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**Developing a Research Program for Intravesical Oxybutynin in Children with Poorly Compliant
Neurogenic Bladders**

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**Developing a research program for intravesical oxybutynin
in children with poorly compliant neurogenic bladders**

Luis Antonio Caldas Guerra

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in Partial
fulfillment of the requirements for the MSc degree in Epidemiology

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Abstract

Statement of the problem: Children with neurogenic bladders and poor bladder compliance are usually managed with bladder catheterization and oral anticholinergic medication. They may become non-responders to the drug or present with severe harms. Oxybutynin intravesically is an alternative therapy.

Methods: CHEO experience (case series) with intravesical oxybutynin. Systematic review of the literature of intravesical oxybutynin in children with neurogenic bladders. Protocol for a RCT is proposed.

Results: CHEO case series and the systematic review suggest intravesical oxybutynin is effective and well tolerated. There was a significant improvement in urinary incontinence and urodynamic outcomes. Published studies are of low level of evidence, and there was no RCT. The incidence of harm was low.

Conclusion: Based on the evidence collected, there is not sufficient justification to recommend this therapy for children with neurogenic bladder. Research with a more sound study design, such as RCT, should be conducted to assess the efficacy of this intervention in children.

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List of abbreviations

CHEO	Children's Hospital of Eastern Ontario
CIC	Clean intermittent bladder catheterization
CONSORT	Consolidated standards of reporting clinical trials
DLPP	Detrusor leak point pressure
DSD	Detrusor sphincter dyssynergy
DSMC	Data and safety monitoring committee
IQR	Interquartile range
MCID	Minimal clinical important difference
OR	Odds ratio
QUOROM	Quality of reporting of meta-analysis
RCT	Randomized controlled clinical trial
RR	Relative risk
TBC	Total bladder capacity
UDS	Urodynamics
US	Ultrasound
UTI	Urinary tract infection

Chapter 1

Background – Neurogenic Bladder and Oxybutynin

1.1. Statement of the problem

Children with poorly compliant neurogenic bladders are treated with oral anticholinergic medications to improve bladder compliance. Efficacy of this treatment may decrease following prolonged treatment, or children may be reluctant to take the medication because of harms associated with it. Inadequate treatment may result in serious morbidity, such as deterioration of bladder function, renal failure and an increased likelihood of surgery to augment bladder capacity.

1.2. Background

The bladder, together with the urethra, form the lower urinary tract. The bladder's main function is to store urine at an adequate capacity and low pressure, and to completely void the urine stored. The detrusor is the muscle of the bladder that is responsible for its complete emptying, and this role is well coordinated with the urethral sphincter during voiding.

A number of conditions can provoke dysfunction of the micturition or impair the ability to store urine. Neurogenic bladder dysfunctions can result from a neurological lesion at the spinal cord or in the brain. When a neurogenic bladder stores urine at a high pressure, it is described as a “poorly compliant neurogenic bladder.” This condition can be detrimental to the kidneys, as high bladder storage pressure and incomplete bladder emptying may lead to urinary incontinence and dilation of the kidneys (hydronephrosis).

Constipation is a common condition associated with neurologic pathologies that can also affect bladder function. It may worsen urinary incontinence, which may impinge upon activities of daily living, including the social life of children, perhaps diminishing their quality of life. Dietary modification, stool softeners or laxatives usually ameliorate it. Cecostomy tubes, used to flush and clean the large bowel, occasionally are necessary to treat recurrent severe fecal impaction.

In children, the most common group of pathologies that can lead to neurogenic bladder are the congenital myelodysplasias, but spinal cord injuries are not uncommon. The management of these children usually includes clean intermittent catheterization (1) to promote regular and complete bladder emptying, and anticholinergic drugs to decrease high bladder pressure.

Anticholinergic drugs effectively improve bladder compliance,^a and the commonly used oral paediatric medication is oxybutynin chloride (0.1-0.2 mg/kg/day, divided into two or three doses).(2,3) Oxybutynin is a tertiary amine which has post-ganglionic atropine-like effects (4), and it is the standard and most widely used anti-cholinergic in children with overactive bladder.(5) It is a potent muscarinic receptor antagonist, which significantly relaxes the bladder muscle, diminishing detrusor overactivity in patients with neurogenic bladders. Diokono and Lapidés first described oral oxybutynin for neurogenic bladder in 1972.(6) It has been demonstrated that oral oxybutynin is effective in decreasing bladder pressure and the occurrence of bladder overactivity, and in improving bladder capacity in children with neurogenic bladder.(7) However, it also has an important action on the parotid gland, causing a significant harm of dry mouth. It can also

^a Bladder compliance is calculated dividing the TBC by the Pressure at the TBC

cause constipation, blurred vision, orthostatic hypotension, confusion, drowsiness, nausea, dry skin and urinary retention.

The “undesired effect” or “side effect”, caused to a participant by the drug being tested in a clinical trial, is often referred as “harm”. It is related to the drug’s safety profile and patient’s tolerance to the treatment being administered. With oxybutynin, some patients are unable to continue treatment because of disabling harms, and this is observed in paediatric and adult populations.(8) As well, continuous treatment may lead to loss of an adequate response over time.

In practice, at the Children’s Hospital of Eastern Ontario (CHEO), the most common indications for intravesical oxybutynin are lack of response to maximal doses of oral administration, or severe harm as a result of oral administration. Interruption of treatment is most frequently in response to severe symptoms secondary to the anti-muscarinic effect, such as intense dry mouth, facial flushing, dizziness or constipation.(9)

Some patients on appropriate doses of oral anticholinergic medication still have a high-pressure bladder, which puts their upper urinary tracts at risk. Alternatively, the drug may be delivered into the blood system by intravaginal, intrarectal and transdermal routes,(10-12) as well as the intravesical instillation of oxybutynin, which has been described by several authors.(13-18) Intravesical administration is used as a substitute for oral administration in patients with severe anti-cholinergic effects, or in combination with maximal oral doses to increase effect in refractory cases.

It has been shown that the first-pass hepatic metabolite of oxybutynin, N-desethyloxybutynin, is associated with anticholinergic harms and is present in the plasma at concentrations 4 to 10 times higher than its parent compound.(2,19) N-desethyloxybutynin seems to cause most of the adverse systemic anti-cholinergic effects,

and avoiding the oral route with drug absorption via the portal venous system seems to bypass this problem. Whenever indicated, intravesical oxybutynin has been used to treat myelodysplastic children in the paediatric urology clinic at CHEO.

1.3. Rationale for the intervention

Intermittent bladder catheterization and/or oral anticholinergic therapy are measures that are often used to control high pressure in neurogenic bladder.(5) Oral oxybutynin is the most common anticholinergic medication used in this situation, based on its safe profile and acceptable harm and response rates. However, with continuous utilization some children's response to the oral treatment wanes and they become refractory to the drug action. In such cases, or when harms contraindicate increasing the dose, the combination of oral and intravesical oxybutynin becomes an attractive option.

1.4. Research question

Does intravesical oxybutynin improve the bladder compliance of children less than 18 years of age with poorly compliant neurogenic bladders, who have had an unsatisfactory response to oral therapy?

1.5. Research objectives

To assess the evidence of the effect of intravesical oxybutynin in children with poorly compliant neurogenic bladders, who became refractory to oral oxybutynin.

The following objectives will be addressed:

- Is intravesical oxybutynin effective in decreasing bladder compliance in children with neurogenic bladder?

- Is the treatment with intravesical oxybutynin well tolerated and feasible to use?
- Do harms or technical problems with the use of intravesical oxybutynin lead to a high withdrawal rate from the treatment?

1.6. Material and methods

This research project will include a report of the experience with intravesical oxybutynin treatment at CHEO, a systematic review of this modality of treatment, and a proposal for a randomized controlled clinical trial to evaluate its efficacy and safety.

1.7. Relevance of this research

Intravesical oxybutynin treatment for poorly compliant neurogenic bladder is used in some clinical centres, but its efficacy and effectiveness have not been scientifically confirmed in the medical literature. Moreover, this therapy is not free of complications. Kasabian *et al.* described 10 dropouts amongst 18 patients including adults and children, and Palmer *et al.* reported that 65% withdrew from intravesical oxybutynin therapy, both due to harms and technical difficulties.(17,20) The lack of clinical consensus amongst specialists and in the literature regarding the utilization of this treatment for paediatric patients with poorly compliant neurogenic bladders, confirm the equipoise in the scientific community.

Chapter 2

Review of the experience with intravesical oxybutynin at the Children's Hospital of Eastern Ontario

2.1. Research question

Does the addition of intravesical oxybutynin improve bladder compliance in children less than 18 years of age with a poorly compliant neurogenic bladder, who are taking oral oxybutynin and have had an unsatisfactory response (i.e., became refractory to oral oxybutynin or discontinued the oral due to unacceptable harms)?

2.2. Objective and hypothesis

Objective: To analyze the accumulated experience at the Children's Hospital of Eastern Ontario (CHEO) with treatment adding intravesical oxybutynin for children less than 18 years of age, with a poorly compliant neurogenic bladder who are taking oral oxybutynin and have had an unsatisfactory response; and to evaluate the effectiveness and safety of the treatment.

Hypothesis: It is hypothesized that the combination of oral and intravesical oxybutynin will improve the bladder compliance of children less than 18 years of age with poorly compliant neurogenic bladders, who are taking oral oxybutynin and have had an unsatisfactory response to oral oxybutynin (i.e., became refractory to oral oxybutynin, or discontinued the oral drug due to unacceptable harms).

2.3. Study design

This was a retrospective analysis, based upon before-and-after evaluation of children treated with intravesical oxybutynin. Children with poorly compliant neurogenic bladders who were non-responders to oral oxybutynin or presented with unacceptable harms with increased oral doses (maximum: 15 mg/day), were treated with the addition of intravesical to oral oxybutynin. Clinical and urodynamic outcomes were assessed pre- and post-intervention (combination of oral and intravesical oxybutynin), at a mean of 6 months. There was no comparison group.

Patients with an “unsatisfactory response” are defined as being patients who were taking oral oxybutynin and who became non-responders to the drug, and patients who developed harms that precluded taking the drug or increasing the dose to improve the response.

2.4. Outcomes

Primary and secondary outcomes, explanations of how to measure/assess them, and their respective units are described as follows:

2.4.1. Primary outcome

- Bladder compliance - measured in mL/cmH₂O

(Ratio of “volume-change/pressure-change” that is measured at Total Bladder Capacity (TBC)) during urodynamics (UDS)

2.4.2. Secondary outcomes

- Total Bladder Capacity (TBC) – measured in mL

(Maximum bladder volume before the patient refers to pain or starts to leak urine while the bladder is being filled during UDS)

- Detrusor pressure at the TBC – measured in cmH₂O

(The difference between the intravesical and intra-rectal pressure measured at the TBC during UDS)

- Detrusor leak point pressure (DLPP) – measured in cmH₂O

(Detrusor pressure of an involuntary urine leak during UDS)

- Neurogenic detrusor overactivity – measured in cmH₂O and as number of events *(Involuntary bladder contractions during the filling phase of the UDS)*

- Urinary tract infections (UTIs)– measured as the number of events

(Monthly frequency of UTIs clinically confirmed and positive urinalysis)

- Episodes of urinary incontinence – measured as number of events

(Weekly frequency of daytime wetting accidents)

- Upper urinary tract abnormalities – measured as dichotomous outcome

(yes/no) (Presence of dilation of the kidney (hydronephrosis) on the ultrasound, or other imaging test)

2.4.3. Harms

- Constipation – measured as dichotomous outcome (yes/no)

(Absence of bowel movement for more than 3 days)

- Systemic harm – measured as dichotomous outcome (yes/no)

(Dry mouth, blurred vision, orthostatic hypotension)

- Dropping out of the study, and reason why – measured as percentage

(Whether the patient refuses to continue clinical follow up)

2.5. Eligibility criteria

2.5.1. Inclusion criteria

Children less than 18 years of age with a diagnosis of a poorly compliant neurogenic bladder treated through the CHEO paediatric urology clinic, who had unsatisfactory clinical response to oral oxybutynin (i.e., become refractory to oral oxybutynin, or discontinued the oral drug due to unacceptable harms).

2.5.2. Exclusion criteria

Neurogenic bladder with adequate bladder compliance

Advanced neurogenic bladder (deterioration of renal function)

Concomitant bladder pathology, such as bladder stones or fistulae

Patients with vesicostomy (incontinent skin stoma)

Urethral pathology that precludes the use of urethral catheterization

Patient / parent unwillingness to catheterize

Previous surgery for bladder augmentation

2.6. Material and Methods

2.6.1. Population and setting

Study population: Children less than 18 years of age with a neurogenic bladder and poor bladder compliance (defined as less than 10 mL/cmH₂O, or bladder pressure above 40 cm/H₂O).

Study sample and setting: Children less than 18 years of age, followed at CHEO paediatric urology clinic with a poorly compliant neurogenic bladder, who were not

responding to the standard treatment with oral oxybutynin, or for whom the incidence of harm precluded maintaining or increasing the oral dose.

2.6.2. Method of review

A 10-year (1995 to 2005) retrospective chart and urodynamics report review was conducted. CHEO's patient database search for ICD-10 code "N-31.9" identified patients with a diagnosis of neurogenic bladder who were being followed at the CHEO paediatric urology clinic. CHEO's Urodynamic Laboratory records were searched to identify the UDSs of these patients, with the corresponding graphs and reports. From these charts and UDSs, patients meeting the inclusion criteria were identified.

Data was extracted from the database of the CHEO Urodynamics Laboratory and from the charts of the selected patients. Two reviewers extracted the data, and the results were checked by each other, to assure quality of the information gathered. A data collection form was used to extract the information about the treatment and outcomes.(Appendix 2.1) Patients were included based on the eligibility criteria listed in section 2.5. The following data was extracted: name, age, neurological diagnosis, ambulatory status, urinary incontinence, UTI, antibiotic therapy, information about oral and intravesical treatment with oxybutynin, occurrence of harms, and UDS parameters pre- and post-intervention. To enhance the quality of data extraction, a second investigator rechecked all the information collected.

2.6.3. Intervention

The regimen of treatment was changed from "oral oxybutynin" to the "combination of oral and intravesical oxybutynin" for patients whom oral oxybutynin

failed to adequately manage incontinence or poor bladder compliance, or for patients who experienced intolerable harms such as dry mouth, constipation, facial flushing or dizziness. A pharmacy-prepared solution containing 5 mg of oxybutynin diluted in 10 mL of sterile water was used for the intravesical intervention. This solution was injected through a urethral catheter twice daily, after the bladder had been emptied (mean dose: 0.4 mg/kg/day), and left inside the bladder until the next catheterization (typically 4 hours later). Oral oxybutynin was continued in 56 patients who did not have significant harms, and the mean oral dose was 0.4 mg/kg/day orally divided thrice daily. Six patients who had had important harm with oral, received intravesical oxybutynin exclusively. Urodynamics were performed pre- and post-initiation of combined therapy, usually six months apart. More detailed information about the intervention, standard patient assessment, and the data collated and analysed is in Appendix 3.1.

2.6.4. Data collection and statistical analysis

Patient demographics (age, gender), baseline and post-intervention measurements (UDS findings, urinary incontinence, UTI, constipation, hydronephrosis and bladder catheterization) were compiled as descriptive statistics. The significance of changes in bladder compliance and other continuous outcomes were assessed using a paired Student's t-test. McNemar's test was used to assess the statistical significance of changes in dichotomous outcomes such as the incidence of harms. Two-sided p-values less than 0.05 were considered statistically significant. Two different groups of patients were treated with intravesical oxybutynin: children who were wheel chair bound and children who were ambulatory. A *post hoc* subgroup analysis was conducted to identify whether there was a difference in response between these two groups, and statistical penalty for this non-

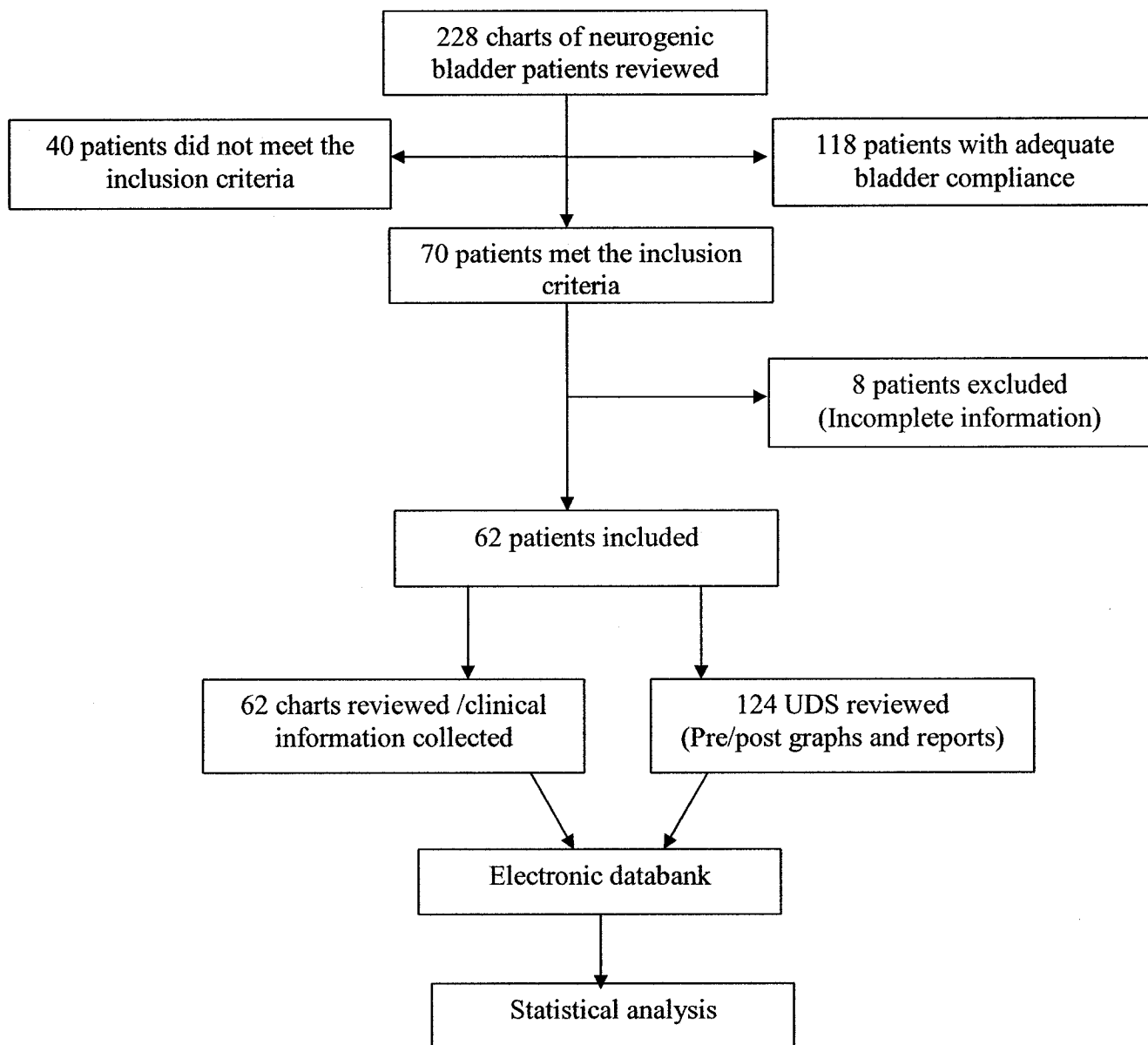
planned analysis was applied; p-value of 0.025 was used instead of 0.05 (Bonferoni correction).

2.7. Results

2.7.1. Demographic and descriptive findings

A search of the list of patients followed at CHEO identified 228 patients less than 18 years of age with neurogenic bladders. The first screening of charts identified 118 patients with adequate bladder compliance and they were not considered further. From the remaining 110 patients, 70 met the eligibility criteria but eight patients had incomplete data and thus were excluded. As the complete-data analysis approach was used for handle the missing data, the 62 patients with complete information were included and analysed. (Figure 2.1)

Figure 2.1 Flow diagram of the review process



The demographics and ambulatory status of the cohort are summarized in Table

2.1. Most of the children (38/62 – 61%) were wheel chair bound.

Table 2.1 Demographics and ambulatory status

Gender		Age	Ambulatory	
M	F	Mean yrs (SD)	Yes	No
31	31	9.5 (4.42)	24	38

The most common cause of neurogenic bladder was myelomeningocele, which was present in 53/62 (85%) of the patients. Other diagnoses were less frequent. The mean follow-up between the pre- and post-intervention assessments was 6 (SD: 3.31; range 1-17) months. The indications for starting intravesical oxybutynin were: disabling harm with oral oxybutynin in 6 patients and insufficient response to oral oxybutynin in 56.(Table 2.2)

Table 2.2 Neurological diagnosis and indication for intravesical therapy

Neurological diagnosis	Indication for intravesical oxybutynin	
	Non-response	Harms
MM 47, LM 6, SCI 2, SA 2, VS 1, CR 1, TC 1, Myelitis 1, Trisomy 1	56 children non-responders to oral oxybutynin	6 children with harms due to oral oxybutynin (Dry mouth 2, constipation 1, anorexia 1, mood swing 1, drowsiness 1)

MM: Myelomeningocele, LM: Lipomyelomeningocele, SCI: Spinal cord injury, SA: Sacral agenesis, VS: Vater Syndrome, CR: Caudal regression, TC: Tethered cord

2.7.2. Primary and secondary outcomes

Primary and secondary outcomes are summarized in Table 2.3. Bladder compliance and DLPP variables were not normally distributed, and the planned Student's t-test was changed to the Wilcoxon sign rank. There was a statistically significant improvement in bladder compliance and DLPP after the introduction of the combination of oral and intravesical oxybutynin ($p < 0.001$, Wilcoxon sign rank test).

Statistically significant improvement was seen in urinary incontinence and bladder overactivity ($p < 0.001$, McNemar's test). Before treatment, 47/62 (76%) of patients experienced urinary incontinence, compared to 31/62 (50%) after treatment, thus the absolute risk reduction was 26% (95% CI: 12.8 to 37.5). Similarly, 40/62 (65%) of patients experienced detrusor overactivity before the treatment, compared to 17/62 (27%) after treatment, representing an absolute risk reduction of 37% (95% CI: 22.6% to 49%).(21) However, there was no statistically significant improvement in UTI ($p = 0.58$; McNemar's test). Before the treatment 12/62 (23%) of the patients experienced UTIs, compared to 9/62 (15%) after the treatment, thus the absolute risk reduction was 8% (95% CI: -6.8% to 17%).

