<td>-43.4, -3.1</td>
</tr>
<tr>
<td>DLPP (cm H$_2$O)</td>
<td>-1.88 (14.2)</td>
<td>15.3 (17.0)</td>
<td>0.074</td>
<td>-1.9, 36.4</td>
</tr>
<tr>
<td>RV (%)</td>
<td>13.1 (31.4)</td>
<td>2.2 (11.6)</td>
<td>0.387</td>
<td>-38.1, 16.2</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>9.6 (26.0)</td>
<td>-12.3 (19.6)</td>
<td>0.097</td>
<td>-48.5, 4.6</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>-6.4 (17.0)</td>
<td>-16.5 (24.4)</td>
<td>0.409</td>
<td>-36.7, 16.5</td>
</tr>
<tr>
<td>Safe volume (ml)</td>
<td>12.4 (88.4)</td>
<td>-163 (84.4)</td>
<td>0.003</td>
<td>-277.5, -73.2</td>
</tr>
<tr>
<td>HRQOL</td>
<td>-1.6 (20.1)</td>
<td>-8.7 (8.5)</td>
<td>0.495</td>
<td>-31.5, 17.4</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

- *Independent samples t test, equal variances not assumed, 2-tailed
Figure 4.8
Figure 4.9
Figure 4.10

CHANGE IN DLPP AT 6 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
CHANGE IN REFLEX VOLUME AT 6 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX

Figure 4.11
Figure 4.12

CHANGE IN % 20 BELOW CAPACITY AT 6 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.13

CHANGE IN %30 BELOW CAPACITY AT 6 MO COMPARED TO BASELINE

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
**Change at 6 months compared to 3 months**

This analysis was performed to assess the time duration of OnabotulinumtoxinA action, as there would not be any expected changes in the oxybutynin group provided the bladder function remained stable and compliance was maintained. It is reported that OnabotulinumtoxinA action lasts 6-9 months after injection. Table 4.10 and 4.14 show the results of gain score analysis at 6 months compared to 3 months.

**Table 4.14: Change score analysis: 6 months - 3 months**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OnabotulinumtoxinA group (N=8)</th>
<th>Oxybutynin group (N=6)</th>
<th>p value</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (ml)</td>
<td>18.7 (74.8)</td>
<td>-58.5 (110.8)</td>
<td>0.183</td>
<td>-198.7, 44.3</td>
</tr>
<tr>
<td>%EBC</td>
<td>4.7 (9.2)</td>
<td>-7.6 (22.8)</td>
<td>0.257</td>
<td>-36.4, 11.6</td>
</tr>
<tr>
<td>DLPP (cm H\textsubscript{2}O)</td>
<td>1.2 (1.1)</td>
<td>3.8 (1.9)</td>
<td><strong>0.037</strong></td>
<td><strong>0.21, 4.9</strong></td>
</tr>
<tr>
<td>RV (%)</td>
<td>-31.7 (43.1)</td>
<td>6.3 (34.6)</td>
<td>0.106</td>
<td>-9.4, 85.5</td>
</tr>
<tr>
<td>20 BELOW (%)</td>
<td>-25.5 (24.3)</td>
<td>-4.8 (10.3)</td>
<td>0.099</td>
<td>-5, 46.4</td>
</tr>
<tr>
<td>30 BELOW (%)</td>
<td>-35.8 (24.5)</td>
<td>-26.8 (32.2)</td>
<td>0.599</td>
<td>-28.2, 46.2</td>
</tr>
</tbody>
</table>

Data are means (Standard deviation) or numbers (%)

Independent samples t test, equal variances not assumed, 2-tailed

In the OnabotulinumtoxinA botulinum toxin group, 3 urodynamic parameters showed deterioration at 6 months compared to 3 months suggesting that the effects of the injection wean off during this time period. These include 20 and 30 below capacities and a decrease in the RV (Fig. 4.14-4.16). These differences were more pronounced in the OnabotulinumtoxinA botulinum toxin group compared to the oxybutynin group. In addition the DLPP decrease was significantly higher in the oxybutynin group compared to the botulinum toxin group (p=0.037 and 0.032, Fig. 4.17). The oxybutynin group continued to show a decrease in the bladder capacity (Fig. 4.18). These results suggest that careful follow up is required in the 3 to 6 month follow up period in those receiving BTX-A injections. A possible measure, which can be instituted in this period, is the restarting of oxybutynin therapy to compensate for some loss of OnabotulinumtoxinA
activity.

Figure 4.14

CHANGE IN REFLEX VOLUME AT 6 MO COMPARED TO 3 MO

TX GROUP

TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.15
Figure 4.16

CHANGE IN % 30 BELOW CAPACITY AT 6 MO COMPARED TO 3 MO

TX GROUP
TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX
Figure 4.17
Figure 4.18

CHANGE IN MCC AT 6 MO COMPARED TO 3 MO

TX GROUP
TX GROUP 1: OXYBUTYNIN
TX GROUP 2: BOTOX

Figure 4.18
Summary of the results:

The study recruited 15 subjects (75% recruitment rate) over a 5-month period of which, 14 (6% drop out rate) completed the 6-month follow-up. There were no crossovers or severe adverse events in both groups. The CIC diaries and HRQOL questionnaire completion rates did not meet the pre-specified rate. 13 of 14 subjects completed the follow up urodynamic studies and ultrasounds. Overall, 6 of the 8 subjects in the botulinum toxin arm will undergo re-injection based on patient desirability and adequacy of clinical response. Incidence of side effects was significantly different in the 2 arms (0% in the botulinum toxin group versus 66% in the oxybutynin group, p=0.01). The baseline clinical and urodynamic variables were similar in both groups. The urodynamic and clinical results at 3 and 6 months were comparable. The effects of botulinum toxin weaned between the 3 and 6-month period.

This pilot study justifies the conduct of a phase III randomized controlled trial to assess the efficacy of OnabotulinumtoxinA injections as primary therapy for pediatric neurogenic bladder in comparison to standard oxybutynin therapy.
Chapter 5

Discussion

Well-designed and executed randomized controlled trials provide the most reliable evidence on the efficacy of proposed health interventions. The conduct of an RCT is time-consuming, expensive and deals with moral and ethical obligations of the researcher towards the participants. The role of an external pilot trial therefore is justified to assess trial feasibility and available resources, weed out potential problems and train personnel [84-87]. An added benefit of conducting a pilot is in situations where a new intervention or a new indication for an existing intervention is being proposed and the researchers want to estimate the level of clinical equipoise as well as incorporate participant input into the final proposed trial. We conducted an external pilot trial to assess the feasibility and acceptability of conducting a phase III RCT comparing the efficacy of first line OnabotulinumtoxinA intra-detrusor injections to standard oxybutynin therapy in children with a spina bifida associated neurogenic bladder.

The study met 3 of our 5 pre-defined feasibility criteria with 75% recruitment rate and 6% drop out rate. The two areas of poor response in this study were with collections of the HRQOL questionnaire and the 48-hour CIC diaries, which were suboptimal but close to our a priori criteria for feasibility. Studies on QOL in spina bifida before and after surgical procedures have been done infrequently [81, 82]. In addition, none of these studies demonstrated clear improvements in the QOL scores despite clinical improvement. Our study showed a similar finding with no changes at the 1 and 6 month scores compared to baseline. A possible explanation for this is the broad nature of the HRQOL questionnaire and lack of specific questions related to continence. Other studies have therefore focused on QOL specific to urinary incontinence like the PIN-Q [101]. The problem with this approach is that the HRQOL is the only validated QOL instrument for children and adolescents with spina bifida. Using generic QOL instruments in this
population may not be appropriate as these children have a myriad of medical, psychological and social issues, which can all impact their QOL. For our proposed trial we could replace this HRQOL questionnaire with a more specific incontinence questionnaire like the PIN-Q or simply limit the assessment to an objective tool assessing continence like the CIC diary. In addition, greater compliance with filling of the questionnaire can be ensured by getting research personnel to run through the questionnaire at follow up visits and phone calls prior to the visit to achieve better response rates. Unanswered questions can be answered at follow up visits to ensure completeness of the forms. This is important as the score generated is a sum of all individual questions and missing answers will impact the total score. With regards to the CIC diaries, the patients could be asked to come to their follow up appointments with a full bladder and assessment could include catheterization in the clinic to measure bladder volume and note whether the patient is dry or not. This gives us a single value as opposed to a 48-hour period, which would be more reliable in estimating the bladder capacity. Another surrogate marker of continence could be the use of pads, which can be quantified by the past month receipts of pads purchased. Since our ideal outcome is to achieve complete dryness, this will be a good measure of the outcome.