Both the TBC and the detrusor pressure at TBC were significantly improved (paired t-test used for continuous variable-single group, $p < 0.001$). Hydronephrosis was unchanged; it was diagnosed by ultrasound in 14 and 15 children pre- and post-treatment, respectively.

A *post hoc* subgroup analysis comparing outcomes for the 24 patients who were ambulatory to the 38 patients who were wheel chair bound showed no statistically significant difference ($p > 0.05$, Bonferroni correction). The Bonferroni correction was used to account for the multi-comparison effect of the *post hoc* analysis, when the chance

of finding a false significant correlation increases (type I error).(22) The level of significance was divided by the total number of tests performed: $\alpha_{\beta}=\alpha/k$ (where k is the number of tests of significance, and they are assumed to be independent; α_{β} : alpha with Bonferroni correction); $\alpha_{\beta} = 0.05/2 = 0.025$ for one *post hoc* comparison. Thus, the level of confidence was raised to 97.5%, and alpha set at 0.025, to account for the subgroup analysis on ambulatory status.

Table 2.3 Clinical and urodynamic outcomes changes (pre/post-intravesical oxybutynin)

Urodynamic outcomes (Unit)	Pre (SD)	Post (SD)	Mean difference (SD)	Change	p value
Bladder compliance (mL/cmH2O)	5.31 (3.67)	19.27 (45.10)	13.96 (44.65)	260%	p<0.001
Total bladder capacity (ml)	200.48 (100.49)	243.63 (118.87)	43.15 (84.58)	22 %	p<0.001
Detrusor pressure at TBC (cmH2O)	47.66 (25.56)	34.42 (22.91)	-13.24 (27.59)	-29%	p<0.001
Detrusor leak point pressure (cmH2O)	49.75 (26.23)	33.02 (17.86)	-16.73	-34%	p<0.001

Clinical outcomes	Pre n/N (%)	Post n/N (%)	Absolute risk reduction % (95% C.I.)	p value
Urinary Incontinence	47/62 (76)	31/62 (50)	26 (13 to 38)	p< 0.001
Bladder overactivity	40/62 (65)	17/62 (27)	37 (23 to 49)	p<0.001
Urinary infection	14/62 (23)	9/62 (15)	8 (-7 to 17)	p = 0.58
Constipation	22	26		
Patients on CIC	62	62		
Hydronephrosis	14	15		

CIC – Clean intermittent bladder catheterization SD – Standard deviation n – Number of patient N – Total of patients

Eight patients did not respond to the combination of oral and intravesical oxybutynin. They had an ileocystoplasty in a longer follow up, in which small bowel was used to augment the bladder.

2.7.3. Harms

Harms were recorded as mild, with difficulty in urethral catheterization and some bleeding in two patients, and some abdominal discomfort in one patient. There was no need to stop the treatment.(Table 2.4) Constipation was not aggravated by the treatment; it was present in 22 and 26 patients pre- and post-therapy respectively, and the difference was not statistically significant. Only two patients had cecostomy, which is used to perform a fleet enema to prevent fecal impaction.

Table 2.4 Harms reported during the therapy with intravesical oxybutynin

Type	n/N	%	Discontinued treat.
Difficulty in catheterization/blood	2 / 62	2	no
Abdominal discomfort	1 / 62	1	no
Constipation (new onset)	4 / 62	6	no
Total	7 / 62	11	

n: number of patients with harm N: total of patients

2.8. Discussion

This was a retrospective review of the accumulated experience at CHEO paediatric urology clinic with treatment using intravesical in addition to oral oxybutynin for patients with poorly compliant neurogenic bladder who had an unsatisfactory response to oral oxybutynin. The last ten years of practice was reviewed, since this intravesical therapy was not available earlier.

Although a trend of declining incidence of myelomeningocele has become evident in our practice, it accounted for 53/62 (85%) of the etiology of the patient with neurogenic bladder, confirming previous report by Stein et al.(23) First world countries have witnessed declines in incidence of congenital pathology such as myelomeningocele, and this may be the result of induced abortion. Improvement in maternal nutrition with

addition of folate to common foods may also have influenced the decline of incidence.(24)

Some authors have routinely used prophylactic anticholinergic therapy in infants with neurogenic bladder with high risk for kidney deterioration(25), but this was not the primary indication of this treatment in this study. Instead, anticholinergic treatment was utilized when upper urinary tract risk factors were detected, such as high bladder pressures on UDS or hydronephrosis on ultrasound. Patients were initially started on oral anticholinergics and intravesical therapy was reserved for those cases that did not respond satisfactorily to oral therapy. This may explain our mean age being slightly higher than other series.(17,26,27)

The statistically significant increase from 5.3 to 19.27 mL/cmH₂O observed in bladder compliance was related to the improvement in TBC and detrusor pressure at TBC, and these are effects of the anti-cholinergic action of oxybutynin. Bladder compliance is the volume divided by the pressure when the bladder is full, and in normal circumstances, the bladder should accommodate an adequate volume of urine at a lower pressure. This physiologic bladder function preserves the upper urinary tract that would otherwise be damaged by persistent high bladder pressure.

The 26% absolute risk reduction in urinary incontinence may be related to the decrease in the number of patients with bladder overactivity. In the same way, the reduction of bladder overactivity may have been responsible for the improvement in DLPP. Oxybutynin is an anticholinergic drug that causes bladder relaxation with a possible anesthetic effect on the afferent C fibers in the bladder epithelium.(28) The anesthetic effect may increase the threshold for triggering of “undesired bladder contractions” during bladder filling; these contractions are believed to be responsible for

the episodes of incontinence between catheterizations in the presence of a competent urethral sphincter.

One patient with previously normal kidneys developed unilateral low-grade hydronephrosis, however it was not clinically significant. The treatment with intravesical oxybutynin did not appear to affect hydronephrosis, but a longer follow up would be necessary for this outcome to be adequately assessed. Elevated intravesical pressure is a well-recognized risk factor for upper urinary tract deterioration (29); clinical series and animal studies have demonstrated the benefits and physiological properties of anticholinergic drugs used intravesically.(30-34) Although oral oxybutynin may improve bladder compliance and protect the kidneys, many patients do not respond to it or develop harms that limit its use.(35)

The primary statistical analysis used Wilcoxon sign rank test (a non-parametric test) to evaluate bladder compliance (primary outcome), as well as DLPP. These two measures appeared not to be normally distributed, so this non-parametric test was the most appropriate because it does not assume that the variable is normally distributed.

Thirty nine percent (24/66) of the patients were ambulatory due to a less severe neurological pathology. However, a subgroup analysis comparing patients who were ambulatory to those who were wheel chair bound showed no statistically significant difference in outcomes. This type of *post hoc* sub group analysis has a potential for misleading interpretations of the results if certain aspects are not observed. As Payne suggested in his work "Fishing expedition probability: The statistics of *post hoc* hypothesizing," there is nothing wrong with an exploratory analysis, since one deals appropriately with the new probability of type I error that arises in sequential comparisons.(36) *Post hoc* tests tend to bias the comparison of effects by increasing the

chance of type I error. A criticism of this approach is that when one raises the alpha level to decrease the chance of type I error, the chance of type II error increases. In other words, an effect or difference could be declared “non-significant” when in fact it is “significant”, and thus a truly beneficial treatment could be missed. For this reason the Bonferroni correction is considered a conservative method. Finally, the most important element a researcher should bear in mind when using a test of significance is that the relationship being tested should be specified *a priori*.(37)

In this study, children and parents were educated about the intravesical therapy by the attending physician, and this was followed by a training section with the urodynamicist nurse who taught them how to instill the solution and to deal with possible complications. Confirming previous findings, there was a high level of acceptance of the intervention by children and family; Palmer et al(20) found no resistance from parents and patients to intravesical oxybutynin because the children usually are on CIC. A pharmacy-prepared oxybutynin solution was used. The convenience of not having to dissolve tablets may have enhanced treatment compliance. Some authors recommend leaving the drug inside the bladder from 30 minutes to 1 hour.(4,17,38,39) In this series, the drug was left in the bladder until the next catheterization 3 to 4 hours later, and no clinical/urodynamic signs of harm were observed.

The mean period between the baseline and follow up assessment was 6 months. During this period, the incidence of harm was low, with only three patients reporting problems (abdominal discomfort in 1 and difficulty with catheterization in two – the latter not related to the drug). In general, this treatment was well tolerated and the patients had good adherence.

Weese et al, reported a series including adults and adolescents, and suggested that patients with inadequate response to oral oxybutynin may have an alternative treatment with intravesical oxybutynin, before being offered a more invasive approach such as bladder augmentation.(34) Confirming this findings, we had only eight patients who did not respond to the combination of oral and intravesical oxybutynin and subsequently had an ileocystoplasty to augment the bladder, using a segment of small intestine.

There are several limitations in this retrospective chart-review study. Retrospective data collection is susceptible to bias; particularly selection and information bias. Measures to minimize these biases included checking of the chart and UDS data, as well as data entry, by a second investigator. The collected data for each patient was carefully reviewed and the information from the chart and UDS reports were compared. The definitions of “neurogenic bladder” and “poor compliance” included specific criteria to avoid misclassification bias.

The nature of the “before-and-after evaluation” may jeopardize internal validity and introduce possible sources of bias. To name some: history, instrumentation, regression to the mean, maturation and dropout are common causes of “difference not due by chance”, and should be addressed to minimize bias. The short period of time over which this assessment was conducted (mean 6 months), to some extent protects against history and maturation bias; these are more prevalent in interventions over longer periods. Instrumentation bias is a difference in measurement not due to chance but to the method of measuring employed, and it is minimized when the same trained person and/or a standardized method is employed in the assessment. In this case-series, the UDS used a standardized technique, and the terminology recommended by the International Continence Society.(40) Regression to the mean bias is seen when “outliers values” tend

to group closer to the mean with repetitive measurements. This can be avoided with the analysis of repetitive measures such as in time series analysis. However in this study, children who improved tended not to repeat the UDS, and sequential measures were not consistently obtained, thus one pre- and one post-intervention UDS for each patient was analysed.

When one asks which type of study would better assess effect of a therapy, the answer based on evidence-based medicine would clearly be “RCT.”(41) Curiously, a number of therapies used in medicine have not had their effect confirmed scientifically. When randomized controlled studies are not available one should rely on studies with lower levels of evidence,(42) however there is no reason not to conduct studies to confirm the effect of a treatment people are exposed to. It has been recognized that not only RCTs but also the systematic review of RCTs are the gold standards for judging the benefits of treatments.(41) Furthermore, when assessing the effect of a therapy that is not in common use, one should consider that results of a study can be distorted not only by bias and confounding, but also by chance.(43) Some threats to validity can be avoided by means of “randomization” and “control group” in the study design, which account for the effects of known and unknown biases and allow for comparisons. Finally, the validity of the study results can be influenced by how well the design, conduct and analysis of the trial was done, and according to Juni et al. “the validity of the findings generated by a study, clearly is an important dimension of quality”.(44)

Although this retrospective review is a weak study design for assessment of effectiveness of therapy, the results suggest that intravesical oxybutynin may be effective for children who became refractory to oral oxybutynin. This finding supports the implementation of further prospective studies.

A carefully designed, conducted, analyzed and reported RCT, is the best means to assess the effect of intravesical oxybutynin in children with neurogenic bladder, and this should be seriously conducted.

2.9. Conclusion

In children with poorly compliant neurogenic bladders refractory to oral oxybutynin or with unacceptable harms, this retrospective review suggests that intravesical oxybutynin is effective and well tolerated when added to the management regimen. There was a significant improvement in urinary incontinence and urodynamic outcomes. The duration of this beneficial effect is not known and merits careful follow-up. The results of this retrospective study should be confirmed by a RCT.

Chapter 3

Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review

Introduction

Children with various types of lesions in the spinal cord can present with neurogenic bladders, a condition in which the bladder partially or completely loses its ability to store urine and to void at low pressure. When the bladder accommodates urine at high pressure, it is said to be a “poorly compliant bladder.” This may cause urinary incontinence, which impacts negatively in quality of life.(45) In the long term, a high-pressure neurogenic bladder poses risks to the kidneys.

A bladder with poor compliance is usually managed with intermittent bladder catheterizations (CIC) and oral anticholinergic drugs, with oxybutynin being the most commonly used. A percentage of these children may become non-responders to the drug, or present with severe harm such as dry mouth, facial flushing, dizziness and constipation. An alternative regimen is the combination of intravesical and oral oxybutynin, which can improve the effect while causing less harm. This systematic review evaluates the evidence of effectiveness of intravesical oxybutynin. Chapter 1 of this thesis contains additional background and rationale regarding this intervention.

3.1. Research question

Does intravesical oxybutynin improve bladder compliance in children less than 18 years of age, with poorly compliant neurogenic bladders who had an unsatisfactory

response to oral oxybutynin (i.e., became refractory to oral oxybutynin, or discontinued the oral drug due to unacceptable harm)?

3.2. Objectives

To evaluate the effectiveness and safety of intravesical oxybutynin in children less than 18 years of age, with poorly compliant neurogenic bladders who had an unsatisfactory response to oral oxybutynin.

The following objectives were addressed:

- Is intravesical oxybutynin better than no treatment?
- Is the addition of intravesical oxybutynin to oral oxybutynin better than oral oxybutynin alone?
- Is intravesical oxybutynin well tolerated and feasible to use?
- What harms are associated with intravesical oxybutynin use?
- Is intravesical oxybutynin associated with non-adherence to treatment?

3.3. Outcomes

3.3.1. Primary outcome

- Bladder compliance - measured in mL/cmH₂O
(Ratio of “volume-change/pressure-change” that is measured at Total bladder capacity (TBC) during urodynamics (UDS)

3.3.2. Secondary outcomes

- Total Bladder Capacity – measured in mL

(Maximum bladder volume before the patient refers to pain or starts to leak urine while the bladder is being filled during UDS)

- Detrusor pressure at the TBC – measured in cmH₂O

(The differential between intravesical and intra-rectal pressures, measured at the TBC during UDS)

- Detrusor leak point pressure (DLPP) – measured in cmH₂O

(Detrusor pressure of an involuntary urine leak during UDS)

- Neurogenic detrusor overactivity – measured in cmH₂O and as number of events

(Involuntary bladder contractions during the filling phase of the UDS)

- Urinary tract infection (UTI)– measured as number of events

(Monthly frequency of confirmed clinically UTI and positive urinalysis)

- Episodes of urinary incontinence – measured as the weekly number of events

(Weekly frequency of daytime wetting accidents)

- Upper urinary tract abnormalities – measured as a dichotomous outcome (yes/no) *(Presence of dilation of the kidney present on the US, or other image test)*

3.3.3. Harms

- Constipation – measured as a dichotomous outcome (yes/no)

(Absence of bowel movement for more than 3 days)

- Systemic harm – measured as dichotomous outcome (yes/no)

(Dry mouth, blurred vision, orthostatic hypotension)

- Dropping out of the study, and reason why – measured as percentage

(Percent of patients refusing to continue the clinic follow up)

3.4. Eligibility criteria

3.4.1. Inclusion criteria

3.4.1.a. Study design

All randomized controlled trials (RCT), non-randomized controlled trials, quasi-experimental studies and non-comparative case series were included.

3.4.1.b. Participants

Children less than 18 years of age, with established diagnosis of poorly compliant neurogenic bladder that had been refractory to oral oxybutynin or had severe harm with this medication, whether or not they are taking oral anticholinergics.

3.4.1.c. Intervention

Oxybutynin instilled into the bladder, with or without oral oxybutynin.

Details about the intervention are found in section 1 of the Appendix 3.1.

3.4.1.d. Outcomes

Primary outcome: bladder compliance

Secondary outcome: TBC, detrusor pressure at the TBC, DLPP, neurogenic detrusor overactivity, UTI, urinary incontinence, upper urinary tract dilation.

3.4.2. Exclusion criteria

3.4.2.a. Study design

Case-control studies (Rationale: This design is not appropriate to assess the intervention. It may convey some information, but it can be unreliable or have low validity.(46)

3.4.2.b. Participants

Patients 18 years of age and older (Rationale: Children metabolize drugs differently and therefore should be assessed separately from adults)

3.4.2.c. Intervention

Intravesical treatment using a drug other than oxybutynin

Animal studies

3.5. Search strategy for identification of studies

3.5.1. Electronic searches

A scoping exercise was first undertaken to assess the availability of studies for this review. Only a limited number of records were identified. Most were case-series, and there were no RCTs. We decided to enhance our search focusing on non-comparative studies, such as before-and-after design.

A comprehensive search strategy identified potentially relevant records using the eligibility criteria described in section 3.4. The following databases were searched using the OVID interface: Medline from 1966 to September week four 2006, Pre-Medline (September 11th 2006), Embase from 1980 to 2006, The Cochrane Central Register of Controlled Trials Library from 1981 to issue 4 (October 2006), and CINAHL from 1982 to 2006. Due to limited financial resources, we restricted this search to papers published in English.

The search strategy used in Medline was:

1. Bladder, Neurogenic/
2. neuro\$ bladder.mp.
3. or/1-2
4. limit 3 to "all child (0 to 18 years)"
5. oxybutynin.mp.
6. 5633-20-5.m.

7. (oxibutinin or oxybutinin).mp.
8. or/5-7
9. Administration, Intravesical/
10. intravesical.tw.
11. 8 and (9 or 10)
12. 4 and 11

Appendix 3.2 outlines the search strategy with the modifications used to adjust to Embase.

3.5.2. Hand searching

Relevant paper-based specialized journals hand searched were: Journal of Urology, British Journal of Urology, Urology and Journal of Paediatric Urology. The reference lists of the retrieved articles were also hand-searched for additional potentially relevant citations.

3.5.3. Grey literature

To identify relevant grey literature documents, the following databases were searched for the maximum period of time available: SciELO search engine from 1997 to 2006 (a model for cooperative electronic publishing in developing countries), ProQuest from 1961 to Sep 2006 (database for dissertations and theses), and LILACS from 1982 to Sep 2006 (Latin American and Caribbean Health Science Literature).

Reports and conference proceedings, letters and editorials were searched electronically and manually. Investigators, authors, a drug industry representative, a pharmacy that supply intravesical oxybutynin, organizations and experts were contacted to obtain additional information.

Specialists were consulted to help to identify proceedings from relevant specialty societies and associations. The previous five years (2001-2006) abstracts of the

following proceedings were searched: American Urological Association, European Society of Paediatric Urology, Canadian Urological Association, International Continence Society and Society for Fetal Urology.

3.5.4. Registries

The two main Internet-based registries for trials protocols were searched for studies on intravesical oxybutynin: “ClinicalTrials” (www.clinicaltrials.gov, a US database) (47) and “Controlled-trials” (www.controlled-trials.com, England).(48) Since 2004 the Canadian Institutes of Health Research has required as a condition of funding that all RCTs have an International Standard Randomized Controlled Trial Number (ISRCTN) and suggested the public Web site of the ISRCTN registry (www.controlled-trials.com).(49) This web site has the following databases: ISRCTN, NHS Trusts clinical trials register, National Health Service Research and Development Health Technology Assessment Program (HTA), Medical Research Council (UK), National Health Service Research and Development Regional Programs, and others. A search of all databases cited above revealed no protocol registered for a clinical trial involving intravesical oxybutynin.

3.6. Methods of the review

3.6.1. Selection of studies

All potentially relevant records were imported to an electronic database (Refworks®). Two assessors screened the records independently, to exclude those considered irrelevant. Hard copies of potentially relevant records were obtained and a

more focused screening excluded additional documents. The studies that fulfilled the inclusion criteria were included.

3.6.2. Assessment of the quality of included studies

Two independent reviewers, both with backgrounds in paediatric urology and one trained in clinical epidemiology, assessed the quality of reporting of the included studies. Quality was defined as the evidence that the study design, conduct and analysis minimized biases in the comparisons.(50) Non-comparative case series were assessed using a quality assessment instrument developed for this research project, based on criteria from a previous study (51) and other instruments.(52-54) This instrument evaluates generic and specific items of the design, conduct and analysis employed in each study. Questions could be answered: “yes”, “unclear”, “no” or “not applicable”, depending on the information requested. A generic section with items such as blinding, information about withdrawals and statistical analysis evaluated the elements of the design. A second part assessed population, intervention, outcomes and comparison.(Appendix 3.3)

3.6.3. Data collection and management

A data collection form was developed to extract relevant information from each report of the included studies.(Appendix 3.4) The same two reviewers completed the data extraction, with each doing half and then verifying the other’s work. A pilot calibration exercise using three studies not included in this review was conducted to clarify any discordance on the data collection form or quality assessment criteria used. Any unresolved disagreement between the reviewers was submitted to a third expert opinion and decided by consensus.

The following data was extracted: title, authors, journal, data and language of publication, population (children with neurogenic bladder), age (less than 18 years of age), intervention (intravesical oxybutynin), comparison (use of control group or placebo) and outcomes (bladder compliance, TBC, etc.) and study design characteristics (type of design, statistical analysis, blinding, etc.).

Descriptive data was summarized in tables and numerical data graphed, both according to pre-determined formats. This report follows the QUOROM Statement guidance.(55)

3.6.4. Handling missing data

Some of the values not reported in the statistical analysis section of individual studies were possible to calculate from the information reported, and in this case it is noted in the text. Reviewers contacted the articles' authors to obtain other missing data, such as age of participants, type of solution used, etc. No imputation methods were used to complete missing data.

3.6.5. Assessment of heterogeneity

Heterogeneity was assessed graphically by examining the forest plot and statistically using the I^2 test.(56) Although there are no rigid cut offs to determine consistency of results, the forest plot should show a nice "stacked pattern" of the treatment effect results on the graph, and the I^2 test should ideally be less than 50%. Meta-analysis combines results from individual studies to obtain an overall weighted estimate of an outcome, however such estimates should be limited to those studies where inconsistency across them is not large.

Clinical heterogeneity of the included studies is important to assess, since it can threaten the external validity of the review's conclusions. Clinical heterogeneity across studies may limit inferences to the study population based on the results obtained. We assessed clinical heterogeneity by looking at parameters such as population characteristics (age - infants versus adolescents; ambulatory status; co-morbidities, etc.), methods of administration of the intervention, non-standardized methods of clinical outcomes measurement, etc.

3.6.6. Assessment of publication bias

Publication bias was assessed visually using a funnel plot (57); the standard errors of the mean changes of TBC and pressure at TBC were used as measures of variability for the construction of the forest plot. In addition, considerations such as whether articles were identified in the grey literature or in a high citation impact factor journal, country of origin, language of publication, were examined. Duplicate publications were detected during the searching process, and they were eliminated to avoid inflation of the effect size of the intervention. Egger's linear regression method to assess publication bias was planned, however its application was not possible due to the small number of studies identified for this analysis, which limited its power.