The process of allocation concealment and randomization are vital to preventing bias in an RCT. In our pilot trial, this process worked effectively but was not assessed using any objective measure in this study. In part, the similar baseline characteristics in both groups attest to this but again have to be interpreted with caution due to our sample size. Any baseline differences in a RCT are secondary to chance and not selection bias and therefore are not a methodological issue. Third party randomization sequence generation and assignment ensured complete allocation concealment in this study. The balanced block randomization used with blocks of 4 ensured relatively equal sizes for the 2 groups with one drop out in the oxybutynin arm.

Blinding of the treating surgeon and the patient in surgical trials is often difficult to achieve but it should be feasible to blind the data collectors and analysts as was done in this study [98]. If Botulinum toxin is injected without general anesthesia and patients continue oxybutynin therapy in both arms, then patient blinding is possible with a sham
saline injection during cystoscopy, accepting the insignificant potential of cystoscopy related complications. This will be important when patient responses form the primary outcome but are not relevant if objective urodynamic criteria are used. In our pilot trial, the data were analyzed blindly but research personnel who were not blinded assimilated and entered the data. This issue can be sorted by having a larger research team and a separate data entry member.

The secondary outcomes of this study demonstrated that OnabotulinumtoxinA intradetrusor injections are a safe option for treating poorly compliant neurogenic bladders. The lack of anti-cholinergic side effects associated with oxybutynin use makes it an attractive alternative, especially in situations where compliance may be affected due to side effects. Therefore, it can be argued that if OnabotulinumtoxinA is at least as efficacious as oxybutynin in improving bladder storage function, then it should be a possible first line option for patients who need CIC and anticholinergic therapy. There are two possible arguments against the primary use of OnabotulinumtoxinA therapy in the pediatric age group. These include the cost of repeated injections compared to oxybutynin therapy and whether repeated injections can be performed safely and will retain efficacy every 3-6 months indefinitely. Anti botulinum toxin antibodies have been reported and can be produced especially after repeated injections [78]. Secondly, the effect of repeat injections in causing bladder muscle damage and fibrosis is unknown though there has been some short- term literature showing safety in this regard [77].

The duration of effect of BTX-A is supposed to be between 6-9 months [33, 34, 39, 40]. Our study demonstrated that the effects tend to wear off between 3 to 6 months. Possible reasons for this may include a more effected bladder at baseline. In addition, our primary urodynamic focus was on bladder compliance and filling pressures and not on the presence or absence of NDO. Botulinum toxin with its dual mode of action on bladder contractility and the sensory afferent system has a more pronounced effect on NDO rather than bladder compliance. Also, in a significantly trabeculated and affected bladder with muscle changes, simple detrusor relaxation may not impact compliance significantly. This may be another justification for earlier Botulinum toxin use rather than as second line therapy as is current practice. The dose our patients received is at the higher limit of what
is advised and therefore increasing the dose to achieve better response is not an option. It is known that the dose-response curve for botulinum toxin is a parabolic curve with no justification for increasing dose beyond 10 U/kg.

Table 5.1 lists the studies performed in pediatric patients with NB using BTX-A. Of the 3 studies comparing results at 3 and 6 months post injection, including our trial, all demonstrated decreasing effects at 6 months (studies 1, 7, 8). The traditional viewpoint that the effects last for 6-9 months is based on adult literature and some pediatric studies (study 2, 4), which show persistent effects at 6 or 9 months.
Table 5.1: Comparison of results of botulinum toxin studies reported for spina bifida associated neurogenic bladder in pediatric patients

<table>
<thead>
<tr>
<th>Author (N)</th>
<th>Study</th>
<th>Dose Drug</th>
<th>Oxybutynin Baseline</th>
<th>∆ at 3 mo.</th>
<th>∆ at 6 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Schulte-Baukloh (20)</td>
<td>Prospective cohort</td>
<td>12u/kg Botox</td>
<td>13-yes 7-no</td>
<td>MDP= 59.6 RV-97.1 MCC-163</td>
<td>MDP= -13 RV-65 MCC-37</td>
</tr>
<tr>
<td>2. Riccabona (15)</td>
<td>Prospective cohort</td>
<td>10U/kg Not specified</td>
<td>No</td>
<td>MDP= 78.7 RV-72 MCC-136</td>
<td>MDP= -36 RV-226 MCC-260</td>
</tr>
<tr>
<td>3. Altaweel (20)</td>
<td>Prospective cohort</td>
<td>5U/kg not specified</td>
<td>Unclear, allowed to use</td>
<td>MDP (I)- 40 MCC (I)- 43 MCC (I)- 146 MCC (I)- 215</td>
<td>MDP (I)= 0 MCC (C)= 22 MCC (I)= 18 MCC (C)= 123</td>
</tr>
<tr>
<td>4. Neel (12+11)</td>
<td>RCT (+Botox vs. Botox + oxybutynin)</td>
<td>12U/kg Not specified</td>
<td>12-yes 11-no</td>
<td>MDP (B)- 66 MCC (B)- 96 MCC (B+O)- 96</td>
<td>Results in Botox group and botox+oxybutynin</td>
</tr>
<tr>
<td>5. Akbar (19)</td>
<td>Retrospective cohort</td>
<td>20U/kg Dysport</td>
<td>Unclear, allowed to use</td>
<td>MDP= 66 MCC= 180</td>
<td>MDP= -20 MCC= 110</td>
</tr>
<tr>
<td>6. Kajbafzadeh (26)</td>
<td>Prospective cohort</td>
<td>10U/kg Botox</td>
<td>No</td>
<td>MDP= 139 MCC= 102</td>
<td>MDP= -56 MCC= 168</td>
</tr>
<tr>
<td>7. Horst (11)</td>
<td>Retrospective</td>
<td>10U/kg Botox</td>
<td>Allowed to use</td>
<td>MDP= 56 MCC= 208</td>
<td>MDP= -10 MCC= 69</td>
</tr>
<tr>
<td>8. Current study (8+6)</td>
<td>RCT (Botox vs. oxybutynin)</td>
<td>10U/kg Botox</td>
<td>No in the Botox group</td>
<td>MDP= 58 RV (%) 34 MCC= 312</td>
<td>MDP= -15 RV (%) 40 MCC= 45</td>
</tr>
</tbody>
</table>


Table 5.1 also highlights several methodological issues in interpreting these studies. Three of these studies did not specify the botulinum toxin serotype or drug used and 3 did not specify or allowed continued use of oxybutynin after injection thus leading to contamination of the treatment arm. A single RCT conducted between Botox versus Botox and oxybutynin groups did not find any significant differences between the 2 groups [27]. This was a poorly conducted RCT with no reported sample size calculations to assess the power of the study. In addition, the dose of oxybutynin used was 0.1 mg/kg, which is a low dose. It is plausible that simultaneous use of oxybutynin can augment the effects of botulinum toxin based on the different mechanisms of action. In addition reporting of maximum cystometric capacity by itself is meaningless as it is age dependent. Ideally EBC should be the outcome reported for assessing bladder capacity. Also, most studies simply reported the differences in means at baseline and 3 and 6 months rather than reporting the mean change score, which is individually calculated for each participant. The baseline urodynamic variables were very diverse in these studies and bring about significant heterogeneity. In the study by Kajbafzadeh et al, the mean detrusor pressures were 139 cm H$_2$O at baseline and decreased to 83 cm H$_2$O at 3 months [25]. This is a significant improvement, but these patients continue to remain at significant risk of upper tract damage and very likely need a bladder augmentation. In interpreting results the success of therapy cannot be measured by numbers but by its impact to the patient. Therefore, based on the current quality of evidence available, there is adequate justification to conduct a proper RCT to assess the efficacy of OnabotulinumtoxinA versus oxybutynin therapy in this population. In addition clarifications regarding ideal dosage, number of intra detrusor injection sites repeated injections and the timing of injection have to be addressed in future studies.

Our results hold external validity as we have selected patients with poorly compliant neurogenic bladders and provided a complete urodynamic and clinical assessment at baseline, 3 months and 6 months. In addition, all these patients were on maximal tolerated oxybutynin prior to entering the trial. There are, however several limitations, which must
LIMITATIONS

We did not meet our required sample size of 20 during the available recruitment period, which would constitute approximately 15% of our final total sample size (150) for a phase III trial. Therefore our effect size for sample size calculations may be underestimated and not be reliable.