3.6.7. Data synthesis

Descriptive tables with characteristics of the populations, differences in treatment, outcome comparisons and harms were constructed. Forest plot and funnel plots were used to display the estimate pooled treatment effect and the assessment of publication bias, respectively.

3.6.8. Data analysis

The quality assessment of the included studies and general information were compiled in tables and graphs for easier appraisal.

Effectiveness of the use of intravesical oxybutynin in children with neurogenic bladders was assessed based on the change in bladder compliance, TBC, and the change in detrusor pressure at the TBC. These measures were obtained during the UDS, which was done pre- and post-intervention. Tolerability and harm were assessed as functions of compliance with treatment, dropouts from the trials, and inconvenience of the procedure. Meta-analysis using weighted mean difference and a random effect model was conducted using the Cochrane RevMan-4.2[®] Software.

3.7 Results

3.7.1. Literature search

There were a total of 739 records identified on the first search of the electronic databases. Fourteen of these records were duplicates and were removed from the database. Searching conference proceedings and reference lists identified an additional five records. A subsequent screening of the title and abstract of the 730 remaining articles identified 37 potential articles for consideration. Of these, 30 articles did not meet the inclusion criteria and were excluded. Seven published studies, and chapter 2 of this thesis “Review of experience with intravesical oxybutynin at CHEO,” were included in this review.^[1-8] The QUOROM flowchart is in Appendix 3.5. The excluded articles are listed at the end of this chapter. The reasons for exclusion were: nine included patients over the age of 18 years^{4,10,14,17,21,22,24,25,27}, six were in languages other than English^{1,9,12,20,26,28}, six studies assessed different outcomes^{2,3,6,11,19,29}, three were review or editorial articles^{7,13,30}, one study focused on pharmacokinetics¹⁶, one study used ambulatory urodynamics¹⁸, one had a heterogeneous group of patients that had had sacral rhizotomy and anterior sacral root stimulator implant¹⁵, one article was followed by an update publication that was included in this review⁵, one used only oral oxybutynin⁸ and one article excluded neurogenic bladders²³.

The hand-search of the specialized journals listed in section 3.5.2 and the reference list of the papers retrieved uncovered no articles that met the inclusion criteria.

The search of protocol registries sites listed in section 3.5.4 identified no clinical trial registration for a protocol using this therapy in children.

3.7.2. Study characteristics

The general characteristics of the studies are reported in table 3.1. A total of eight studies were included, there were seven published articles [1-7] and one unpublished [8] study. The seven published studies were identified on the Medline database and six were published in the Journal of Urology, which is the official publication of the American Urological Association and the citation impact factor is 3.592. Greenfield et al. [1] published the first study in 1991 and the most recent one was published by Ferrara et al [7] in 2001. The unpublished article [8] is considered grey literature (chapter 2 of this thesis).

There were five retrospective studies and two prospective studies; the design was not clear in the study by Kaplinsky et al [4]. Seven studies used a “single group before-and-after design,” in which no control group was used; there was no RCT. Ferrara et al [7] published a retrospective study comparing intravesical to oral oxybutynin, and this was the only series using a comparison group. The primary objective was to assess “effectiveness” in five studies, “effectiveness and harms” in two studies, and in another study the objective was not clear. Although the primary objective varied, all studies assessed the effectiveness of the intervention.

Table 3.1 Characteristics of the articles included in the systematic review

First author	Journal	Year	Language	Database	Study design	Objective of assessment	Type	Control group
Greenfield	J Urol	1991	English	Pubmed	B-A	Effectiveness (TBC and P at TBC)	Retrospective	Not used
Connor	J Urol	1994	English	Pubmed	B-A	Continence, TBC, P at TBC and Bladder compliance	Prospective	Not used
Kasabian	J Urol	1994	English	Pubmed	B-A	Effectiveness (TBC and P at TBC)	Retrospective	Not used
Kaplinsky	J Urol	1996	English	Pubmed	B-A	Unclear (Effectiveness, long-term)	Unclear	Not used
Painter	J Urol	1996	English	Pubmed	B-A	Long-term effect on TBC, pressure at TBC and continence	Retrospective	Not used
Buyse	J Urol	1998	English	Pubmed	B-A	Effectiveness, harms and treatment compliance	Prospective	Not used
Ferrara	Br J Urol	2001	English	Pubmed	QE	Harms and efficacy between oral and intravesical oxybutynin	Retrospective	Oral oxy
Guerra	Thesis Ch 2	2006	English	Not pub.	B-A	Effectiveness and harms	Retrospective	Not used

ID: identification of the study, QE: quasi-experimental, B-A: before-and-after study, UDS: urodynamics, J Urol: Journal of Urology, Br J Urol: British Journal of Urology

3.7.3. Quality assessment

A descriptive analysis of the quality assessment of the included studies is shown in table 3.2. All eight studies used the inclusion criteria “children less than 18 years of age with established diagnosis of poorly compliant neurogenic bladder that had been refractory to oral oxybutynin or had severe harm with this medication”, and seven clearly stated the research question. “Blinding” or *a priori* “sample size calculation” was reported in no study. Although most of the authors reported the number of patients who discontinued treatment and the reasons why, they did not use their outcomes in the analysis. The tests employed for statistical analyses were reported in 5/8 (62.5%) of the studies. Information about the intervention, dose and means of administration were reported in detail in almost all studies; in one study the dose used was not clear.

Although harms were well reported, several articles did not report or were not clear about the results of primary and some secondary outcomes.

Table 3.2 Quality assessment of the studies included in the systematic review

Research question and Type of design	Number of studies that met the criteria			
	Yes	Unclear	No	N/a
Was the question about assessment of effectiveness clearly stated?	7	1		
Type of study design	RCT:0 CCT:0 QE:1 B-A:7 CC:0 CS:0			

Generic items	Yes	Unclear	No	n/a
Adequate generation of random sequence for allocation patient for intervention:	0	0	1	7
Adequate concealment of allocation:				8
Adequate blinding:			8	
Was there a priori sample size calculation?			8	
Did they describe withdrawals?	7	1		
Did they use Intent-to-treat analysis?				8
Did they report the type of statistical tests used?	5		3	
Did they report "p values" of the tests?	6		2	
Did they report confidence intervals?	1		7	

Specific items	Yes	Unclear	No
Population			
Did they use correct inclusion/exclusion criteria?	8		
Children < 18 years of age with poorly compliant neurogenic bladders?	7	1	
Intervention			
Did they describe how to perform the intervention (Intravesical oxybutynin)?	8		
Did they report the dose of oxybutynin used?	7	1	
Outcomes:			
Primary:			
Did they report Bladder Compliance (before and after)?	2		6
Secondary: Did they report?			
Total bladder Capacity:	6	1	1
Pressure at total bladder capacity:	6	1	1
Detrusor neurogenic overactivity	4		4
Detrusor sphincter dyssynergy		1	7
Urinary incontinence	7		1
Harms: Did they give information about:			
Significant harm (Dry mouth, blurred vision, constipation, orthostatic hypotension)	8		
Were there withdrawals due to harms?	5		3

RCT: randomized controlled trial, CCT: non-randomized controlled clinical trial, QE: quasi-experimental, B-A: before-and-after, CC: case-control, CS: cohort studies

3.7.4. Population and clinical diagnosis

A total of 297 children were treated with intravesical oxybutynin. Their gender, age and clinical diagnoses are presented in Table 3.3. Six studies reported mean ages; and ranges from 4 months to 18 years. Girls accounted for 30% to 60% across the studies. Ninety three percent of the children (277/297) had neurogenic bladder as sequelae of myelomeningocele.

Table 3.3 Population demographics and clinical diagnosis of the studies included in the systematic review

Author	Gender	Age range yrs	Mean age yrs	Clinical diagnosis (total 235 children)
Greenfield	7 M, 3 F	4 to 18	Not reported	MM 9 and imperforate anus 1
Connor	9 M, 4 F	1 to 18	8.7	MM 28
Kasabian	Not reported	4 to 12	7.7	MM 11
Kaplinsky	15 M, 13 F	3 to 18	Not reported	MM 27 imperforate anus 1
Painter	18 M, 12 F	1 to 17	8.6	MM 42
Buyse	6 M, 9 F	0.3 to 14	6.1	MM 12, LMM 1, CD 1 and SCI 1.
Ferrara	Not reported	0.25 to 10	4.2	MM 101
Guerra	31 M, 31 F	2 to 17	9.5 (4.4)	MM 47, LMM 6, SCI 2, SA 2, VS 1, CD 1, TC 1, Myelitis 1, Trisomy 1
Total: 297 (277 MM, 20 others)				

M: male, F: female, MM: myelomeningocele, LMM: lipomyelomeningocele, CD: caudal dysplasia, SCI: spinal cord injury, SA: sacral agenesis, VS: VATER syndrome, TC: tethered cord

3.7.5. Intervention

Participants included in the studies received a mean dose of 10 mg/day of oxybutynin, instilled into the bladder through a urethral catheter. The drug was prescribed to stay inside the bladder “until the next catheterization” and “for 30 to 180 minutes” in 4 and 1 studies respectively, while three other studies did not report this information. The duration of the treatment across studies varied from 3 to 36 months. As reported in Table 3.4, only Buyse et al [6] and Guerra et al [8] reported use of oxybutynin chloride pre-prepared solution for instillation into the bladder. In all other studies, the

children used 5 mg pills of oxybutynin crushed and diluted in sterile water, and the parents usually prepared the solution.

Table 3.4 Intervention characteristics, dose, length of time that oxybutynin was left inside the bladder and duration of the treatment

Author	Type of Instillation	Control group	Intravesical instillation			Control Group (Oral oxybutynin)		Length months
			(n)	Dose	Time left in bladder	(n)	Dose	
Greenfield	Crushed pill	No	10	10 mg/day	Until next CIC	No		3
Connor	Crushed pill	No	28	10 mg/day	Not reported	No		6.5
Kasabian	Crushed pill	No	11	10-20 mg/day	30-180 minutes	No		6
Kaplinsky	Crushed pill	No	28	10 mg/day	Until next CIC	No		35
Painter	Crushed pill	No	42	10 mg/day	Until next CIC	No		13
Buyse	Solution	No	15	0.2 Kg/day	Not reported	No		24
Ferrara	Crushed pill	Yes	67	0.1-0.2 Kg/day	Not reported	34	0.1-0.2 mg/kg/day	36
Guerra	Solution	No	62	10 mg/day	Until next CIC	No		6

n: initial number of patients submitted to the intervention and control group,
 Note: The total number of patients treated was 297 (263 intravesically and 34 orally)

3.7.6. Outcomes

3.7.6.a. Bladder Compliance

Mean change in bladder compliance, the primary outcome of this review, was reported only by Ferrara et al [7] and Guerra et al [8]. It was possible to calculate this measure for the study by Kaplinsky et al [4] using values of “TBC” and “Pressure at TBC” for each individual patient reported in a bar graph. Connor et al [2] reported that 12/13 of the patients experienced improved bladder compliance but did not report the values. In general, this information was incompletely reported, and the results available are displayed in Table 3.5.

Table 3.5 Bladder Compliance change (pre/post intravesical oxybutynin, in mL/cmH2O)

Author	Intravesical Oxybutynin							Control Group							
	Pre	SD	Post	SD	Mean change	SD	Mean change (%)	Pre	SD	Post	SD	Mean change	SD	Mean change (%)	
Greenfield			NR												
Connor			Reported that 12/13 of the patients improved but informed no values												
Kasabian			NR												
Kaplinsky	2.0		9.4		7.4		370.0								
Painter			NR												
Buyse			NR												
Ferrara*	8.5	6.1	16.0	11.0	7.5		88.2	8.1	6.3	14.8	11.6	6.7		82.7	
Guerra	5.31	3.67	19.27	45.10	13.8	44.65	260								

NR: Not reported * Calculated from bar graph with values of TBC and Pressure at TBC for each patient.

3.7.6.b. Total Bladder Capacity and Pressure at Total Bladder Capacity

Most studies reported pre- and post-intervention mean values of TBC and pressure at TBC. Greenfield et al [1] and Connor et al [2] failed to report the values of these outcomes and mentioned only the percentage of improvement for each patient or “percent range” of improvement. Table 3.6 summarizes the values of TBC and pressure at TBC for each study and their respective standard deviations. The standard errors of the “mean changes” of TBC and pressure at TBC were calculated based on information from studies, and they were used as measures of variability for the forest plots. Figures 3.1 and 3.2 are the forest plots and the results of tests to assess heterogeneity for TBC ($I^2=61.9\%$) and pressure at TBC ($I^2=69.0\%$). These plots suggest a moderate level of inconsistency across studies. The pooled mean difference for TBC using a random effect model was 79.7 mL (95% CI: 55.7 to 103,7). The pooled mean difference for pressure at TBC using a random effect model was -16.4 cm/H2O (95% CI: -22.8 to -10.0).

Table 3.6 Changes in TBC and pressure at TBC (pre/post treatment with intravesical oxybutynin)

ID	Intravesical Oxybutynin						Total Bladder Capacity (mL)										
	Pre			Post			Mean change (%)			Control Group							
	Pre	SD	Post	SD	Post	SD	Mean change	SE	Mean change (%)	Pre	SD	Post	SD	Post	Mean change	SE	Mean change (%)
Greenfield							10 to 140		11 to 335								
Connor									41								
Kasabian	159.30	113.40	246.00	128.70	86.70	19.70	86.70	19.70	54.4								
Kaplinsky	99.7	85.5	199.6	97.3	99.9	25.72	99.9	25.72	100.0								
Painter	209.0	103.0	282.0	148.0	73.0	28.52	73.0	28.52	34.9								
Buyse	114.0	54.7	214.0	78.1	100.0	25.75	100.0	25.75	87.7								
Ferrara*	132.0	103.0	226.0	118.0	94.0	12.68	94.0	12.68	71.2	128.0	107.0	214.0	110.0	86.0	15.7	67.2	
Guerra	200.48	100.49	243.63	118.87	43.15	10.74	43.15	10.74	21.5								

* Calculated from a graph with values for each patient

Pressure at total bladder capacity (cm/H₂O):

ID	Intravesical Oxybutynin						Control Group											
	Pre			Post			Mean change (%)			Pre			Post			Mean change (%)		
	Pre	SD	Post	SD	Post	SD	Mean change	SE	Mean change (%)	Pre	SD	Post	SD	Post	Mean change	SE	Mean change (%)	
Greenfield							15 to 75		33 to 66									
Connor									-47									
Kasabian	47.30	22.52	36.6	21.40	-10.70	6.25	-10.70	6.25	-22.62									
Kaplinsky	60.1	31.8	35.6	20.00	-24.4	6.31	-24.4	6.31	-31									
Painter	63.0	24.0	56.0	31.0	-7.0	2.84	-7.0	2.84	-11.1									
Buyse	57.0	25.6	30.8	15.8	-26.2	6.75	-26.2	6.75	-46.0									
Ferrara*	53.0	30.0	34.0	11.0	-19.0	2.35	-19.0	2.35	-35.8	49.0	28.0	30.0	13.0	-19.0	2.9	38.8		
Guerra	47.66	25.56	34.42	22.91	-13.24	3.5	-13.24	3.5	-29.1									

* Calculated from a graph with values for each patient

Figure 3.1 Forest Plot (Total Bladder Capacity)

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review
 Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
 Outcome: 01 Total Bladder Capacity (mL)

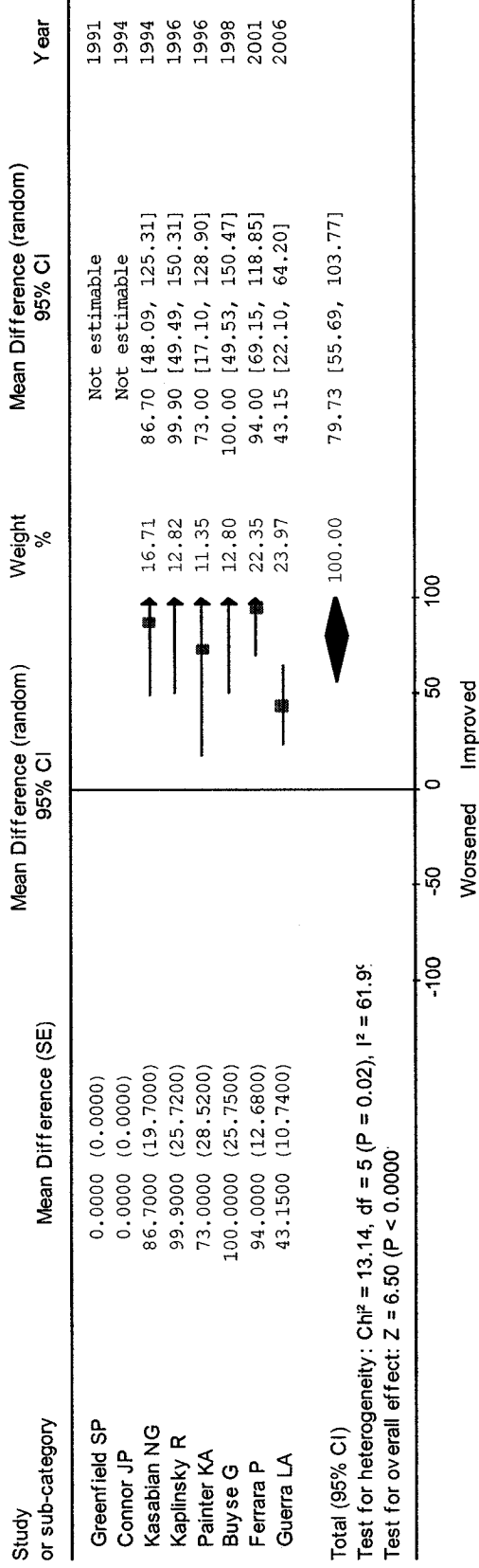
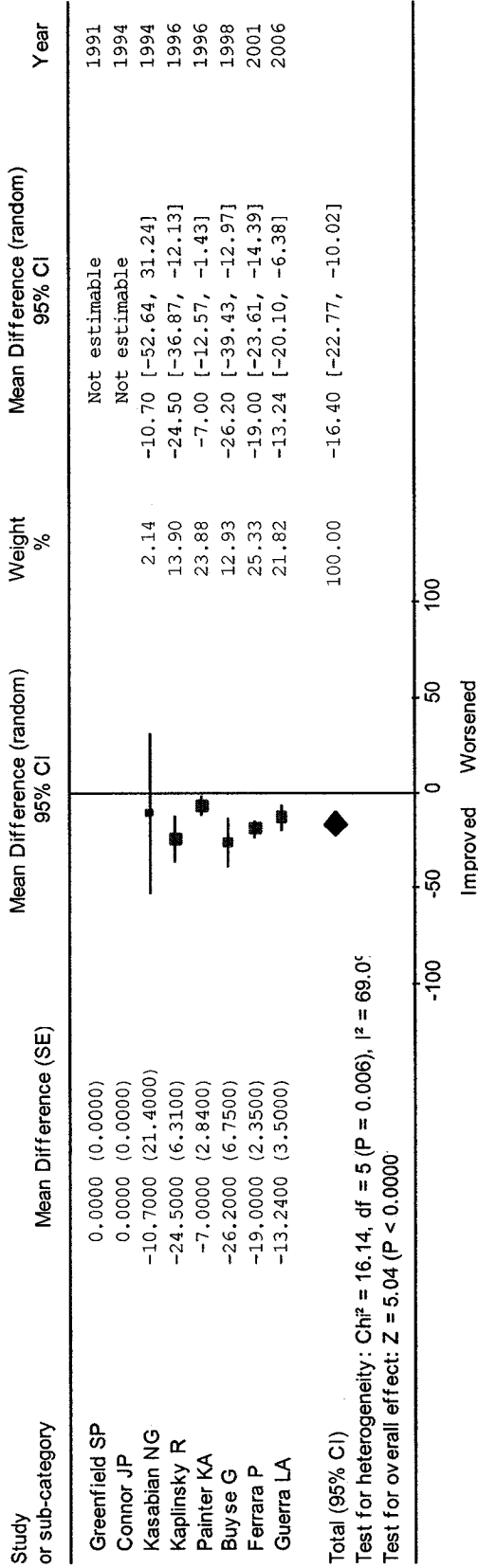


Figure 3.2 Forest Plot (Pressure at Total Bladder Capacity)

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review

Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison

Outcome: 02 Pressure at TBC (mL/cmH2O)



3.7.6.c. *Detrusor Leak Point Pressure (DLPP), Detrusor Neurogenic overactivity and Detrusor-Sphincter Dyssynergy (DSD)*

Table 3.7 displays the results of the detrusor parameters. Ferrara et al [7] and Guerra et al [8] were the only ones to report the DLPP, and both found statistically significant improvements. Detrusor neurogenic overactivity improved in 33% to 76.9% of the patients across studies. DSD was addressed only by Buyse et al [6], who reported on 11 children with DSD but did not report the change after treatment.