The absence of blinding of the physician and patients could potentially lead to assessment bias, especially with the QOL questionnaire and clinical assessments. This will however be an unlikely issue for the objective urodynamic variables and the CIC diaries, which would be the primary outcomes in a proposed trial. Selection bias was minimized by randomization just after the eligibility visit and by allocation concealment.

This trial does not account for possible compliance bias in both groups. In the oxybutynin group, secondary to side effects, compliance to oxybutynin therapy is a concern. This is actually the justification to seek an alternative treatment option like Botulinum toxin for this population. Serum levels of the active metabolite of oxybutynin can be monitored to assess compliance. On the other hand, those receiving botulinum toxin can also take oxybutynin post injection leading to contamination. The limited sample size in this study does not allow any firm conclusions to be made on the efficacy of botulinum toxin in comparison to oxybutynin. In addition, no corrections have been made for the multiple outcomes assessment done in this pilot trial. This inflates the individual Type I error but since the clinical and urodynamic analysis was secondary in this trial, this correction was not performed.

CONCLUSIONS

Our recommendation based on this pilot study is to conduct a phase III trial to explore the first line use of OnabotulinumtoxinA compared to standard oxybutynin therapy. The primary end point proposed would be the DLPP based on clinical significance and
reliability of obtaining the measure. This variable is a direct measure of bladder compliance and will assess the effect of botulinum toxin A on a different aspect of bladder function rather than detrusor overactivity, which has been well researched at this point. Modifications to the pilot trial are proposed in the final protocol detailed below. Accepting the limited sample size, OnabotulinumtoxinA use appears to be safe in the short term and shows comparable urodynamic and clinical effects as oxybutynin therapy without associated anticholinergic side effects.
Chapter 6

Proposed Phase III protocol

**Study compounds:** OnabotulinumtoxinA (Botox®) and Oxybutynin (Ditropan®)

**Phase:** 3

**Study objective:**
To compare the efficacy of intra-detrusor injection of OnabotulinumtoxinA for the treatment of non-compliant pediatric neurogenic bladder in children 5 to 18 years of age to standard oxybutynin therapy at maximal tolerated dosage.

**Clinical hypothesis:**
OnabotulinumtoxinA has an acceptable safety profile when injected into the detrusor muscle in children with neurogenic bladders. The improvement in bladder compliance measured by urodynamics is comparable to standard oxybutynin therapy. Unlike oxybutynin, OnabotulinumtoxinA is not associated with anti-cholinergic side effects.

**Study design**
**Structure:**
Multicenter, randomized, evaluator blinded, parallel group superiority trial

**Duration:** Patients will participate in the study for duration of 24 weeks from randomization into the oxybutynin arm and 24 weeks from day of OnabotulinumtoxinA injection in the botulinum toxin arm

**Study treatment groups:**
Simple randomization will be performed to assign patients into 2 treatment groups:

1. Intervention group: OnabotulinumtoxinA 10 U/kg to maximum dose of 300 U
2. Control group: Oxybutynin 0.2-0.4 mg/kg up to 4 times a day
Treatment regimen:
Intervention group: All patients will undergo pre injection urine culture and microscopy to rule out an active UTI and all menstruating females will undergo a pregnancy test. A single treatment of OnabotulinumtoxinA will be administered using rigid or flexible cystoscopy as 30 intra-detrusor injections of 0.5 ml each evenly distributed, sparing the bladder trigone. Administration will be under general anesthesia for all patients under 10 years of age. For patients ≥ 10 years of age, administration can be performed without anesthesia if acceptable to the patient. Standard latex precautions will be maintained for all injections. The patients randomized to the OnabotulinumtoxinA group will stop their oxybutynin on the day of injection. The patients can request a single retreatment any time after the 12-week’s visit if there is deterioration in their urinary continence status or restart oxybutynin if that is the preferred option from their perspective.
Control group: Patients will continue with their pretrial dose of oxybutynin. This will be the maximal tolerated dose (maximum total dose 40 mg/day) established over a period of at least 6 months prior to trial initiation.

Visit schedule: Patients will undergo an eligibility visit and be randomized on day 1 after consenting. This will also constitute the baseline visit. All patients will have scheduled visits at 6 weeks; 12 weeks and 24 weeks post treatment. Patients in the OnabotulinumtoxinA arm can request re-treatment after the 12-week visit and an additional visit will be planned for patients who document a clinical deterioration in continence or CIC volumes after the 12-week visit. At that visit, patients will present with a 48-hour CIC diary and will decide whether they opt for a re-injection or restart oxybutynin therapy. Patients will exit the trial at the end of 6-month follow up.

Study population characteristics:

Number of patients: The study sample size based on the variable DLPP is 150 with 75 in each arm, allowing for a 10% drop out rate and allowing for 80% power and an α of 5% (Table 4.2). This number is based on an improvement of 10 cm H₂O in the DLPP in the
OnabotulinumtoxinA arm compared to the oxybutynin group. This is the upper 95% confidence limit of the 3-month change in DLPP in the 2 arms in our pilot trial and therefore provides some justification in selecting this effect size.

Inclusion criteria:
1. Spina bifida associated neurogenic bladder patients 5-18 years of age.
2. Urodynamic or videourodynamic study done within the last 6 months demonstrating an upper motor type of lesion associated with neurogenic detrusor overactivity and/or poor bladder compliance requiring use of anti-cholinergic medications.
3. No prior augmentation cystoplasty.
4. Currently performing clean intermittent catheterization.
5. All patients under treatment with oxybutinin at a maximal tolerated dose ranging between 0.2 -0.4 mg/kg/day for at least 3 months duration.
6. Consent and assent given to participate in trial.

Exclusion criteria:
1. History of lung disease, recurrent aspiration or severe neurological impairment, which may increase risk of OnabotulinumtoxinA toxicity or anesthesia.
2. Positive urine culture with symptoms of a UTI.
3. Known allergy to OnabotulinumtoxinA.
4. Myasthenia gravis.
5. Positive pregnancy test.
6. Patients with a tethered cord demonstrated on MRI or a recent change in continence status would be excluded.

**Response measures:**

**Primary**- The primary response variable will be the detrusor leak point pressure (cm H$_2$O) defined as the detrusor pressure at first onset of passive urethral leakage using standard slow fill video cystometry.

**Secondary**- Secondary variables will include urodynamic variables like reflex volume;
maximum cystometric capacity and percentage expected bladder capacity for age, 20 and 30 cm volumes and safe volume. Other secondary variables will include continence as a binary variable (wet if using pads, dry if no pads used), CIC volumes on the 48-hour CIC diary and side effects. In the OnabotulinumtoxinA group, the time from injection to requirement of reinjection or restarting oxybutynin therapy will be recorded to estimate the duration of action. In addition, giving the choice to the patient will allow assessment of patient preference with regards to the 2 treatment options. In addition, ultrasounds will be used to monitor for the presence or absence of hydronephrosis and the videocystometry will monitor presence or absence of VUR.

**Blinding and randomization**
Randomization will be performed centrally using a pre-generated sequence sealed in opaque envelopes, which will be opened by a trial nurse after consent is obtained. A balanced block randomization sequence will be generated with blocks of 10 each. The patient and treating physician will not be blinded but allocation concealment will be maintained. A research nurse blinded to the treatment will perform the data entry of the CIC diaries and side effects during follow up visits. An urologist blinded to the treatment will interpret the urodynamic studies. The treating physician will continue follow up and ensure safety.

**Safety**
A data monitoring and safety board will be set up prior to trial initiation to monitor each patient entering the trial. All adverse events in each group will be duly recorded after discussion in the DMSB.

**Statistical analysis**
SPSS version 20 will be used to perform the statistical analysis at the end of 6 months of follow up. There are no interim analyses planned. An intent-to-treat analysis will be performed for all variables irrespective of protocol deviation or crossovers. No participants will be excluded from analysis based on missing values of some outcome variable.
Continuous outcomes will be analyzed using analysis of covariance (ANOCOVA), assuming significant correlation between the pre and post scores. This method of analysis adjusts the post-score based on the pre-score and allows for gain of precision. 95% confidence intervals and p values will be reported for all outcome measures, with significance set at $\alpha = 0.05$. Chi square test will be used for binary variables provided expected frequencies are $> 5$ for each cell. Significance will be at $\alpha = 0.05$.

**Schedule of visits and procedures**

The following will be obtained at the initial eligibility visit: (1) written informed consent (2) history of relevant conditions and current medications (3) a physical examination including determination of patient's height, weight, and body surface area (4) baseline ultrasound of the kidneys and bladder (5) Videocystometry if not performed within the last 6 months (8) CIC diary.