Table 3.7 Detrusor parameters changes pre/post intravesical oxybutynin

Author	DLPP	Detrusor neurogenic overactivity	DSD
Greenfield	Not addressed	Not addressed	Not addressed
Connor	Not addressed	10/13 (76.92%) improved bladder overactivity	Not addressed
Kasabian	Not addressed	2/6 (33.3%) children had complete resolution and the remaining 4/6 (66.6%) improved	Not addressed
Kaplinsky	Not addressed	Not addressed	Not addressed
Painter	Not addressed	Not addressed	Not addressed
Buyse	Not addressed	"Significant improvement post treatment", but did not give percentage or number of patients improved	11 children with DSD, but did not mention how many improved
Ferrara	Decreased in 64% of the patients Intravesical oxy: from 53 to 34 cmH ₂ O (36%) Oral oxy: from 49 to 30 cmH ₂ O (39%)	Improved in 49% of the patients Intravesical oxy: from 46 to 29 cmH ₂ O (37%) Oral oxy: from 44 to 26 cmH ₂ O (41%)	Not addressed
Guerra	Decreased from 49.75 (26.23) to 33.02 (17.86) cmH ₂ O (34.0%). (P<0.001)	Resolved in 17/40 (57.5%) of the patients (p<0.001)	Not addressed

Oxy: Oxybutynin

3.7.6.d. *Urinary Incontinence and Urinary Tract Infection*

All papers but the one by Ferrara et al [7] reported on continence status. In general, the authors defined "continence" as completely dry periods between bladder catheterizations, and "improvement" as a decreased use of sanitary pads, or incontinence

only at night. Buyse et al [6] reported in 8/13 (62%) studies “social continence” after the intervention but did not define social continence. Percentage of patients “continent and improved” after treatment ranged from 36 to 83 %. (Table 3.8)

Urinary Tract Infection was not addressed in most papers. Buyse et al [6] mentioned that “there was no UTI related to the procedure”, however he does not comment on number of UTIs pre- and post-treatment. Ferrara et al [7] reported statistically significant improvement in UTIs amongst 69% of the patients, with 70% in the oral group and 68% in the intravesical group. Guerra et al [8] reported no significant improvement in UTIs.(Table 3.8)

Table 3.8 Urinary incontinence and UTI changes pre/post intravesical oxybutynin

Authors	Urinary incontinence		UTI
	Dry and Improved n/N (%)	Comments	Comments
Greenfield	8/10 (80.0%)	5/10 (50%) became completely dry and 3/10 (30%) became dry during the day	Not addressed
Connor	8/13 (61.5%)	5/13 (38%) became dry and 3/13 (23%) reported reduction in "sanitary pads"	Not addressed
Kasabian	5/6 (83.3%)	5 became continent and 17% and (1/6) still had minimal incontinence	Not addressed
Kaplinsky	17/21 (80.9%)	12/21 (57%) became dry and 5/21 (24%) were dry only during the day	Not addressed
Painter	21/29 (72.4%)	3/29 (10%) became dry and 19/29 (66%) decreased sanitary pads use	Not addressed
Buyse	8/13 (62.0%)	Achieved "social continence" (The authors do not define social continence)	There was no UTI related to the procedure, but did not report pre/post change
Ferrara	Not reported	Continence was not addressed	69% of patients improved UTI episodes (70% in the oral and 68% in the intravesical oxybutynin group)
Guerra	17/47 (36.1%)	17 of 47 (36.1%) of patients became dry between bladder catheterizations (p<0.001)	5/14 (35.7%) patients improved number of episodes of UTI, but not significant (p=0.58)

n: number of patients improved, N: number of patients with incontinence before the intervention

3.7.6.e. Harms

All studies adequately reported the occurrence of harms related to the intervention. Constipation, secondary to, or worsened by intravesical oxybutynin, was not reported as a common occurrence in most studies. Although Kaplinsky et al [4] reported two patients with severe constipation they were concomitantly using oral oxybutynin. Table 3.9 lists the occurrence of harms. The most common were those secondary to the anticholinergic effect on the muscarinic receptors, namely dry mouth, facial flushing, constipation, blurred vision and orthostatic hypotension or dizziness. Buyse et al [6] had a patient with transient supraventricular tachycardia, which subsided after reintroduction of the oxybutynin, and in the study by Ferrara et al [7] two patients discontinued due to cognitive disorders.

Table 3.9 Incidence of harms related with the intravesical oxybutynin therapy

Author	Constipation	Systemic harms	Percent (95% CI)
Greenfield	"No local or systemic harm observed". No constipation mentioned	None of the patients had harms related to intravesical treatment	0 %
Connor	No constipation observed	1 patient using home oxygen had significant decrease in PO ₂ % and withdrew	8% (-7 to 22%)
Kasabian	No constipation observed	1 facial flushing, 1 dry mouth, 1 hematuria and UTI	50% (10 to 90%)
Kaplinsky	2 patients had severe constipation, but were taking also oral oxybutynin	7/21 (25%) presented anticholinergic harm (dry mouth, dizziness, constipation, hyperactivity and seizures) related to intravesical treatment	43% (22 to 64%)
Painter	"None of the patients had systemic harms" (Do not mention constipation)		0%
Buyse	No constipation observed	Of the 7 children included in the trial due to the intolerable harm to oral oxybutynin, 3 resolved and 4 had only minimal facial flushing and xerostomia. In 1 child transient supraventricular tachycardia shortly after starting intravesical therapy did not recur after the reintroduction	38% (12 to 65%)
Ferrara	No constipation observed	Oral oxybutynin group- 11 patients (facial flushing-4, facial flush and fever-2, dry mouth-1, dry mouth and fever-1, vomiting-1, diplopia-1 and mydriasis-caumaesthesia-1) Intravesical oxybutynin group- 6 (facial flushing-1, drowsiness and facial flushing-2, cognitive effects such as attention deficit and difficult in basic arithmetical operations -2, hallucinations-1)	8% (2 to 14%)
Guerra	22 and 26 patients with constipation pre/post tx. Not stat. significant.	Abdominal discomfort in one patient and difficulty in urethral, catheterization with some bleeding in another two patients	11% (3 to 19%)

3.7.6.f. Withdrawals and Type of Statistical Analysis

Overall, 297 children were initially treated with intravesical oxybutynin and 66/297 (22.2%) discontinued, leaving 231 children for analysis. Harms were responsible for 28/297 (9.4%) of discontinuation, and the most common causes were those secondary to anticholinergic effects. “Other causes” were responsible for 38/297 (12.8%) of the withdrawals, and the most frequent one was the inconvenience of the procedure, including crushing the oxybutynin pills to prepare the solution. Ferrara et al [7] reported eight patients that discontinued treatment due to worsening of their clinical conditions such as vesico-ureteric reflux, recurrent UTI and post-void residual urine. (Table 3.10)

Table 3.10 Reasons for withdrawals from the intravesical oxybutynin

Authors	Treated (N)	Withdrawals due to harms	Withdrawals due to other causes	Total withdrawal
Greenfield	10	No withdrawal	No withdrawal	No withdrawal
Connor	28	1	14 (inconvenience of the procedure)	15
Kasabian	11	3	2 (Inconvenience of the procedure)	5
Kaplinsky	28	7	No withdrawal	7
Painter	42	No withdrawal	12 (3 for recurrent UTI and 9 due to inconvenience of procedure)	12
Buyse	15	No	inconvenience of procedure-1 and problem with CIC at school-1	2
Ferrara	IV: 34 Oral: 67	Intravesical: 6 Oral: 11	IV: No patient dropped out Oral: 8 patients due to Worsening of VUR, PVR or recurrent UTI	25
Guerra	62	No withdrawal	No withdrawal	No withdrawal
Total	297	28 (9.4%)	38 (12.8%)	66 (22.2%)

IV: intravesical, VUR: vesico-ureteric reflux, PVR: post-void residual urine, UTI: urinary tract infection

The numbers of children that started and discontinued the treatment are summarized on Table 3.11. All eight studies considered for analysis those children who were compliant with the therapy (intravesical oxybutynin), excluding all children who discontinued treatment. This approach is similar to the “analysis per-protocol”, which is a terminology used in interventional studies, and implies that the analysis accounted only for the patients compliant with the therapy. When withdrawals are not included in the analysis, the measured effect of an intervention tends to be inflated.

Table 3.11 Number of patients treated, discontinued and analyzed

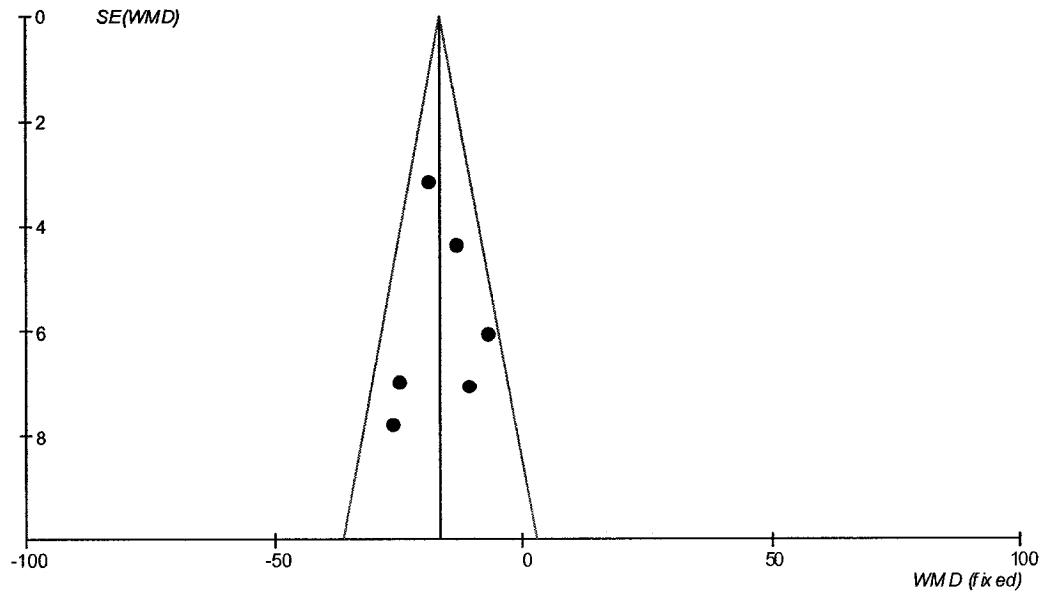
Author	Started treatment	Discontinued treatment	Analyzed
Greenfield	10	0	10
Connor	28	15	13
Kasabian	11	5	6
Kaplinsky	28	7	21
Painter	42	12	30
Buyse	15	2	13
Ferrara	101	25	76
Guerra	62	0	62
Total	297	66 (22.2%)	231 (77.8%)

3.7.6.g. Publication bias

Figure 3.3 is the funnel plot for pressure at TBC with a symmetrical pattern of distribution of the measures of treatment effect around the pooled weighted mean difference. This visual pattern does not suggest publication bias.

Figure 3.3 Funnel Plot Pressure at TBC – Weighted mean difference versus Precision

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review
Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
Outcome: 04 Pressure at TBC (cm/H2O)



3.7.6.h Sensitivity analysis

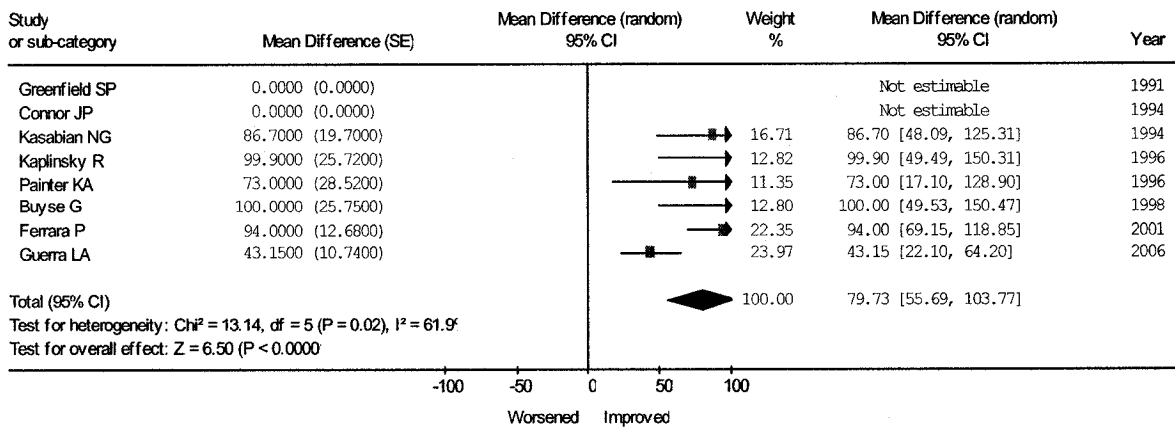
Sensitivity analysis was performed by excluding the results of the study by Guerra et al [8] (chapter 2), from the studies identified in the literature. The rationale for this choice was based on the observation that this study had the smallest treatment effect for TBC and a moderately small effect for pressure at TBC. The explanation for this difference may be a higher quality and completeness of the reporting results observed in the study [8]. This difference was attributed to the fact that the study [8] is part of a thesis.

Sensitivity analysis (1): Figure 3.4 shows that the exclusion of study [8] changed substantially the I^2 for TBC from 61.9% to 0%, and notably decreased the inconsistency of results. This change could be explained by the relatively smaller improvement in TBC noted in this study, contributing to heterogeneity of results when it is included.

Figure 3.4 Forest Plots (TBC) - Sensitivity analysis (1)

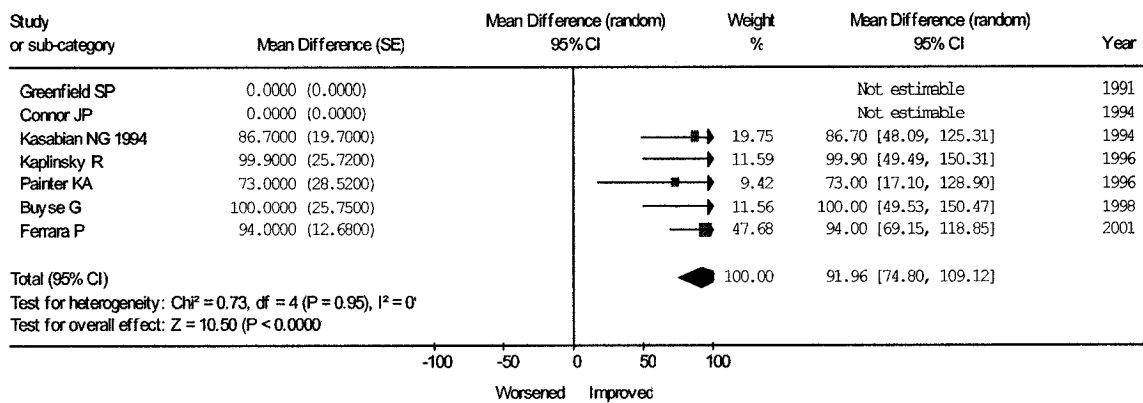
Including study [8]

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review (Version 1)
 Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
 Outcome: 01 Total Bladder Capacity (mL)



Excluding study [8]

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review
 Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
 Outcome: 07 Total Bladder Capacity (mL)

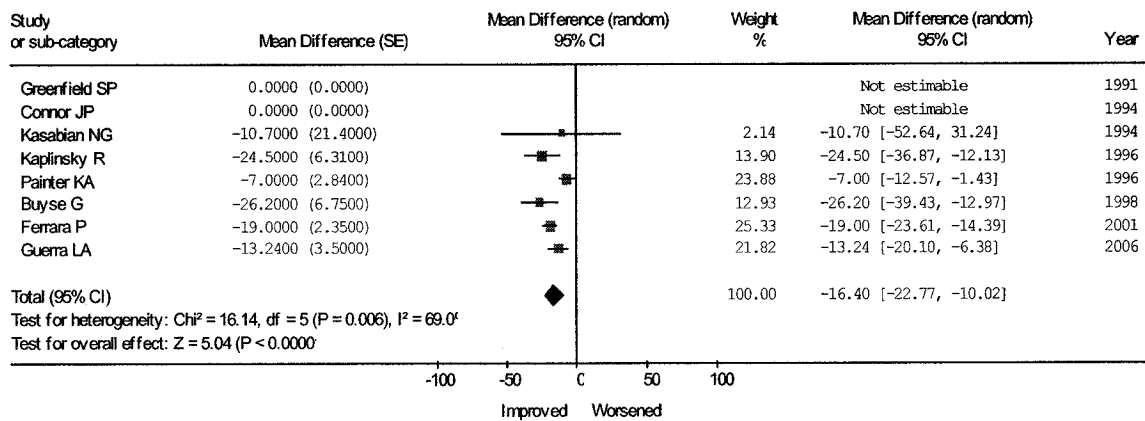


Sensitivity analysis (2): The exclusion of study [8] increased I^2 for Pressure at TBC from 69.0% to 74.6%, increasing inconsistency. Hence, if the study [8] is left in, it improves the consistency of results for this variable. (Figure 3.5)

Figure 3.5 Forest plots (Pressure at TBC) - Sensitivity analysis (2)

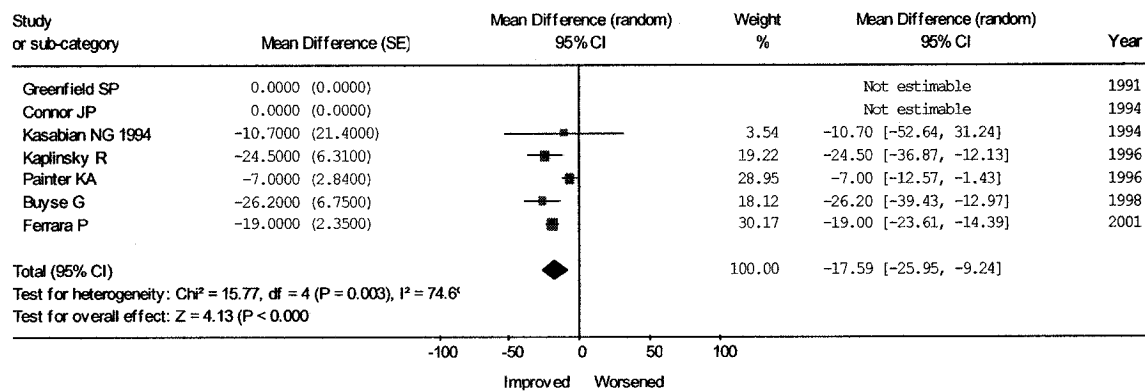
Including study [8]

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review (Version 1)
 Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
 Outcome: 02 Pressure at TBC (mL/cmH2O)



Excluding study [8]

Review: Intravesical oxybutynin for children with poorly compliant neurogenic bladders: a systematic review (Version 1)
 Comparison: 01 Intravesical Oxybutynin - Before-and-after comparison
 Outcome: 08 Pressure at TBC (mL/cmH2O)

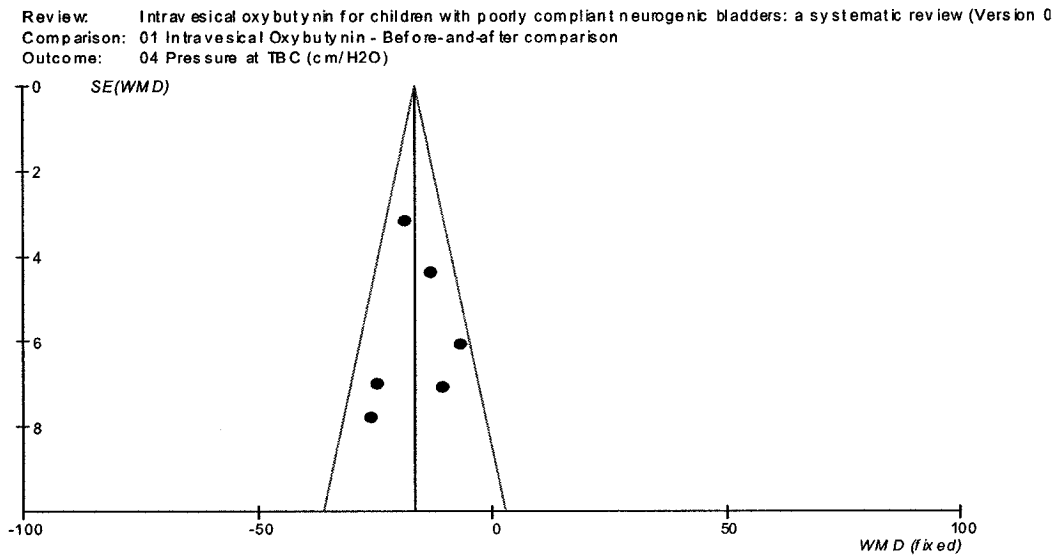


Sensitivity analysis (3): Figure 3.6 displays the funnel plots for publication bias assessment including and excluding the present study [8]. No change in the pattern was observed upon excluding this study from the analysis. There is a symmetrical distribution around the weighed mean difference in both plots. It shows robustness of this analysis in regards to the inclusion of the referred study.

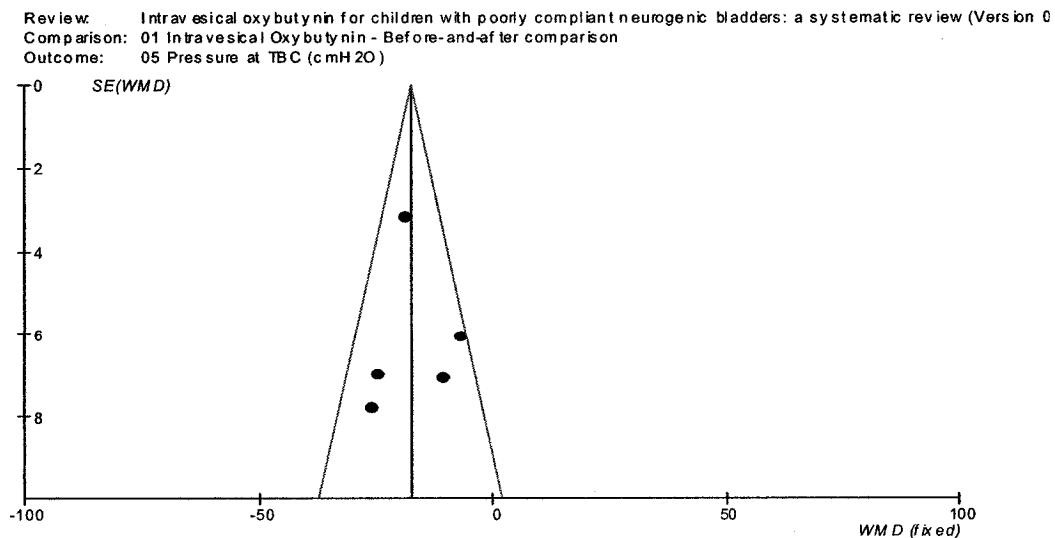
Figure 3.6 Funnel Plots (Pressure at TBC) – Sensitivity analysis (3)

Weighted mean difference versus Precision

Including study [8]



Excluding study [8]



3.8. Discussion

This systematic review suggests that intravesical oxybutynin is a potential alternative treatment for children with neurogenic bladders refractory to oral therapy with oxybutynin or for those who experienced severe harms using this drug orally. However, the level of evidence of the studies is low and not ideal to guide clinical practice or policy makers. These findings are of concern because neurogenic bladder is not rare in children (23), the management of its morbidities demands high expenditures from the health-care system, and it impairs quality of life. In this scenario, a systematic review would help physicians and other health care practitioners in decision-making. Unfortunately, no study of sufficient size or adequate design was identified, such as a randomized controlled trial, which would provide a stronger level of evidence.

3.8.1. Literature review

Four main databases were searched for high citation impact factor journals, and 3 large databases for grey literature. All papers included in this review came from high citation impact factor journals and they were all retrieved in either Medline® or Embase®. The only paper identified in the grey literature was chapter 2 of this thesis (the CHEO case-series). There is some debate whether it is necessary for the literature search to include both largest databases. Sampson and colleagues (58) reported that searching in Medline® but not Embase® risks biasing a meta-analysis by finding studies that show larger estimates. Interestingly, this methodologic study showed significantly smaller estimates by 29% in Embase-unique trials (OR=0.71, 95%CI: 0.56 to 0.90), but influenced the pooled estimate by an average of only 6% OR=0.94, 95% CI 0.88–0.99).

They concluded: “Embase in the context of a thorough search makes a small contribution to the overall estimate of intervention effectiveness in systematic reviews.”

Fergusson and colleagues (59), assessing methodological issues in meta-analyses, found similar results in their analysis of the effect of the literature search in meta-analysis, where Medline missed 8 of 74 (11%), and Embase 10 of 74 (14%) studies. From the 8 studies missed in the Medline, hand searching of references identified 2 and contacting industry representatives identified the other 6 studies. They concluded that one should consider the costs and benefits of searching Embase, since Medline coupled with review of the references identified the majority of the trials.

Searching for grey literature is difficult and sometimes frustrating. There are limited specialized databases available, the sources of publications are challenging to find and even a dedicated search can still be incomplete. Despite all efforts to include grey literature, there are a large number of publications available worldwide that are not indexed in large or convenient databases, and the likelihood of missing some of this evidence is a reality. Dickersin pointed out that presentations of abstracts and theses are more likely to be published in full if they have “positive or significant results”.(60) Incomplete searches and inclusion of studies may lead to publication bias.(61) The inclusion of grey literature in meta-analyses may decrease the effect of the intervention being assessed.(62) Hopewell et al. published a Cochrane review, in which they analyzed the effect of an intervention comparing published trials to trials from grey literature. On average they found a 9% higher treatment effect size in published studies (ratio of odds ratios for grey versus published trials 1.09; 95% CI: 1.03 to 1.16).(63)

3.8.2. Language restriction

Due to constraints of resources, this review was limited to papers published in the English language; this decision was not based on the quality of publication in English language. Six papers published in languages other than English were excluded. In general, 78% of published meta-analyses have language restrictions, and more than 90% of them are restricted to the English language.(64) Although this is a debatable issue with no strong evidence to support this approach, the language restriction criterion does not seem to alter the results significantly. Moher et al reviewed 79 meta-analyses and assessed whether language restriction affected the estimate of the effectiveness of interventions evaluated in RCTs.(65) This research showed no evidence that this restriction lead to biased estimates of intervention effectiveness. These authors replicated their findings more recently.(66) As was mentioned in section 3.8.1., Fergusson et al (59) reviewed the impact of methodological issues on the results of meta-analyses, in the context of a large technology assessment project on blood transfusion. There was very little impact on estimates of effect related to inclusion or not of non-English language, country of study origin and type of publication. Making this issue more debatable, another study assessed the completeness of reporting, design characteristics and analytical approaches of 133 RCTs published in English between 1989-1994, and 96 published in French, German, Italian, or Spanish during the same time.(67) The authors found no significant differences between trials published in English and other-language trials with regard to completeness of these items, and recommended the inclusion in systematic reviews of all trial reports irrespective of the language in which they are published.

3.8.3. Quality of the studies

3.8.3.a. Methodological quality: There was a small number of studies addressing intravesical oxybutynin in the paediatric population, and the quality assessment showed several weaknesses in the reporting of the results. However, all the included studies clearly stated the research question and used adequate inclusion criteria. Population, intervention, dose and means of administration were well described, ensuring the reproducibility of the study.

Overall, changes in primary and secondary outcomes were well discussed but their actual values were not fully reported in some included studies. For instance, the primary outcome “bladder compliance”, which is the most important parameter of improvement, was mentioned in most of the introduction or discussion sections but only 2/8 (25 %) of studies actually reported the values. Kaplinsky et al [4] reported a bar graph with the TBC and pressure at TBC of each patient pre- and post-treatment, and it was possible to calculate the bladder compliance from the graph. TBC and detrusor pressure at TBC were reported in most studies, however, Greenfield et al [1] and Kaplinsky et al [4] did not report their values. Instead, they reported the percent of improvement for each patient. One does not know the pre- or post- values, so this type of report is incomplete and can be misleading. Another frequently missing piece of information was the mean change and variability (SD, SE or 95% CI) of some outcomes, which made it difficult to combine the results.

The quality of a clinical trial can be related to several methodologic aspects involving the design, conduct, analysis, and reporting of the trial results. According to Gludd, methodological studies suggest that inadequate randomization in published

reports, is associated with more positive estimates of intervention effects, whereas the influence of double-blinding and follow up is less clear.(68) Assessing methodological quality of clinical trials is an essential step for a correct interpretation of the trial results, and physicians and policy-makers should be aware of it.

3.8.3.b. Study design: Buyse et al [6] and Connor et al [2] published the only two prospective studies, but used no comparison arm. Thus, they were classified as single group before-and-after studies. This is not a strong design to assess effectiveness of an intervention. Although it is not clear, the paper by Kaplinsky et al [4] seems to be a retrospective review. The study published by Ferrara et al [7] was the only one that compared children taking oral to those using intravesical oxybutynin, however it was a retrospective study.

In summary, the majority of the included papers are of a low level of evidence. Most were retrospective reviews with single group before-and-after evaluation or prospective case-series using no control group. According to Benson and Hartz, “observational studies have some advantages over RCTs such as lower cost and a broader range of patients, and it should be an option when RCTs are impossible or unethical.”(69) However, one should avoid non-experimental studies for assessing therapy, since they frequently lead to false positive conclusions about efficacy.(42) RCTs have been recognized as the best method of establishing the value of a new therapy (70), and together with systematic review of RCTs have become the “gold-standard” for judging whether the treatment does more good than harm.(42) Before-and-after study design used to assess therapy has a large possibility of bias and threatens internal validity, and the ideal way to improve this is by using a quasi-experimental or experimental design.

This usually introduces an element of comparison such as a control group, or multiple observations as in a time series study.(71)

DLPP and detrusor overactivity are clinically important risk factors for kidney deterioration but they were poorly reported. Although Ferrara et al [7] listed them in the material and methods section they were not mentioned in the results. Only 4/8 (50%) of the studies reported on detrusor neurogenic overactivity, with improvements ranging from 33 to 76 %. Ferrara et al [7] mentioned significant improvement in overactivity but did not quantify it. The under-reporting of these outcomes may be due to an excessive focus on the TBC and pressure at TBC by most physicians.

3.8.4. Intervention

Although the optimum dose for intravesical instillation has not been determined, published studies suggest that an oral dose of 0.2 mg/kg/day could be safely used intravesically.(2,3) Haferkamp and colleagues (72) described an improved response on UDS and urinary continence as the intravesical dose was escalated from 0.3 to 0.9 mg/kg/day, and no significant increase in harm was observed. Most papers in this review used 0.2 mg/kg/day (average of 10 mg/day), and recommended to leave the drug in the bladder until “next catheterization” or for “3 to 4 hours”.

The time the drug was left inside the bladder does not seem to affect the response to it or to increase harms.(73) According to Saito and colleagues, retention of the solution in the bladder could be a problem for neurologically normal patients with overactive bladders.(74) On the other hand, in patients with neurogenic bladders that do not void spontaneously and rely on CIC to empty their bladders, retention of the solution inside the bladder is not a problem if there is no severe detrusor overactivity.

Six of the 8 studies (75%) used intravesical oxybutynin in the form of diluted crushed pills in sterile water. However, “inconvenience of the procedure” was pointed out in four studies as being the cause of dropout from the treatment, and it was responsible for 26/38 (68%) of all dropouts not related to harm. Some participants found it boring and time-consuming to be crushing and dissolving pills twice a day to make the solution for instillation, and this is clearly one limitation of the procedure. Although not on the market, the pre-prepared solution (purified oxybutynin and sodium chloride 154mEq/l dissolved in sterile water, 5 mg/5mL and pH 5.85) used by Buyse et al [6], makes the process easier and more comfortable. Guerra et al [8] used a pharmacy prepared solution in which oxybutynin powder was dissolved in sterile water, 5mg/10 ml and pH 4.55 (information obtained from the pharmacist responsible, contacted during this review). This solution can be readily prepared in pharmacies, and it may enhance the compliance with the treatment. Based on these studies, the intravesical route seems to be an attractive possible alternative mode of administration. Other modalities of oxybutynin administration include transdermal (75), intravaginal (10,76) and intrarectal (11), some of which are still under investigation.

3.8.5. Primary outcome

Unfortunately, most studies failed to report bladder compliance, which is the landmark improvement for neurogenic bladder. Ferrara et al [7] compared intravesical instillation with oral oxybutynin and reported 74% increase in bladder compliance, with no statistical significance between the two groups. If one compares the absolute value of mean change in bladder compliance between Ferrara et [7] and Kaplinsky et al [4] studies, they appear similar, 7.5 and 7.4 mL/cmH₂O, respectively. However, when the baseline levels are taken into account, there is a much higher percent improvement in

Kaplinsky's study (370.0%) versus Ferrara's (88.2%). This difference is due to the lower baseline mean compliance observed in Kaplinsky's group, which could represent a population of patients with more advanced bladder disease.

Bladders with worse compliance have a greater likelihood of causing obstruction in the upper urinary tract. High bladder pressure can create functional obstruction to the ureters, causing delayed urine excretion and impairment of the renal function. As pointed out by Vaidyanathan and colleagues, oxybutynin helps patients to retain a larger volume in the bladder at a low pressure, avoiding detrimental effects upon the kidneys.(33) Controlling bladder compliance could delay or render unnecessary surgical intervention such as bladder augmentation (34), which may otherwise be necessary in chronic non-responders to oral anticholinergic therapy.

One striking aspect of this review is the way the continuous outcomes results were reported and interpreted. As previously defined, bladder compliance is the ratio of the "volume change" over the "pressure change" during bladder filling in the UDS. The value of this ratio, and obviously its change, is most important when drawing conclusions about the effect of this intervention. Most of the studies in this review reported only mean improvements of "TBC" and "Pressure at TBC" separately and independently, and for the whole group of patients. The interrelationship of these two parameters was not appreciated. An increase in TBC in a particular patient is meaningless if the Pressure at TBC does not decrease simultaneously or at least remain stable.

Bladder compliance is quite a challenging variable to use as a parameter of follow up in children, because it changes with age. Pressure at TBC is a more reliable parameter to assess upper tract risk, but one needs to correlate it with TBC in the same patient. Using before-and-after measurements to assess outcomes, it is important to know the

correlation between the “pair of measurements”, because they are not independent observations. For this reason, we were not able to calculate mean change of bladder compliance from the reported “overall” means changes of “TBC” and “Pressure at TBC”. The report of favourable mean improvements in TBC and Pressure at TBC is of course interesting. It may suggest, but does not unequivocally ensure, improvement of bladder compliance. In a review, one cannot infer about bladder compliance based on means of these variables because the correlation amongst the measurements, pre- and post-intervention, was not reported.

Since it was largely unreported, no inference could be made about effectiveness of this intervention based on bladder compliance. Hence, it was elected to use pressure at TBC as the outcome for the assessment of effectiveness. One can draw two important messages from these findings, the first one is to report bladder compliance adjusted for age, the most important and meaningful primary outcome related to this research question, and the second is to report the necessary elements that allow statistical meta-analysis such as values of treatment effect and variability, statistical tests employed and p-values. These facts are extremely important in research and may reflect how the statistical analysis was conducted. Investigators should work closely with statisticians, getting adequate support not only to analyze but also to report the results adequately.

3.8.6. Total bladder capacity and pressure at total bladder capacity

In general, all studies reported statistically significant improvements in TBC and pressure at TBC, except for the study by Kassabian [3] that reported no statistical significant change in pressure at TBC. The statistical (I^2) and graphical (forest plot) analyses suggested moderate inconsistency across study results for both TBC and

pressure at TBC. The rationale for the sensitivity analysis excluding the study [8], was based on the observation that it has a better quality and completeness of report, which may be a result of being part of this current work. However, the sensitivity analysis excluding the study [8] showed a small change of the pooled estimate of pressure at TBC, and a more important change in TBC. On the other hand, the inclusion of this study decreased slightly the I^2 from 74% to 69% and gave a better “stacked pattern” on the forest plot for pressure at TBC. Inclusion of the referred study apparently increased consistency and demonstrated the robustness of the results for this variable. However, I^2 test for TBC changed from 61% to 0% after excluding this study, reflecting the much smaller change observed in this variable in the study [8].

Based on the results of the sensitivity analysis, it was decided to pool the estimates of pressure at TBC because the primary outcome was not available for comparison across all reports. To further support this decision, pressure at TBC is an important element on kidney safety in neurogenic bladder.(8) Pooled mean difference for pressure at TBC was -16.4 cmH₂O (95% CI: -22.77 to -10.02), which is considered an acceptable improvement for a paediatric population. The decision not to pool TBC values was based on the large change in heterogeneity showed by the I^2 test during the sensitivity analysis, demonstrating that pooling this data may lead to misinterpretation. Both statistical changes referred to above can be appreciated in the pattern of the forest plots. Due to the moderate inconsistency of results across studies, a random effect model was used to pool the estimates. This model accounts for the intra study variability.

In summary, the pooled estimate treatment effect for pressure at TBC showed a statistically significant improvement of -16.4 cmH₂O, comparing combination treatment with intravesical plus oral oxybutynin, to oral oxybutynin. Although it is still a matter for

further investigation, the improvement of the urodynamic parameters after intravesical instillation may be a result of the anti-muscarinic action on the cholinergic receptors and to the local analgesic effect on the sensitive C fiber in the detrusor fibers.(28) The optimum time frame to assess a durable effect of this intervention is still unknown.

The length of treatment with intravesical oxybutynin ranged from 3 to 36 months across the studies. Kaplinsky [4] believes that the pharmacological effect is durable in those who had an initial response in the UDS, and in their experience TBC markedly increased during extended follow up. On the other hand, Painter [5] observed only 53% durable long-term response and claimed that their results were consistent with the 55% response in another long-term study of intravesical oxybutynin in adults published by Prasad et al.(77)

3.8.7. DLPP, DSD and Detrusor Overactivity

The activity of the detrusor muscle is of vital importance to the management of neurogenic bladder, since its “overactivity” or “lack of synchronism with the urethral sphincter” (dyssynergy), can generate high a pressure inside the bladder. Detrusor overactivity was addressed in 5 out of the 8 papers and all of them reported improvement in the number of bladder contractions, varying from 33 to 77 %. Such improvement can hypothetically be secondary to the aforementioned topical analgesic effect on the sensitive C fibers of the detrusor muscle, increasing their threshold for contraction. DSD and DLPP were addressed only in one and two studies respectively, and there was not sufficient information to draw conclusions.

3.8.8. Incontinence

In general, a marked improvement in urinary incontinence with use of intravesical oxybutynin was reported, with most studies showing a high level of “dry and improved”. There are some concerns with regard to the internal validity of the assessment of incontinence in the studies. Although “dry” is something concrete and easy to assess, “improved incontinence” is very subjective and varies substantially depending on who is reporting it. There was report of “social continence;” it is difficult to quantify and was not defined in the report what is “social” and what it represents for each individual patient. Possibly, the number of “soaked sanitary pads” could be more reliable, but it would be still far from the ideal. Again the definition of “soaked” is variable, and maybe weighing the pads could improve precision. However, weighing pads at “each change” to assess the amount of urine leaked is time-consuming and usually abandoned by the patients. These issues threaten internal validity of the studies. Urinary continence improves quality of life in patients with neurogenic bladder, but this perspective was not addressed by the studies. Vaidyanathan and colleagues reported an improvement in quality of life after combination of CIC and intravesical oxybutynin in five adult patients with neurogenic bladders.(33)

3.8.9. Harms and Withdrawals

Harm is associated with withdrawal from medical treatment, and has impacts on compliance with the treatment. Not uncommonly, authors fail to report harm, and even in study designs such as RCTs there is a trend to report more benefits than harms.(78)

This review showed 66/297 (22.2%) participants discontinuing the intravesical therapy, with 28/297 (9.4 %) secondary to systemic harms. Most authors agreed that

oxybutynin was well tolerated intravesically, but also that the occurrence of harm was not insignificant. The incidence of harm with the intravesical route was lower than the published incidence with oral administration, and this is in keeping with the rationale for its use. Weese and colleagues reported that the published incidence of significant harm with oral therapy ranges from 57 to 94%.⁽³⁴⁾ As mentioned in chapter 1, N-desethyloxybutynin is the first-pass hepatic metabolite of oxybutynin, and is associated with its anticholinergic effects.⁽⁷⁹⁾ N-desethyloxybutynin seems to cause most of the adverse systemic anticholinergic effects, and avoiding the oral route with drug absorption via the portal venous system lessens this problem. Intravesical oxybutynin has been used to treat myelodysplastic children with neurogenic bladder in the paediatric urology clinic at CHEO, based on this premise. However, as this review has shown, even using this route, harm is still possible and it is probably secondary to drug absorption through the bladder mucosa, as reported by Massad et al.⁽¹⁵⁾ The possible occurrence of harm should be discussed with the patient and family before starting the treatment, especially if the indication for intravesical oxybutynin was “non-response to oral drug” with no previous experience of harm. As well, patients may fail to report mild grades of harm, so the real incidence may be higher. Another common reason for discontinuing the treatment was the inconvenience of crushing pills to prepare the intravesical solution. Although this kind of limitation was not observed by Greenfield et al [1], it was largely reported in other studies and could be resolved using a pharmacy prepared solution. Such a solution is not available on the market, but it can be readily prepared by a pharmacy, it is convenient and it could enhance compliance with treatment and decrease withdrawal as stated by Buyse et al [6]. Technical problems with urethral catheterization are not

commonly observed because these patients have generally used catheterizations to empty their bladders for a long time.

3.8.10. Sensitivity Analysis

As discussed in the outcome section, the study presented in chapter 2 by Guerra et al [8] was part of the work developed for this thesis, and the better quality and completeness of results reported should be attributed to this fact. To assess the impact of the inclusion of this study in the review, we performed a sensitivity analysis.

The TBC variable was more sensitive to the exclusion of this study and changed from 79.73 mL to 91.96 mL (13%), while pressure at TBC changed from -16.40 to -17.59 cmH₂O (6%). The inclusion of this study greatly increased the inconsistency in TBC results, but it decreased the inconsistency in pressure at TBC. The variable pressure at TBC was more robust, and although the I^2 score was moderately elevated, it had an acceptable pattern of consistency on the forest plot and thus was pooled. In general, the inclusion of this study did not distort the results of the review.

3.8.11. Publication Bias

According to Thornton and Lee, publication bias awareness appeared in the literature for the first time in 1956 when Smith MB, the editor of the *Journal of Abnormal Social Psychology*, acknowledged that papers with negative results were less likely to be published in his journal.(61) Dickersin refers to centuries-old cautions against publication bias by prominent scientists, and according to her: “Clinicians who depend on systematic reviews and meta-analyses based solely on published data deciding on a patient’s treatment course could be causing harm if studies that could influence the

review results are omitted”.(60) Because publication bias may arise from an incomplete literature search (61), one should be concerned with a systematic review that shows few papers to support evidence, and all efforts should be employed by clinician and decision makers not to miss information. Guided by this principle, authors of systematic reviews should try to assess all the available evidence in the literature but also be aware that possible omission can happen in this complex network called “Literature”.

In this review, few studies reported on bladder compliance making it difficult to assess reliably publication bias using our *a priori* primary outcome. However, using pressure at TBC, our second most important variable, the funnel plot showed a symmetrical distribution around the mean effect, suggesting no publication bias. This surprising result should be interpreted with caution. One should anticipate possible publication bias in this review because all included studies came from high citation impact factor journals. This may be the result of the small number of papers available to construct the funnel plot, so this interpretation should be made with caution. Asymmetry on the funnel plot, with most of the studies displaying positive results, is commonly seen in the presence of publication bias where studies with negative results or small effect sizes are less likely to be published. Conversely, in the absence of bias, the graph should have a symmetrical inverted funnel shape because studies with less precision will show larger variability of treatment effect at the bottom of the graph, while studies with high precision will have less variability and be displayed at the top of the graph.(57) As stated in methods section 3.6.6., the Egger linear regression method to assess publication bias was not used due to the small number of trials included, which limits its power.

3.8.12. Other biases

Most studies analyzed in this review were retrospective, which potentially have several sources of bias such as selection and information biases. In this type of study, patients first received the treatment sometime in the past, and later on they are classified or included in a group for analysis based on information gathered from charts or registries. At this point, he/she can be misclassified due to the retrospective nature of this evaluation. For instance, to select groups with the same characteristics or to classify outcomes/exposures retrospectively, one needs to rely on information recorded in the medical files. This information may be incomplete or imprecise and lead to bias. In summary, the methodology of retrospective assessments may convey some information, but it can be unreliable or of low validity.(46)

Measurement bias is a type of information bias, defined as a systematic error introduced by differences in scales or units. UDS parameters were used to compare bladder outcomes in the individual studies. One would easily appreciate that a UDS measurement done in Europe could differ from one done in North America. The machines that measure them or the method used to calculate them may differ. Pooling UDS reports with different standards may be a source of measurement bias.

Another source of systematic error is recall bias, where for example patients may minimize an important event in the past, and give greater emphasis to something that happened recently. Although a classical definition of recall bias includes a differential level of accuracy in information provided by “two groups being compared” (80), like case-control or cohort studies, non-comparative studies can also be susceptible to this type of bias. Inevitably assessors rely on questionnaires or telephone calls to evaluate clinical

results, as the one used by Buyse et al [6]. When someone is asked over the phone about some harm or event that has happened, patients may recall selectively the most recent or the most intense, and bias may arise. Another aspect worthy of mention is that the internal validity of such instruments should be validated to avoid other types of bias.

Finally, most of the studies in this review had few participants, and this may affect the purported effect of the intervention. Four of the eight studies analyzed data on fewer than 14 treated participants, which usually leads to a large variability in the outcomes measures and/or a larger and unrealistic treatment effect size. Moreover, smaller studies are in general conducted and analyzed with less methodological rigor than larger studies.(81)

3.9. Ethics

As suggested by Virginia Sharpe^b in her article “Why do no Harm?,” health professionals have an obligation to avoid harm to their patient, even when the definition of “harm” can be interpreted by several perspectives and theories.(82) This commitment to participants in research, as she added, reflects on the accountability of professionals and institutions to the moral obligation and pledge to do no harm.

No discussion about the ethical implications of the intervention was found in the included articles. Amongst other issues, this therapy involves children and as any other treatment, it may cause unexpected harm. Although traditionally parents and physicians have made decisions on behalf of children in regards to medical issues (83), this attitude has recently evolved. Physicians and health professionals should involve older children and adolescents in decisions regarding treatment options, while of course being sensitive

^b Virginia Sharpe is a visiting scholar at the Center for Clinical Bioethics at the Georgetown University.

to their capacities and limitations. These ethical issues should be discussed in such studies, and contrasted with the possibility of harms secondary to the intervention, especially in research involving greater than minimal risk.

3.10. Limitations

Systematic review is a retrospective analysis and susceptible to several sources of bias.(84) Information and selection bias (sometimes selection bias is referred as a type of information bias) are commonly seen in retrospective studies. In this review, they may have been introduced at the time of classification of the patients as having “neurogenic bladder”, or when defining cases with “poor bladder compliance” for example. Both classifications depend on information gathered retrospectively from medical records. Harms were recorded based on patients’ reports to the medical staff, and the accuracy or completeness of this information may depend upon the way the patient is approached. Differences in the way the information is obtained could bias the results of various studies, and in a retrospective review there is no control over these events that have already happened. The definition of the eligibility criteria for the review may create selection bias, for example, by using inappropriate restrictions or inclusion criteria. A series of studies may be selected with a heterogeneous population that biases and threatens the external validity of the conclusions.

The quality assessment of the studies was done using an instrument developed specifically for this review, and this may be a strength, or a limitation at the same time. We found no validated instrument or checklist with a focus on features common to our study, and decided to construct one. As it has been pointed out, when one is constructing checklists to assess quality of studies, details such as “how” and “why” the items were

included should be discussed.(85) The rationale for the construction of this questionnaire was to assess specific items commonly used in neuro-urology research, and it may allow comparisons amongst other systematic reviews in this field. We used generic items that assess design, conduct, analysis and report based on validated instruments (52-54) and specific items common to neurogenic bladder. Whether the face and content validities were adequate is not known, therefore, further studies to validate this checklist should be done.

Since intravesical oxybutynin is relatively understudied in paediatric urology, the lack of experience with this therapy and the small number of published reports limit the available evidence. Thus, the restriction of the inclusion criteria to age less than 18 years may have precluded a more comprehensive assessment of this treatment, and adding adults could have enriched the results. However, drug metabolism in children has different behaviour and features, and they should not be analyzed together with adult patients. One could even argue that adolescents and children should be analyzed separately, because the physiology in an infant differs in many aspects from that in a 17 year old adolescent.

All of the studies in this review except one were before-and-after evaluations of the intervention, and the only comparative study was a retrospective paper. These are weak study designs that carry a high likelihood of biased assessment of the intervention. The absence of RCTs, controlled trials or more robust study designs limits the opportunities for a full meta-analysis.

Another important limitation was the fact that most of the studies had not reported bladder compliance, the primary outcome chosen for this review. This urodynamic parameter translates as a “clinically safe condition of the bladder,” which usually spares

the kidneys from damage in patients with neurogenic bladder. Instead, Bladder Capacity and Pressure at Bladder Capacity were assessed separately as measures of treatment effect, and this limits our ability to draw conclusions and make inferences.

Language restriction is a limitation of this review, since the information written in languages other than English, was not included.

3.11. Conclusions

This review examined studies with low levels of quality of evidence, assessing effectiveness of intravesical oxybutynin in the paediatric population with neurogenic bladder. Most studies were retrospective case series, included no control group for comparison and were poorly reported. There are several potential sources of bias. In general, this therapy increases the mean TBC and decreases pressure at TBC for the “group of patients as a whole”, however little information was reported about the effect of intravesical oxybutynin on bladder compliance for each “individual patient.” Although the incidence of harm was lower with the use of the intravesical route, harms may still occur and should be discussed with patients and family. Based on the evidence collected in this review, there is not sufficient justification to recommend this therapy for children with neurogenic bladder. Research with a more sound study design, such as RCT, should be conducted to assess the efficacy of this intervention in children.

3.12. Included studies

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3.13. Excluded studies

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Chapter 4

Proposal for a RCT:

Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial of efficacy and safety

4.1. Introduction

4.1.1. Scientific background

Children with neurologic pathology of the spinal cord may present with neurogenic bladder, as discussed in chapter 1. It commonly results in high storage pressure in the bladder, incomplete voiding and urinary incontinence. Severe cases of chronic high-pressure bladder may cause kidney dilation and renal failure. The most effective treatment is clean intermittent bladder catheterization (CIC) and oral anticholinergic medication, with oxybutynin being the most commonly used. Children who have an unsatisfactory response to this regimen and who maintain high pressures in their bladders, experience more morbidities. Intravesical oxybutynin is an alternative therapy to improve bladder compliance; that is, the ability to accommodate larger volume at a lower pressure.

4.1.2. Rationale for the RCT

The CHEO case series reported in chapter 2 is one centre's accumulated experience with intravesical oxybutynin in children with poorly compliant neurogenic bladder who were non-responders to oral oxybutynin. It suggests that intravesical

oxybutynin may be effective, but this evidence was based on a retrospective review with a low level of evidence.

Chapter 3 was a systematic review of the effectiveness and safety of intravesical oxybutynin in children with neurogenic bladder. Eight studies of weak design were identified, that suggested effectiveness and low incidence of harm. This review concluded that there is no strong evidence in the literature to support the use of this treatment in children with neurogenic bladders.

A randomized controlled trial (RCT) is needed, in the face of the lack of evidence supporting this therapy in children. This chapter is a RCT protocol to assess efficacy and safety of intravesical oxybutynin in children with poorly compliant neurogenic bladders, who became non-responders to standard doses of oral oxybutynin. The study protocol is the formal document specifying how the trial is to be conducted.(86) This document will be the manual to guide professionals and researchers involved throughout the planning, conduct, analysis and reporting phases.

4.2. Objectives and Hypothesis

4.2.1. Objective

This RCT is to compare the efficacy and safety of treatment with intravesical oxybutynin versus high dose oral oxybutynin, in children with poorly compliant neurogenic bladders who are non-responders to the standard dose of oral oxybutynin.

4.2.2. Hypothesis

It is hypothesized that in children with poorly compliant neurogenic bladders who do not respond sufficiently to standard doses of oral oxybutynin, intravesical oxybutynin

will increase bladder compliance. Furthermore, it is hypothesized that intravesical oxybutinin will increase bladder compliance more effectively and with less harm than high doses of oral oxybutinin.

4.3. Methods

4.3.1. Registration of the trial and conflict of interest

4.3.1.a. Trial registration

Before the start of this trial, the protocol will be publicly registered with “Current-controlled trials” and the identifying number and URL address will be available on the protocol abstract and in the full text of the final publication. Thus, comparison of the protocol with the trial results may ensure transparency regarding deviation from the original research plan. Important changes must be appropriately justified, and their effects on the internal and external validity of the results must be assessed.

4.3.1.b. Rationale for trial registration

The Declaration of Helsinki, last review updated in 2000, states: “the design of all studies should be publicly available.”(87) This was an important addition to this worldwide accepted document of ethical principles that guide the practice of medical research. It is an international call for transparency and public disclosure of the protocol research. Trial registration is helpful in maintaining the integrity of the research as planned, and in avoiding bias in meta-analysis that can arise from selective reporting of outcomes.(88)

The Ottawa statement is an initiative to advocate for the practice of trial registration, and according to it, “the protocol information and results from all trials related to health or healthcare – regardless of topic, design, outcomes, or market status of

interventions examined – should be registered and publicly available.”(89) This statement expressed the rationale for registration of protocols that is based on ethical and scientific principles such as respect for the investigator-participant agreement, open and rapid access to information, reduction of unnecessarily duplicated research, accountability with regards to ethical standards, and transparency of trial design and methodology. It also helps in the identification and prevention of biased under- or over-reporting of research and increases the availability and reliability of evidence. The statement recommends that regardless of whether or not the results are being published, the outcomes and analyses specified in the protocol that was approved by the institutional review board committee, as well as data on harm should be registered. The minimum information to be registered before the enrolment of the first participant in the trial should include the type of intervention, outcomes that will be assessed and details regarding informed consent. As the trial progresses, the full protocol, data collection forms and results should be registered. Protocol registration also guarantees intellectual property, because the public documents have the dates of registration or posting.(89)

In summary, the registration of a protocol is to ensure consistency with the final report of the study, obviating methodological deviations that may occur during the conduct and analysis of the trial. Registration is also to diminish publication bias, and to help to avoid wasteful, indiscriminate, or unnecessarily duplicated research.(88) Several international groups provide this service on the Internet. There are hundreds of trial registries worldwide but most are institutional, and they are managed in isolation.(90)

4.3.1.c. Disclosure of conflict of interest and financial involvement

The authors involved in this trial will disclose financial relationships or conflicts of interests of any sort related to the study. Any funds received from drug companies, or

from governmental or private institutions will be reported. Should this trial be partially or completely industry sponsored, it will have an external statistical analysis of the raw data by an independent statistician at an academic center, to validate the results. The principal investigator will indicate that he had access to the complete raw data and is responsible for the data integrity and the accuracy of the analysis.

4.3.1.d. Rationale for disclosure of conflicts of interest and financial involvement

It is important to identify potential direct or indirect financial and material gain to the investigators from the clinical research they are involved with, and their relationships with sponsoring entities. The financial or other possible conflict of interest disclosure is part of the recommendations added to the Declaration of Helsinki and updated in 2000.(91) To guarantee transparency and to avoid detrimental effects of these interests on the study results' accuracy or completeness, it is recommended that complete disclosure of all relevant relationships and potential financial conflicts of interest, regardless of amount or value.(92) Even with the protest of financial interests, credible medical journals and the medical community have accepted protocol registration and disclosure of interest, as actions put in place to prevent distortions seen in the past.(93) One intriguing aspect of this debate is the systematic review published by Lexchin et al in 2003, in which there was evidence that industry sponsored research was more likely to produce results favoring their own products than studies funded by other sources, OR: 4.05 (95% confidence interval 2.98 to 5.51).(94) The authors suggest that there are systematic biases in research funded by the pharmaceutical industry.

Trial registration and full financial disclosure coupled with an independent statistical analysis of the raw data in an industry-sponsored trial, can do nothing other than preserve the quality and credibility of health research.

4.3.2. Steering committee and role of the investigators

It is important that activities and functions be clearly assigned, to ensure smooth running of the trial with no misunderstandings or confusion.⁽⁹⁵⁾ Specific roles such as patient care or data analysis in the clinical trial will be the responsibility of the person trained in that field. However, there are activities or functions that could be undertaken by a variety of professionals, and when the responsibilities are not clear, misunderstanding and confusion may arise. The role of each investigator participating in this trial will be assigned as follows:

4.3.2.a. Steering committee

The principal investigators and the co-investigators involved in the trial will comprise the steering committee that will manage the trial, as shown in table 4.1. Experienced experts in the design, conduct, analysis and reporting of clinical trials will participate in this team that will manage and coordinate the trial. The steering committee will accumulate the role of executive administration of the trial, and its members will vote for the deliberations and decisions related to the trial management. It has professionals with expertise in statistical analysis, clinical trial methodology and paediatric urology, and all of them have experience with paediatric research. The steering committee is also responsible for the publication of the trial's results.

Table 4.1 Organization and activities of the steering committee

	Composition	Responsibilities	Agenda of meetings
Steering committee	Principal investigator	Administrative coordination	Every 4 weeks
	Paediatric urologist (2)	Review recruitment goals	
	Clinical epidemiologist (1)	Organize and follow the randomization and allocation process	
	Trial statistician (1)		
	Clinical nurse (1)	Assess follow up and compliance with treatment	
	Urodynamicist nurse (1)	Check for protocol violations	
		Report safety issues to DSMC	
	Guarantee ethical principles		
	Resolve conflicts amongst investigators		
	Write all published reports from the trial		

The steering committee will receive, from the Data and Safety Monitoring Committee (DSMC, section 4.5.1), the interim analysis reports blinded to the group assignments, and will make the necessary decisions based on clinical and statistical analysis, if applicable.

4.3.2.b. Principal investigator (paediatric urologist)

- Inform the medical community about the purpose/scope of this research
- Plan the overall recruitment program
- Educate staff about the trial and how to approach participants

- Participate in the informed consent process
- Be the primary contact for physicians and other medical personnel
- Be available to answer questions and to review recruitment goals
- Be responsible for the trial management and documentation
- Be responsible for the accuracy of the data and credibility of the trial

Note that the principal investigator, for ethical reasons, will not recruit or follow the participants (discussed in section 4.3.7.b).

4.3.2.c. Physician co-investigators (2 paediatric urologists)

- Screen the study population for possible participants
- Recruit and enroll potential candidates
- Obtain informed consent and make sure participant/parents understand it
- Order baseline and post intervention measures
- Explain and prescribe the intervention for the participants
- Provide the outcomes results and harm records to the trial coordinator
- Be involved and treat any harm caused by the intervention

4.3.2.d. Clinical nurse working at paediatric urology clinic

- Screen and recruit potential participants to the trial
- Assist the participant/family with the bowel protocol for constipation
- Teach the family how to fill out the harms checklist, and voiding and stool calendars
- Supply and collect the forms and data extraction sheets
- Make all necessary telephone contacts with the participant or family

4.3.2.e. Urodynamicist nurse

- Perform all the urodynamic studies (UDSs) for the participants
- Organize and maintain the records of all UDS done during the study
- Orient the children and parents regarding bladder catheterizations
- Teach and train participants/parents to execute the intervention
- Be the consultant person for inquires/difficulties related to the intervention

4.3.2.f. Clinical epidemiologist with experience in clinical trials

- Be responsible for the methodological content of the trial
- Provide expertise for the decisions related to strategy
- Monitor the trial development and plan necessary adjustments

4.3.2.g. Trial statistician

- Create the allocation sequence for the assignment of participants
- Deliver to the physician the group assignment for each participant
- Plan and conduct the appropriate statistical analyses during the trial
- Identify incomplete or inaccurate data
- Assess the reliability of the data extracted
- Conduct statistical analyses, in consultation with the principal investigator

4.3.2.h. Research assistant

- Assist the investigators with the administrative activities of the trial
- Organize and maintain the records, files and all paperwork
- Input and maintain an updated electronic databank with all data collected

4.3.3. Training the professionals and staff on the clinical trial methods

This trial protocol will be used as the “operations manual”^c for the many activities of the involved staff. It will also be used to train the personnel in the functions and actions that must be implemented during the trial. An initial presentation and training session will include a comprehensive explanation of the objectives and goals, clarifying how to use the protocol to help overcome any difficulties. This session, to be presented by the principal investigator, will educate and motivate the personnel involved regarding the tasks and challenges they will face during the study. It will be followed by another training session focusing specifically on the recruitment and enrolment processes and their implementation, as delineated in section 4.3.7.

4.3.4. Study Population

4.3.4.a. Population with the condition of interest

The population with the condition of interest for this study is all children less than 18 years of age who have the diagnosis of neurogenic bladder.

4.3.4.b. Study population

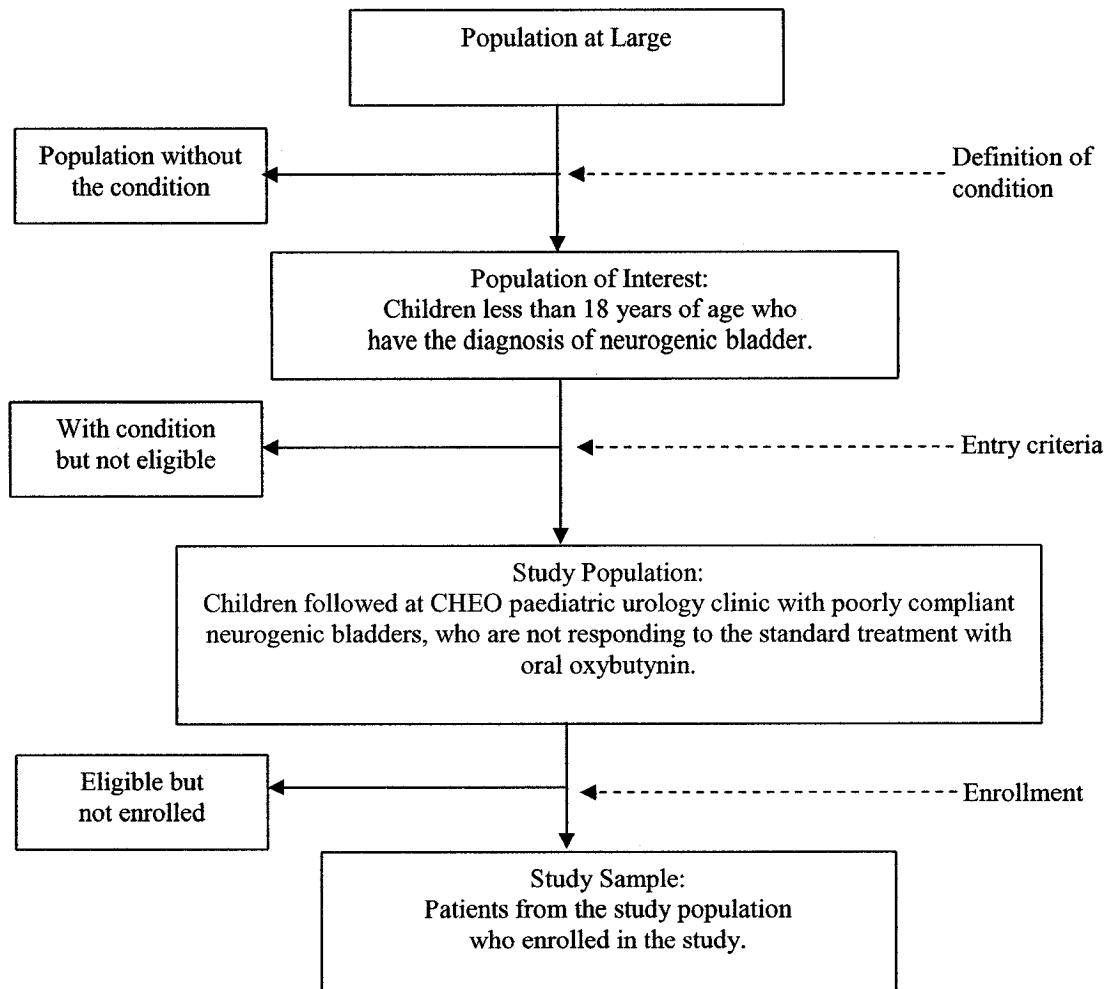
The study population encompasses all children followed at the CHEO paediatric urology clinic with poorly compliant neurogenic bladders, who are not responding to the treatment with standard dose of oral oxybutynin (10 to 15 mg/day). These children must meet the eligibility criteria outlined in section 4.3.6.

^c Term emphasized by Pocock in 1983 (86)

4.3.4.c. Study sample

The study sample will be all patients from the above study population that met the eligibility criteria and who actually enroll in the study. Figure 4.1 shows the relationship amongst these populations.(Friedman 1998, p 31)(96)

Figure 4.1 Relationship between the population groups



4.3.5. Setting and location of data collection

This study will recruit children from those who have been followed at the paediatric urology clinic at CHEO. An academic teaching hospital affiliated with the University of Ottawa, Canada, CHEO is a paediatric hospital that provides tertiary health care for children less than 18 years of age. It is a hospital open to the community at large in the National Capital Region and surrounding cities, as well as northern communities. It

serves an area with approximately 600.000 children. The Urology Division has three fully trained paediatric urologists who attend an average of 6000 consultations per year. The division is equipped with a video-urodynamics unit that is operated by a specialized urodynamicist nurse trained in paediatric urodynamics. The hospital has comprehensive resources for uro-radiology investigation. A multidisciplinary team of paediatric urologists, orthopaedic surgeons, a dietician, an orthotist and a nurse, follows the children with spinal dysraphism. In 2005, there were 360 visits of patients with spinal dysraphism at CHEO.

4.3.6. Eligibility

4.3.6.a. Inclusion Criteria

- Children younger than 18 years of age, with a diagnosis of poorly compliant neurogenic bladder, who have been managed with a standard dose of oral oxybutynin (0.2 to 0.4 mg/kg/day – maximum 15 mg/day) for at least 3 months prior to enrolment, and who had insufficient improvement in bladder compliance (i.e.: whose bladder compliance is less than 10 mL/cmH₂O, whose bladder pressure at TBC is higher than 40 cmH₂O, and those who failed to achieve a change from baseline with oral oxybutynin)
- Participants of both sexes will be included.
- English and French speaking participants will be enrolled. A Francophone nurse, and translation of the informed consent and assent forms, will be available to facilitate Francophone participation.

Note that low bladder compliance is defined as less than 20 mL/cmH₂O (97), or an increase in pressure exceeding 10 cmH₂O per 100 mL increment during UDS.(98)

4.3.6.b. Exclusion Criteria

- Moderate harm, precluding the use of oral oxybutynin
- Previous bladder augmentation
- Severe vesicoureteric reflux
- Urethral stricture that precludes urethral catheterizations
- Current clinical urinary tract infection
- Unsuccessful bowel management despite the bowel protocol for intestinal constipation. This includes a high-fiber diet, vegetables and fruits, oral laxatives or fleet enemas. Bowel movements must be regular, every second or third day. They may be spontaneous, or be induced with oral medication or fleet enema
- Emotional limitations or lack of familial support
- Hypersensitivity to oxybutynin
- Medical conditions in which it would be unsafe to use an anti-cholinergic medication
- The use of concomitant drugs that would confound the efficacy evaluation
- The use of concomitant drugs that would be unsafe with an anti-cholinergic medication

4.3.6.c. Rationale for the inclusion criteria

- *Inclusion of children less than 18 years of age:* Children have a different metabolism and pharmacologic response to drugs, compared to adults. Including adults in the trial could produce a mixed group of participants with heterogeneous pharmacological responses to the intervention. When

the group enrolled is excessively heterogeneous, the relevance and interpretation of the trial may be questioned.(Spilker 1991, p 147)(99) Inclusion of adults could result in data that was inadequate or inappropriate to address the clinical objectives, and may threaten the external validity of the results. Based on these factors, the age was restricted to less than 18 years.

- *Unsatisfactory response or harm:* Oxybutynin is the current standard anticholinergic drug in children.(8) It has shown effectiveness and it is the most commonly used drug for management of paediatric poorly compliant neurogenic bladder and daytime incontinence.(20,100-102) Children with neurogenic bladders who do not respond to anticholinergic treatment or who present with significant harm precluding the use of an adequate dose of oxybutynin, often need a bladder augmentation. In this major surgical operation a part of the bowel is used to increase the size of the bladder. Intravesical oxybutynin is an alternative means to improve bladder compliance, which may delay or preclude such major surgery and its potential morbidities.(34) One must remember that although this intervention uses the intravesical route of administration, some of the drug is absorbed through the bladder mucosa, thereby gaining access to the blood stream (15) and it may cause systemic harm as well.
- *Gender:* Both sexes present the same physiopathology and response to this treatment (103), so there is no justification for restriction according to gender.

4.3.6.d. Rationale for the exclusion criteria

- *Severe harm precluding the use of oral oxybutynin:* Children who had significant harm with a standard dose of oral oxybutynin cannot be randomized to higher doses of oxybutynin, thus they are excluded for safety reasons.
- *Previous bladder augmentation:* The segment of the bowel or stomach used as a patch to augment the bladder is still capable of drug absorption.(104,105) Thus, the potential assimilation of higher amounts of the drug to the blood stream creates a different pattern of systemic response that is not observed in patients with intact bladders. This physiologic difference means that inclusion of these participants would increase heterogeneity of the cohort. The increased systemic drug absorption would preclude an unbiased interpretation of the intervention effect in this group. To avoid bias, they were excluded from the study.
- *Severe vesico-ureteric reflux:* Neurogenic bladder can cause severe secondary vesico-ureteric reflux that backwashes large amounts of urine to the kidneys during filling of the bladder. Reflux could flush the drug to the collecting system of the upper urinary tract, and the effect on this structure could not be predicted. It would also remove the drug from the bladder, diminishing the local effect, and possibly give a biased result of intervention efficacy.
- *Urethral stricture that precludes urethral catheterizations:* Participants with urethral strictures have an obvious limitation to regular urethral catheterization, and were excluded. Although some participants are still

able to catheterize the urethra using small or special catheters, the regularity of successful catheterizations and therefore drug administration cannot be ensured.

- *Current clinical urinary tract infection:* Frequent catheterization creates a propitious situation for bladder colonization by bacteria. However, positive urine culture does not imply UTI in participants on CIC, unless clinical symptoms are present such as fever and chills.

Neurogenic bladder is a known risk factor for detrusor overactivity and UTI. On other hand, UTI is related to neurogenic bladder and detrusor overactivity but is not part of the common pathway between the risk factor (neurogenic bladder) and the outcome (detrusor overactivity). Hence, UTI can act as a confounder for the causal association of neurogenic bladder and detrusor overactivity. It was decided to exclude participants with clinical diagnosis of acute UTI (positive urine culture plus fever or chills) to eliminate this confounder. However, after a child has been treated for a UTI and has been asymptomatic, with a negative urine culture, he/she will be able to enroll.

- *Unsuccessful bowel management:* Constipation is a known risk factor for urinary incontinence in children (106), and it is thought to be a potential confounder for the causal association of neurogenic bladder and detrusor overactivity. It has been shown that patients with neurological involvement of the lower limbs are prone to developing significant intestinal constipation.(107) On the other hand, constipation can exacerbate bladder overactivity and is related to neurogenic bladder,

although constipation is not the primary cause. Excluding constipation is an attempt to avoid a potential confounder; thus children with severe constipation were excluded from the trial.

- *Emotional limitations:* This includes children with poor familial support, or psychological or emotional conditions that may prevent an adequate level of compliance with the intervention.
- *Sensitivity to oxybutynin:* Drug sensitivity is an obvious contraindication of the use of the drug in either oral or intravesical routes of administration.
- *Drugs that would confound the efficacy evaluation:* Drugs with anticholinergic action such as atropine, tolterodine, scopolamine, etc, could interact with oxybutynin and modify the effect under investigation. In an effort to avoid bias, participants cannot use these drugs during the trial.

4.3.7. Recruitment and enrolment

Considerations about recruitment and enrolment

The recruitment of participants for this trial will start after the approval of the protocol by the ethics committee. Recruitment can be defined as the process of enrolling participants in a clinical trial and it is a most important step, since the success of a trial depends upon enrolment of a sufficient number of participants. Other types of recruitment such as investigator, health professionals and sponsors will not be considered in this work.(Spilker 1992, p 5)(108) The rate of recruitment of participants in paediatric trials is often slow, and insufficient participant enrolment is the most common reason of trial failure.(109) The investigators usually overestimated by many fold the number of participants available for the trial; this attitude may reflect the lack of consideration of the

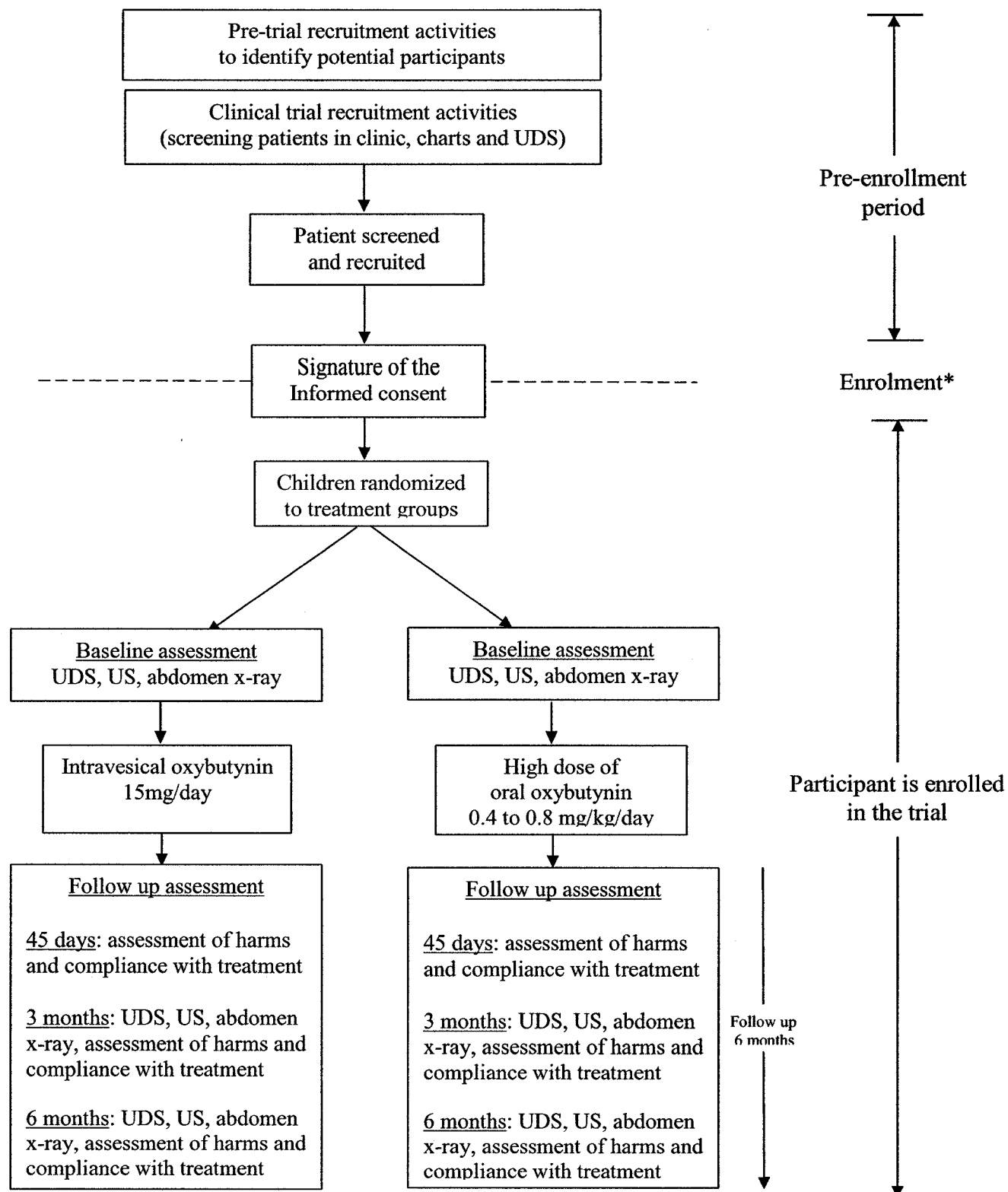
participants' willingness to adhere to the trial, or their true interest in the treatment being tested.(Spilker 1992 p 4)

4.3.7.a. Flow diagram of the study design

The processes of screening, recruitment, enrolment and randomization of the participants are outlined in Figure 4.2. In the pre-recruitment stage, the population of patients with neurogenic bladder will be identified amongst the patients who attend the urology clinic. The screening of potential candidates will proceed as outlined in section 4.3.7.c. Note that participants are considered enrolled upon the signature of the informed consent. The recruitment and enrolment of participants will continue sequentially during the whole trial. The participants enrolled will be randomized to both therapies as described in section 4.3.12, and will be assessed at baseline, and at 45-day, 3-month and 6-month follow up.

Figure 4.2 Flow diagram of the study design

(Source: Spilker 1992, p 6)



*The signature of the informed consent marks the enrolment of the participant in the trial

4.3.7.b. Training the staff on the recruitment process and defining roles

- *Training the staff on recruitment:*

A pre-recruitment phase will start with a training session which all the investigators involved in the trial will attend. The recruitment of the participants will be done by any one of the investigators: the two attending paediatric urologists, the clinical nurse who works fulltime at the urology clinic or the urodynamicist nurse. The relationship between the potential participants and investigators poses an ethical consideration about how to conduct the recruitment. Spilker considers that in any superior-subservient relationship between two persons, it is impossible to know if the subservient person feels comfortable to decline an apparent “invitation.”(Spilker 1992, p153) For obvious reasons, the physician is the person with the greatest influence in the participants’ decision whether or not to enroll in the clinical trial. Thus, the physician should act with neutrality to avoid coercion; the patient may feel forced to enter in the trial just to not “disappoint the doctor.” However, the patient may also feel pressured by the physician’s staff, like the nurse or urodynamicist for instance. This ethical concern will be discussed, and it will be asked of the staff to approach patients impartially, and to let them feel comfortable to decide. Under no circumstance should the patients receive an inferior quality of care from the physician or staff because of a refusal to enter in the trial. Measures to diminish this potential coercion are: to ask the patient to talk to friends and family about the study, to get a second opinion from an independent physician and to give a copy of the informed consent to the patient before discussing the trial.(Spilker 1992, p154) Due to these ethical implications, the principal investigator should not recruit or be responsible for the follow up of the participants.

The research hypothesis, objectives and methods of the trial will be presented and discussed in detail, making them familiar to all trial staff. The eligibility criteria and the profile of an “ideal candidate” to entry in the trial will be presented. Consequences of protocol deviations will be discussed, such as the risk of enrolling a heterogeneous population, threatening the external validity of the trial’s results. This training will address issues related to approaching a potential candidate, information to discuss with the participant/family and how to explain the study. It should be clear to all participants what kind of benefit the trial could bring to him/her and to the population with this condition. The investigators involved in the screening and recruitment must be familiar with these issues and be prepared to discuss them thoroughly with the candidates and families. The recruitment strategy with the schedule of dates and targets of enrolment and the process to review the recruitment progress will be presented, as well as strategies to enhance it as described in this text.

- *Defining roles for the recruitment:*

After the training, one of the investigators will be elected the “recruitment coordinator”, and will be in charge of the recruitment process.

The recruitment coordinator will:

- Organize and carry out the recruitment plan
- Maintain records of the screening process
- Identify areas of enhanced recruitment
- Assist the investigator with “public relations” efforts within the hospital and medical community
- Train and supervise the staff to answer participant’s inquires about recruitment

- Review recruitment in light of recruitment goals with the investigators
- Implement a strategy to enhance recruitment if necessary, such as phone calls, letters, written reminders, etc.

All staff involved in the trial will participate in the recruitment and enrolment of participants as outlined in section 4.3.7.c., and they should:

- Be familiar with the screening process
- Be familiar with the eligibility criteria
- Serve as a back up to enroll participants, if some investigator is not available

4.3.7.c. Process of screening

The screening process is to identify potentially eligible participants who may enter the trial. The participant should have the condition of interest; that is neurogenic bladder with poor compliance, non-responding to a standard dose of oral oxybutynin, and the participant should potentially have some benefit from the intervention. The duration of the study is three and half years and the screening and enrolment of participants will be done sequentially for three years. The investigator must complete a screening record form.(Appendix 4.1)

The screening of possible participants will be carried out in *three ways*:

1- By the paediatric urologists attending in the clinic.

Children with neurogenic bladders are followed at the CHEO Paediatric Urology clinic, where the urologist takes a full urological history and asks about intestinal function. Routinely, ultrasounds are obtained every 12 months to assess the presence of kidney dilation (hydronephrosis). An initial UDS is obtained as a baseline assessment, and it is repeated if there is persistent high bladder pressure,

increases in kidney dilation on ultrasound, worsening of urinary incontinence, urinary infections or impaired renal function. These children are usually doing CIC to empty their bladders. During these visits, if the urologist identifies a potential candidate, the opportunity to participate in this study will be offered.

2- By screening the charts of the patients with a diagnosis of neurogenic bladder.

A review of the charts of patients followed at the paediatric urology clinic will identify potential participants who meet the inclusion criteria. A paediatric urologist and a trained nurse will conduct the review of the charts of patients with a diagnosis of neurogenic bladder. When a potential participant has been identified an invitation letter (Appendix 4.2) will be sent to the family outlining the objectives of the trial and including some initial information. A telephone call one week later will follow this first contact, when a nurse trained to recruit will make the first assessment of the family/patient motivation to participate.

3- By the urodynamicist nurse at the time of the UDS.

During the UDS the urodynamicist nurse routinely interviews the child and parents about issues related to incontinence, urethral catheterizations, constipation, use of an anticholinergic drug, UTIs, etc. This clinical information is written on the report of the UDS. Based on the answers and on the pattern of the UDS graph, the nurse should identify potential candidates for the clinical trial. This information will be conveyed to the attending paediatric urologist who will review this data and together they should decide about the recruitment.

In summary, the screening of participants will be done during a regular follow up visit at the paediatric urology clinic, during the UDS and through a chart review. This is a very specific population of children with the disease of

interest, and no external campaign or media advertisement will be used to attract volunteers. The eligible candidates who agree to participate will sign the informed consent (Appendix 4.3), which in this trial is the last part of the screening process.

4.3.7.d. The enrolment of participants

Participants will be considered enrolled in the trial upon the signature of the informed consent, which gives his/her agreement to enter the study. Since trial duration will be three and half years and the treatments six months long, participants will be enrolled sequentially during three years. The enrolment will occur as a candidate becomes available.

4.3.7.e. Recruitment goal

The sample size calculation, presented in section 4.3.11, indicated that 286 participants would be needed to ensure adequate power to detect treatment effects and harms. The planned recruitment of participants to the trial is to enroll 95 patients per year in the first two years, and 96 in the third year.

4.3.7.f. Informed consent and assent

The informed consent (Appendix 4.3) will be signed during a visit to the urology clinic. One of the physician investigators will witness that that all necessary information has been fully disclosed, and that in his opinion the participant/parents have understood it all. Children younger than seven years of age must give their assent (Appendix 4.4), which may be verbal and must occur in the presence of a witness. A parent or guardian must sign the informed consent form as well. After the consent has been obtained, another meeting with the urology clinical nurse is scheduled. At this point, the parents and participants have already received the initial information about the study from the

attending paediatric urologist. The nurse will review with them the objectives and goals of the study and the direct and indirect benefits the study could bring to the participant and to the population with the same condition. A folder and pictures will be used to help with understanding the anatomical aspects of the disease and to inform them in which part of the body the treatment will take effect. At this meeting, participants will learn about the intervention and the importance of being compliant with the treatment. They will be educated about the possible harms secondary to the therapy and how they present. Participants will have the phone contact of the nurse and physician for any inquiry about the study or related medical or general issues. In the case of a participant contacting the nurse, she will contact the physician investigator responsible for following the participant and update him about the facts. In the case of an emergency, the urology division provides 24-hours a day/7-days a week coverage at the emergency department at CHEO and will be available to assess the participant.

Rationale for the informed consent: This protocol preserves the principles outlined by the declaration of Helsinki, updated in 2000.

4.3.7.g. Measures to enhance the recruitment

- The principal investigator will present lectures for the physicians, nurses and other professionals working at CHEO in related areas such as paediatrics, rehabilitation, physiotherapy, neurology and orthopaedics.
- A letter will be sent to the paediatricians and family physicians working in the Ottawa area, informing them about this trial. The direct benefits the participant could get from the trial and the benefits other patients with neurogenic bladder could gain will be discussed. These physicians will be asked to invite patients who may be willing to enroll in this trial.

- Support associations for children with neurologic disease will be contacted. They will be invited to attend the lectures about the trial at CHEO, and written material about the study will be sent as well.
- Trial publicity will be implemented through the media. We will post advertisements in local newspapers and on the radio, inviting children and families to participate in the trial.
- Should the trial demonstrate a low rate of recruitment, we will invite other centers to join the study. This strategy aims to increase participants' enrolment and to maintain the power of the statistical analysis.

General issues

Ethical implications and limitations such as confidentiality of the data will be discussed with the investigators.

The investigators will receive information about the written material and forms that will be used to record the data during the trial. A calibration exercise will be conducted simulating data from three participants, and any doubt will be addressed and clarified.

4.3.8. Intervention

Children with poorly compliant neurogenic bladders who are not responding to a standard dose of oral oxybutynin will be randomized to receive intravesical oxybutynin (intervention group) or higher doses of oral oxybutynin (control group).

After a patient has been randomized, a form will be used to collect information on demographics, diagnosis, intervention and follow up.(Appendix 4.5) Data on outcomes and harms will be collected on separate forms.(Appendixes 4.6 and 4.7) The research

assistant will input this information into an electronic databank, which will be double-checked by one of the investigators (blind to the participant), to ensure quality of the data.

4.3.8.a. Rationale for the intravesical administration

As outlined in section 4.2, it is hypothesized that in children with poorly compliant neurogenic bladders not responding to standard doses of oral oxybutynin, intravesical oxybutynin will result in a better improvement of bladder compliance compared to higher doses of oral oxybutynin. Part of this improvement will probably be secondary to less harm caused by the intravesical administration compared to oral. After oral oxybutynin has been absorbed by the gastrointestinal tract, it passes through the liver where the active metabolite N-desethyloxybutynin is formed.(12,110,111) This oxybutynin metabolite is responsible for most of the anticholinergic harm experienced with this therapy.(2,19) In theory, the intravesical route of administration may obviate this passage through the liver and decrease the incidence of harm, and may increase compliance with treatment.

The systematic review showed that oral oxybutynin is associated with anticholinergic harm, which may limit the patient compliance with the treatment. As these patients are already under intermittent bladder catheterizations, intravesical oxybutynin is usually well accepted, and together with a lower harm profile it may increase adherence to the treatment.

4.3.8.b. Description of the intervention

For the intervention group, the oxybutynin will be delivered intravesically as a solution in sterile water. It is to be instilled into the bladder two times a day at a dose of 0.4 mg/kg/day - maximum 15 mg/day, for a period of 6 months. The participants should

empty their bladders as done routinely, and then inject the solution using the same urethral catheter used for CIC. The medication is to be left inside the bladder until the next catheterization 4 to 6 hours later, when it is removed during the next CIC to empty the bladder.

The solution is to be prepared by the CHEO's central pharmacy and will contain 5 mg of oxybutynin in 10 ml of sterile water. These children have been doing bladder catheterizations to empty their bladders, and they usually find no difficulty adhering to this treatment. The urethral catheterization technique requires adequate hand washing and appropriate hygiene of the penis or vulva before the procedure, but there is no need to use sterile gloves. A small amount of lubricant is used to help with the passage of the catheter through the urethra.

4.3.8.c. Control group

Higher doses of oral oxybutynin will be administered to the control group. The children included in the trial are refractory to oral oxybutynin, and were previously taking a standard normal oral dose of 0.2 to 0.4 mg/kg/day divided in 3 doses, maximum 15 mg/day. After they have been allocated to control group, the dose of oral oxybutynin will be increased to a dose of 0.4 to 0.8 mg/kg/day divided in 3 doses, maximum 20 mg /day.

4.3.8.d. Proposed duration of treatment

After the participants have been randomized, they will receive the treatment for a period of six months. During this time, they will be assessed for outcome changes, compliance with treatment, presence of harms, and dropouts. Any case of dose adjustment because of harm will be reported. The number of participants that discontinue the treatment will be reported and analyzed in the group to which they were initially allocated (intention-to-treat analysis).

4.3.9. Duration of the trial, follow up and dropouts

4.3.9.a. Duration of the trial and treatment

The planned duration of the trial is three and half years or until the 286th participant has completed 6 months of follow up.

Recruitment will occur sequentially during the first 3 years of the trial.

4.3.9.b. Proposed frequency and duration of follow up

After the beginning of the treatment, the participants will be followed for a period of 6 months, which is the duration of the treatment. Visits to urology clinic will be scheduled for 45-day, 3-month and 6-month follow up. At each visit to the paediatric urology clinic, the clinical nurse will interview the participant and reinforce that the anticholinergic medication and bowel protocols must be followed carefully and consistently. The planned duration of the trial is 3 and half years, when at which time the statistical analysis will be conducted.

The planned assessment of participants is as follows:

At the 45-day visit:

- Participants will be assessed by the urologist, who will record clinical information with regard to harms and compliance with the treatment. Participants should bring back the checklist containing the possible harms with the use of oxybutynin, which was given at the trial enrolment. Participant/parents will be asked about possible unexpected symptoms or harms.

- The clinical nurse will assess if the intervention is being done correctly in both groups and if the participant has had any difficulty with it.

At the 3-month visit:

- The same assessment done at 45 days, and another checklist of harms filled by the participants/parents will be collected.
- Both groups (intervention and control) will be reassessed by means of an abdominal ultrasound, plain x-ray of the abdomen and UDS.

At the 6-month visit:

- The same assessment done at 3 months (including the US, plain x-ray of the abdomen and UDS)

4.3.9.c. Measure of adherence to treatment

Adherence to treatment is defined as receiving at least 75% of the treatment. Adherence will be assessed through a monthly telephone call and during clinic visits (at 45 days, 3 and 6 months). A participant who misses an appointment will receive a phone call the same day, to ascertain the reason for the absence and to reschedule. A consultation reminder letter will also be sent after two missed appointments.

4.3.9.d. How dropouts and missing data will be handled?

Dropouts

The primary analysis will take into account participants with complete data and those whose missing outcomes were handled using the last outcome carried forward approach (LOCF). Baseline and general characteristics will be compared between dropouts and participants for whom we have complete set of data, to assess if they differ significantly. In other words, it will be evaluated if there were systematic baseline differences between the group that dropped out compared to the group with follow up; in

the case of significant differences between this two groups, bias may have been introduced.

To make the appraisal of attrition bias easier and to permit a possible qualitative judgement, the baseline characteristic of the patients who dropped out and those who continued in the trial will be shown in the same table.(112) The number of patients who dropped out will be displayed in a flow diagram recommended the CONSORT statement.(113)

Missing data

No statistical modeling procedure for data imputation will be used. For the intention-to-treat analysis, the LOCF will be applied to complete the missing outcomes. Missing data will be analyzed with regards to the frequency distribution of the incomplete data per variable. Should the frequency of the missing data in this trial be higher than 10 %, the reasons for this incompleteness will be investigated and a sensitivity analysis will be conducted.

The hypothesis under investigation in this RCT is an improvement in bladder compliance in 6 months of follow up. As the primary outcome will be measured at baseline, 3-month and 6-month follow up, in the case of a missing value at the 3- or 6-month follow up, the measurement obtained at baseline or at 3 months, will be carried forward to complete the missing data and enhance the intention-to-treat approach. The LOCF approach imputes the missing values with the individual's last observation, with the assumption that the missing observation is exactly the same as the one previously measured. It is a conservative approach, which assumes that the missing value has not changed compared to earlier measurements, and that there is no uncertainty in this estimate.(114)

Defining missing data: There are different types of missing data, and the most commonly discussed are the missing data completely at random (MCAR) and the missing data at random (MAR). In the MCAR, the probability of the missing data is not related to its value or to any other baseline or outcome value. In the case of a MAR, the probability of the missing value is not related to the value, after controlling to another variable.(115) Wood et al describe them with other terms: “the missing data is MCAR if the probability of a missing outcome is the same for all participants of a trial and do not depend on baseline covariates or outcome observations; the missing data is MAR if the probability of a missing value depend on any observed data, including baseline or outcome observation”, and finally, the missing data is not at random (MNAR), when the probability of the missing data depends on unobserved outcomes, as well as on observed data.(114)

Rationale for handle missing data: While randomization of participants creates a balance in baseline characteristics between the trial groups, differential attrition between arms may unbalance the groups with regards to qualitative characteristics, and it may introduce attrition bias.

There is some controversy as to what extent missing data should be considered a source of bias. According to Dumville et al, Schulz and Grimes suggested that less than 5% is of little concern, whereas more than 20% of missing outcomes will most likely lead to biased results.(112) For this trial, a 10% cut off was decided upon, and if the proportion of missing data is higher, a sensitivity analysis will be conducted to examine the robustness of the results of the primary analysis under different assumptions. For example, for the primary analysis, the LOCF approach will be used to handle the missing data, and the sensitivity analysis will use the complete case, and repeated measure

approaches. These last two approaches that will be used in the sensitivity analysis will test two assumptions that are different from the one used in the LOCF approach: the assumption that the excluded group are a random sample of all randomized subjects, and the assumption that the missing outcomes can be inferred by the individual's observed data. If the sensitivity analysis confirms robustness of the results, then the LOCF assumption used to handle the missing outcomes will carry less uncertainty.

4.3.10. Outcomes

Our primary outcome and most of the secondary outcomes are physiologic outcomes, and they are measured during the UDS. Urinary incontinence and harms are the only subjective outcomes. The data collection forms for outcome and harms are shown in Appendixes 4.6 and 4.7.

The outcomes are listed with unit of measurements and definitions:

4.3.10.a. Primary outcome

- Bladder compliance - measured at 6 months of follow up, in mL/cmH₂O,
(Ratio of "volume-change/pressure-change" that is measured at TBC during UDS)

4.3.10.b. Secondary outcomes

- Total Bladder Capacity (TBC) – measured in mL
(Maximum bladder volume before the patient refers to pain or starts to leak urine while the bladder is being filled during UDS)
- Detrusor pressure at the TBC – measured in cmH₂O
(The difference between the intravesical and intra-rectal pressure measured at the TBC during UDS)

- Detrusor leak point pressure (DLPP) – measured in cmH₂O
(Detrusor pressure of an involuntary urine leak during UDS)
- Neurogenic detrusor overactivity – measured in cmH₂O and number of events
(Involuntary bladder contractions during the filling phase of the UDS)
- Urinary tract infections (UTIs)– measured as the number of events
(Monthly frequency of UTIs clinically confirmed and with positive urine culture)
- Episodes of urinary incontinence – measured as number of events
(monthly frequency of daytime wetting accidents)
- Upper urinary tract abnormalities – measured as dichotomous outcome (yes/no)
(Presence of dilation of the kidney on the ultrasound)

4.3.10.c. Harms

- Constipation – measured as dichotomous outcome (yes/no)
(Absence of bowel movement for more than 3 days)
- Systemic harm – measured as dichotomous outcome (yes/no)
(Dry mouth, facial flushing, blurred vision, orthostatic hypotension)
- Dropping out of the study, and reason why – measured as percentage
(Whether the patient refuses to continue clinical follow up)

4.3.10.d. Actions to enhance quality of the outcome measures

To enhance quality and increase the reliability of the outcome measurements, a few processes will be implemented:

UDS - Standardization and training

- A training session organized by the principal investigator will update the urodynamicist nurse and the paediatric urologist investigators about the International Continence Society's standardization for UDS.(40) This training exercise will review the protocol recommended for the urodynamic evaluation. The terminology employed on the UDS reports will follow this standardization to avoid misinterpretations. The objective of this training is to improve the quality of the outcome measurement during the UDS and its report.

Reliability of the findings in the UDS

- The same urodynamicist nurse will perform the pre/post UDS
- The UDS pre/post will follow the same standardized technique (Appendix 4.8)
- Two investigators (urodynamicist and paediatric urologist) will check the report of the UDS findings for agreement

Training parents and participants how to fill the forms

- The clinical nurse will teach parents and participants how to record the information on the stool and catheterization calendars
- The items on the checklist of harms will be explained by the clinical nurse, who will train the family how to fill it in

4.3.11. Sample size calculation

This RCT is part of research to assess the efficacy and safety of intravesical oxybutynin in children with neurogenic bladder. The systematic review (chapter 3) showed that there are few studies assessing effectiveness of this therapy. Searching

clinical trials registries from North America and Europe (CliniTrials.gov and Current Controlled Trials) it was found that no clinical trial protocol on intravesical oxybutynin in children is presently registered, which could convey information about population parameters. Hence, the data from the CHEO's case-series was used to estimate the population parameters.

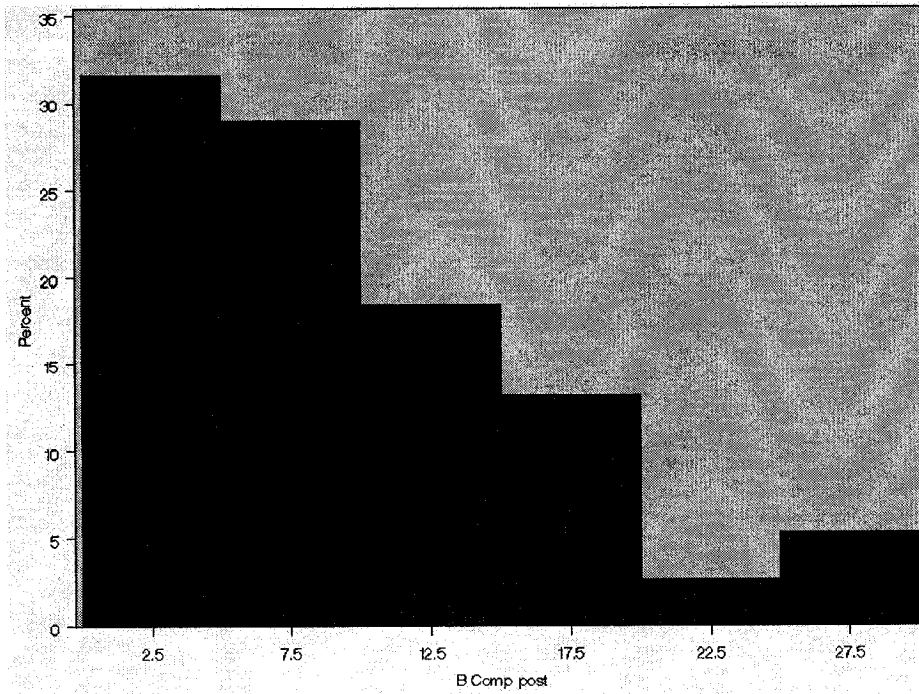
The expected minimally clinical important difference (MCID) for this RCT is an improvement of 20% of bladder compliance in the intervention group (intravesical oxybutynin) compared to the control group (high dose of oral oxybutynin).

Population parameters: The population mean (μ) and variability (σ) for bladder compliance in children with neurogenic bladder was based on the CHEO case-series reported by Guerra et al (chapter 2). However, the inclusion criteria of this retrospective review were very broad: "children less than 18 years of age, who had unsatisfactory clinical response to oral oxybutynin or severe harms." Nothing was said about the severity of the neurogenic bladder of the patients, and different grades of neurogenic bladder were analyzed in the same group. For this RCT, inclusion criteria say that participant should have "bladder compliance less than 10 mL/cmH₂O or pressure at TBC higher than 40 cmH₂O", which selects a more homogenous group of patients with more advanced disease. Hence, the population parameters for sample size calculation were extrapolated from a group of patients of the CHEO case-series, who were selected using the same inclusion criteria of the RCT protocol: "bladder compliance less than 10 mL/cmH₂O or pressure at TBC higher than 40 cmH₂O." Thirty-eight patients fulfilled the inclusion criteria.

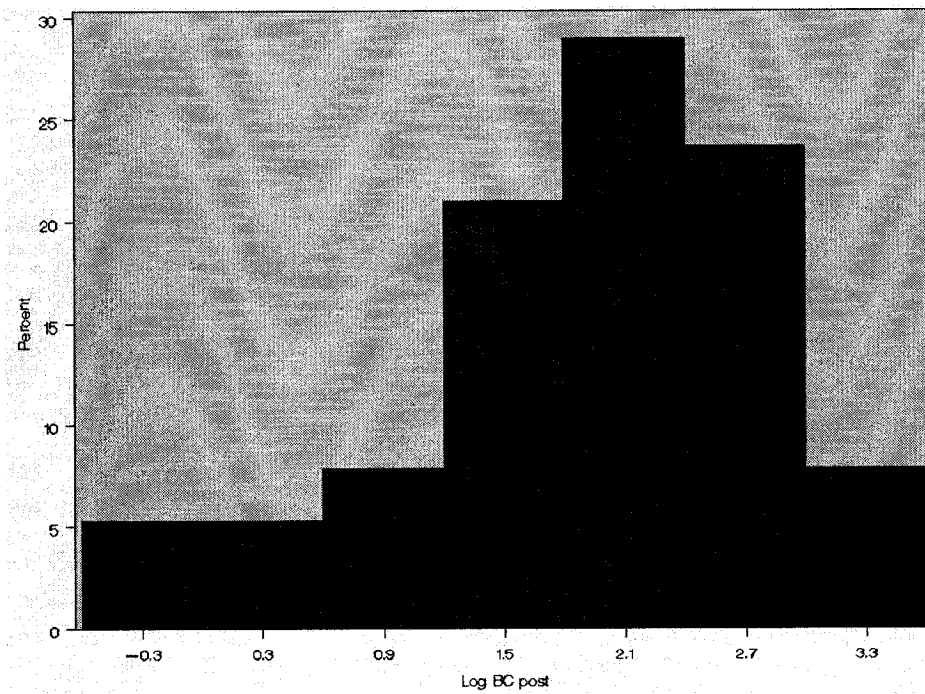
The analysis of this subgroup of patients showed a distribution of bladder compliance variable greatly skewed to the right, in the linear scale. This skewness was

expected since this variable is a ratio of two other variables, named TBC and Pressure at TBC. It was decided to transform bladder compliance distribution to a logarithmic scale, and it showed a pattern that approximated a normal distribution. (Figure 4.3 - A and B)

Figure 4.3 Bladder compliance distributions



A) Bladder compliance distribution in a linear scale – Greatly skewed to the right.



B) Bladder compliance distribution after log-transformation – Less skewness but still a tail to the left.

The log-transformed distribution of bladder compliance post-intervention has a mean 1.9 and a standard deviation 0.93.

Based on the data from the systematic review, and on consensus amongst specialists consulted, the MCID was set at a 20% difference, favouring the intervention group. Thus, it was hypothesized that the mean post-intervention log(bladder compliance) will be 1.9 (SD=0.91) in the intervention group, and it will be 1.52 in the control group. The MCID is 20% of log(bladder compliance) $1.9 = 0.38$. The formula to calculate the sample size for two independent samples was used. A two-sided test and a statistical power of 80% (beta 0.20) and a type I error of 5% (two-tailed) was chosen.

The calculation of the sample size was done as follows:

Intervention group log(bladder compliance) = 1.9 mL/cmH₂O

Control group log(bladder compliance) = 1.52 mL/cmH₂O

Population variability (σ) = 0.91 mL/cmH₂O

95% Confidence, $Z\alpha = 1.96$ Power 80%, $Z\beta = 0.84$

MCID (20% improvement) between groups, $\delta = 1.9 - 1.52 = 0.38$ mL/cmH₂O

$$\begin{aligned} \text{Formula: } 2N &= 4(Z\alpha + Z\beta)^2 \sigma^2 / \delta^2 = 4 \times (2.8)^2 \times (0.91)^2 / (0.38)^2 = \\ &= 25.969216 / 0.1444 = 180 \end{aligned}$$

4.3.11.a. Provision for one interim analysis

A provision for one interim analysis was done using the O'Brien and Fleming criteria for adjustment of the sample size.(Jenisson 2000, pp 29-30)(116) It was used the constant 1.008 to determine the group sizes of two-sided test with two groups of observations, alpha 0.05 and power 80%.

$$\text{Sample sized } 180 \times 1.008 = 182$$

4.3.11.b. Correction of the sample size for possible dropouts

To correct the sample size for possible dropouts (10%) and non-compliance with treatment (10%): Correction factor, $1 / (1-Ro)^2 = 0.64$ (Ro is the total of dropout and non-compliance).

The total sample size corrected for dropouts is $182 / 0.64 = 286$ participants (143 participants in each arm).

4.3.12. Randomization

4.3.12.a. Rationale for randomizing participants to intervention and control

There are several ways to assign participants to interventions in a clinical trial, and in the majority of the trials this process is performed at the level of the individual subject.(117)

Randomization is a technique that ensures that each participant in the trial will have the same known chance to be assigned to either the intervention or control group. It should have an adequate sequence generation, and the sequence of allocation should be unpredictable.(113) According to Friedman, “Randomization tends to produce study groups comparable with respect to known and unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid significance levels.”(Friedman 1998, p 61)

Randomization does not ensure that there is an equal distribution of characteristics between treatment groups, and to achieve this one needs to stratify participants in groups and to randomize them into each group independently.(Spilker 1991, p 69) Minimization is another method used to reduce such baseline differences, in which participants are classified by levels of prognostic factors as they are assigned to the

groups, and the sum of the factors is obtained for each treatment. The allocation of each new participant takes into account the total sum for each treatment up to that point, and the participant is assigned to the treatment that has the least total marginal sum.(Pocock 1983, p 84)(86)

In regards to pre-specified probability, the randomization can be fixed or adaptive. In the fixed method, the participant has the same probability of being assigned to intervention or control, and it does not change during the trial. Conversely, an adaptive randomization method changes the allocation probability during the trial. For instance, this change aims to correct imbalances in the number of participants or participants' characteristics, or to adjust the allocation according to the response of participants to the treatment.

In summary, random allocation of participants to treatment groups avoids investigator preferences in the assignment of participants to groups (selection bias), provides balance between treatment arms in regards to known and unknown factors and guarantees the validity of statistical tests without the statistical modeling assumptions.(117) The importance of a well conducted randomization is emphasized by Vail and Gardener: “errors in the randomization process may create fatal flaws that cannot be remedied in the statistical analysis and thus careful attention should be paid at this point of the trial.”(118)

4.3.12.b. Randomization schedule for this trial

Participants will be stratified in two strata according to their age: “children less than 7 years of age” and “children from 7 to 18 years of age”. They will be randomized to intervention (intravesical oxybutynin) and control (high dose of oral oxybutynin)

groups within each stratum. A fixed allocation randomization with an equal probability (1:1) will be used.

Rationale for the stratification of participants by age: There is limited experience reported in the literature on the absorption and metabolism of the oxybutynin in children. Based on our clinical experience and in consultation with colleagues, a cut point of seven years of age was selected as a stratification factor. It is hypothesized that infants and children younger than 7 years of age may have less systemic harm to either oral or intravesical oxybutynin, which could lead to a better compliance with the treatment and a better response compared to older children. This hypothesis supports the stratification of the study participants in two strata as mentioned above. The process of randomization will allocate participants within each stratum to intervention and control group, and by doing so control for bias introduced by age. The statistical analysis will determine the effect size within each stratum and the crude response including both strata. If significant difference between crude and within-strata effect size was observed, then bias by age could have been introduced.

There was a suspicion that the ambulatory status of the participant may affect the response to the intervention tested in this trial; it was hypothesized that ambulatory children would have a better prognosis with this intervention. However, such a subgroup analysis (ambulatory versus wheel chair bound) was conducted on the CHEO's case series presented in chapter 2, and it showed no difference in the outcome of these two groups. No publication has been identified confirming this hypothesis in the paediatric literature, and there is no evidence to support stratification of the randomization with regards to ambulatory status. However, a pre-planned subgroup analysis will be conducted to explore this possibility in the statistical analysis.

4.3.12.c. Method to generate the random allocation sequence

The randomization schedule will follow a computerized random-number generator, using a random permuted blocks process created by the statistician involved in the trial. The blocks will have three different lengths and the order will vary randomly (i.e., random permuted blocks). The investigators will not know the block sizes. The trial statistician is the only person who will know the size of the blocks and will reveal the allocation list only at the end of the trial. A larger block size will be used to increase the protection of the concealment of treatment assignment. As discussed previously, no clinical justification could be identified for stratification of the randomization.

Rationale: Blocked randomization is used to achieve balance in the number of participants assigned to treatment and control groups. A small block size such as a block of two for example, is not ideal because it may facilitate breaking the code for the next allocation, if one knows the last treatment assigned.

Random permuted blocks randomization without stratification should also use a larger block size to maintain the concealment of the allocation. However, when stratified randomization is used, it is more difficult to decipher the code due to the multiplicity of possible allocation sequences created by the strata; on the other hand when several strata are used the blocks need to be of small size.(Pocock 1983, p 77)

4.3.12.d. Method to implement the concealed random allocation sequence

A central telephone and a pager number will be available to contact the staff member responsible for revealing the group assignment for each participant based on the random allocation sequence. The trial statistician will operate this service and deliver the patient assignment. Since the participant is assigned to the group during an elective visit to the clinic, this central service will work on weekdays, from 8 am to 5 pm. At the time

of assignment of a participant, the physician will call the central number and the statistician, who will record name, sex and age of the participant, will reveal the treatment group. This information will be used later to confirm if the patient received the correct allocation. To guarantee the concealment of allocation until the participant is assigned to a group, this sequence cannot be previously revealed to any investigator.

Rationale: Allocation concealment is intended to remove selection bias by not allowing investigators to influence which participant will be assigned to the intervention or control group. It is not a very complex process to implement and according to Daya, every trial should use it.(119) The concealment should be kept effective until after all participants are enrolled in the trial and the treatments have been assigned.

4.3.12.e. Who will enroll participants?

Participants will be formally enrolled in the trial by the paediatric urologists who will obtain the informed consent. The clinical nurse and the urodynamicist nurse will participate in the enrolment process and will actively:

- Assess the eligibility of the participant for the trial
- Explain the details and discuss the trial with the participant/family
- Explain the informed consent for the participant/family
- Explain the assent form for children older than 7 years
- As discussed in section 4.3.7.b., the principal investigator will not enroll participants

4.3.12.f. Who will assign participants to their groups?

The paediatric urologist investigator will assign participants to either intervention or control group, based on the allocation list created and delivered by the trial statistician, as detailed in section 4.3.12.c. and 4.3.12.d. Under no circumstance will the list of assignments be revealed to any investigator before the end of the trial.

4.3.13. Blinding

4.3.13.a. Participants and physicians

Two points were important when it was decided not to blind the participant and the physician to the intervention in this trial. First, the primary outcome is a physiologic variable, and the participant's knowledge of the intervention is not expected to influence it. Most of the parameters studied in this trial are urodynamic measurements, and in neurogenic pathologies these are not typically susceptible to voluntary interference. Second, the two interventions are distinct in nature, and blinding would require more involved procedures, and it is not clinically justified.

4.3.13.b. Outcome assessors and statistician

All the personnel who are involved in the assessment and analysis of the outcomes will be blind to the intervention. This includes the nurse urodynamicist, the nurse who will interview patients about harms, and the statistician. This decision was based on the belief that the knowledge of the treatment could introduce bias in the assessment or analysis of the data. Physicians and the

clinical nurse who will deal with clinical management of the participants will not be blinded to the intervention assigned.

During the UDS for example, an assessor not blinded to the intervention, could unintentionally change the standardized technique and fill the bladder more patiently until it achieves an acceptable capacity. Conversely, the filling phase of the UDS could be interrupted at the first vague sign of a participant's discomfort. In any of these scenarios, bias could be introduced. Thus, the urodynamicist nurse will be blind to the intervention the participant was assigned.

In another situation, the nurse interviewing the participants/family about harms could over-estimate or under-play the importance of some answers if she knows which treatment the patient is taking. Harm assessment can be quite susceptible to bias by the participant's opinion about the treatment received, and the assessor can modify this perception. For this reason two nurses will be involved: one nurse, blinded to the intervention, will interview the participants and assess the occurrence of harms and subjective outcomes such as constipation and incontinence; a second nurse who knows the treatments assigned will follow the participant at clinic and will assess their compliance with the treatment.

There are several ways to analyze the same data, and different perspectives can be drawn depending on the statistical tools employed. Not knowing the intervention each group was submitted to, the statistician can work "blindly" on the analysis of the data, and more confidently produce an impartial analysis.

4.3.13.c. Rationale for blinding clinical trials

Any or all of three important elements may be blinded in a trial: participants, investigators and assessors.(Pocock 1983, p 90) Subjective outcomes like pain or depression are more likely to be biased when participants know if they are receiving treatment or placebo. Objective outcomes, such as death or hypertrophy of the myocardium, are less subject to bias, and blinding participants in this case is less important. However, the person who is performing the echocardiogram could bias the assessment of the myocardium on the echocardiogram, as in the example above, and blinding of the technician should be considered. A way of overcoming this problem in a RCT is to keep participants and investigators (physicians, nurses, statistician, technicians, etc) unaware of the treatment the participant is receiving. Finally, although blinding is a strong methodological component, it is important to judge the real need for blinding, and more specifically, who should be blinded.

After having conducted the trial, the investigator wants to know if the difference observed in the treatment effect is really due to the new intervention being evaluated or due to an extraneous factor such as bias. Systematic error in a trial, which is known as bias, can arise from several sources during the trial design, conduct, analysis or interpretation. The difference in effect observed could be secondary to bias rather than due to the intervention being tested, and in many situations, blinding the trials' participants can avoid this to some extent.

Blinding may be technically easier or more difficult to implement, depending on the type of trial. For instance, explanatory trials (those that evaluate efficacy of a new therapy under ideal, restricted, and controlled conditions) tend

to be more amenable to blinding than pragmatic trials, in which more flexibility is allowed for the participant.(120) Blinding of participants or investigators is not always possible, but it should be pursued when one believes that the knowledge of the treatment could distort the results.

4.3.14. Statistical methods

Participants will have the same measurements conducted at baseline and at follow up after the treatment. As discussed in section 4.3.11, the primary outcome bladder compliance is calculated as the TBC divided