The follow-up visits will occur at 6, 12 and 24 weeks. Patients will have access to additional care if needed. At each visit a complete urological assessment will be performed and details about the side effects of each intervention will be recorded. Patients in the oxybutynin arm will receive prescriptions for the drug at baseline, at 4 weeks and 12 weeks. The following additional assessments will be performed:

**6 weeks:** Patients will return to clinic with a completed 48-hour CIC diary. In addition, assessment of continence and CIC volume will be done and side effects will be noted. Patients in the oxybutynin arm will be given another prescription after checking the number of pills used during the month.

**12 weeks:** Patients will return to clinic 3 months with a completed 48-hour CIC diary and will undergo an urodynamic study and KUB (Kidney, Ureter and Bladder) ultrasound. In addition, assessment of continence and CIC volume will be done prior to urodynamics. Patients in the oxybutynin arm will be given another prescription after checking the number of pills used during the month.
24 weeks: Patients will return to clinic at 6 months with a completed 48-hour CIC diary and undergo an urodynamic study and KUB ultrasounds. In addition, assessment of continence and CIC volume will be done prior to urodynamics.

Conclusion
This phase III trial is proposed as the first RCT comparing standard anticholinergic therapy using oxybutynin and botulinum toxin intra-detrusor injections as first line treatment for children with a spina bifida associated poorly compliant neurogenic bladder. We hypothesize that this alternate therapy will benefit this population of patients by providing comparable or superior improvements in bladder storage function without the side effects of anticholinergic medications. Our pilot trial enabled us to select DLPP as our primary response variable and calculate the sample size required for a superiority trial. In addition, the response and results of the CIC diaries and QOL instruments allowed us to appropriately modify the follow up protocol. Based on our recruitment time lines and available patient pool, we propose to conduct this trial as a multicenter trial involving other pediatric centers across Canada.
References


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Appendices

1. HRQOL questionnaire

Quality of life in spina bifida questionnaire — Part 1: age 5–12 years

How much do you feel your child:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>
1. … is treated with respect and dignity by others?  
2. … feels good about her/himself?  
3. … is able to do some things as independently as possible?  
4. … is able to get into the houses of his/her friends?  
5. … accepts his/her physical limitations?  
6. … will be able to choose a career of his/her own?  
7. … has the chance to continue to study the things in which he/she is interested?  
8. … has the chance to learn to swim?  
9. … participates in the same recreational activities as other children?  
10. … has the opportunity to play indoors?  
11. … has the opportunity to play outdoors?  
12. … participates in games at recess?  
13. … feels capable or skillful in some sport or hobby or other activity?  
14. … is stared at by others?  
15. … is treated as if he/she were different?  
16. … is healthy?  
17. … is integrated in the school system?  
18. … is able to use public washrooms that are accessible and private?  
19. … has access to the community via ramps and elevators?  
20. … is accepted and valued in our society?  
21. … attends a school that has a positive attitude towards children with disabilities?  
22. … is in an environment that does not contain a lot of obstacles?  
23. … has someone to confide in outside of the immediate family?  
24. … has friends?  
25. … has a supportive family?  
26. … feels welcome in other children’s homes?  
27. … receives praise for things that he/she is able to do?  
28. … feels important?  
29. … is treated with respect by others?  
30. … feels that she/he can accomplish her/his plans?  
31. … expresses her/his emotions?  
32. … has the opportunity to do everything the other children do in school?  
33. … is able to learn well in an environment that is favorable to children with disabilities?
34. … is motivated to learn?
35. … is able to attend a camp for children with disabilities?
36. … feels that the examinations and treatments at the hospital or clinic are respectful?
37. … feels that the examinations and treatments at the hospital or clinic are private?
38. … feels related to as a whole person by the doctor?
39. … is able to deal well with being in the hospital?
40. … feels in control of the situation in medical appointments and treatments?
41. … is learning to deal positively with his/her disability?
42. … is becoming appropriately independent in areas of self-care, mobility, and self-catheterization?
43. … will be able to live independently in the future?
44. … possesses self-confidence?
Quality of life in spina bifida questionnaire — Part 2: age 13–20 years

How much do you feel:

1 2 3 4 5

1. … that you are treated the same as everyone else?
2. … that you have a supportive family?
3. … that you are accepted just as you are?
4. … that you are able to talk to one or both of your parents?
5. … that people enjoy being with you?
6. … that you are happy with yourself?
7. … that you are able to speak up for yourself?
8. … that there is hope for the future?
9. … positive about yourself?
10. … that other people respect you?
11. … satisfied with your school programme?
12. … able to participate in group activities?
13. … that you are able to have a special friend?
14. … like you are treated the same as the other kids?
15. … that you are able to take care of yourself; for example brushing your hair and teeth?
16. … that you are able to feed yourself?
17. … that you are able to help with some or all of your catheterization?
18. … that you are able to participate in some or all of your own bathing?
19. … that you have a lot of pain?
20. … that you can stand up for your rights?
21. … that you can make your own choices and decisions?
22. … that you are as independent as you are able to be?
23. … that you can use the telephone?
24. … that people listen to your opinions?
25. … that you are treated with respect and dignity at your medical appointments?
26. … that you have a say in your medical treatment?
27. … that you understand what your medical condition will be like in the future?
28. … that your are getting good care at your spina bifida clinic?
29. … that your doctors, nurses and others who treat you know about spina bifida?
30. … that people see you and not only your disability?
31. … that you will have a suitable home in the future?
32. … that you have privacy and accessibility in public washrooms?
33. … that you are able to use the kitchen at home?
34. … that your present washroom is suitable for you?
35. … that you are able to participate in outdoor activities?
36. … that you have the physical strength to do sports like swimming, skiing, etc.?
37. … you are able to go out on dates and to parties?
38. … challenged and encouraged through sports?
39. … successful or skilled in some sport or other activity you like?
40. … that there will be job opportunities for you in the future?
41. … you are able to get an education for a job that interests you?
42. … that you have a career goal in mind?
43. … able to hold down a part-time job?
44. … that you will be able to have children in the future?
45. … that you will marry?
46. … that you have somebody with spina bifida to look up to and to have as a role model (example) for you?
47. … that you have a close friend who is like you in many ways?
REB approval

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Sumit Dave
Review Number: 17787
Review Level: Delegated
Approved Local Adult Participants: 0
Approved Local Minor Participants: 20
Protocol Title: A Pilot Study Comparing the Effects of Botulinum Toxin A and Standard Oxybutynin therapy as First Line Treatment for the Poorly Compliant Pediatric Neurogenic Bladder
Department & Institution: Surgery, London Health Sciences Centre
Sponsor:
Ethics Approval Date: August 12, 2011 Expiry Date: March 31, 2013
Documents Reviewed & Approved & Documents Received for Information:

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<tr>
<th>Document Name</th>
<th>Comments</th>
<th>Version Date</th>
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<tr>
<td>Revised UWO Protocol</td>
<td>Revised study objectives, methodology and inclusion criteria</td>
<td></td>
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<tr>
<td>Revised Letter of Information &amp; Consent</td>
<td>version 4 - June 2011</td>
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<tr>
<td>Other</td>
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This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Consensus Guideline, and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership requirements for REBs as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB’s periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB recertification number IRB 00000940.

Ethics Officer to Contact for Further Information:

<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janice Sturtzel</td>
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Curriculum vitae

Name: Sumit Dave

Post-Secondary Education & Degrees:
1994 – 1999: MCh, All India Institute of Medical Sciences, Pediatric surgery, Postgraduate, Paediatric Surgery and Urology, Clinical Study - Urodynamic evaluation in the extrophy-epispadias complex; Experimental Study - Hepatocyte transplantation in syngenic rat spleen, Supervisor: Dr. D. K. Mitra, New Delhi, India
1988 – 1993: MD, Jawaharlal Institute of Postgraduate Medical Education and Research, Doctor (Medical), Medicine, Pondicherry, India

Honors & Awards:
2010 - 2011 Residents’ Clinical Teaching Award, Awarded to the most outstanding clinical teacher for the UWO Urology Residents for the 2010-2011 academic year. Type: Distinction, Local, University of Western Ontario, London, Ontario, Canada

2010 - 2011 University Students’ Council Teaching Honour Roll, Excellence in teaching in undergraduate medical education, Local, University of Western Ontario, London, Ontario, Canada

2007 - 2008 Clinical Clerks Teaching Award for Pediatric Surgery, Most outstanding faculty teacher in Division of Pediatric surgery for clinical clerks 2007-2008, Schulich School of Medicine & Dentistry, Department of Surgery, Division of Paediatric Surgery, Local, London, Ontario, Canada

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Publications:


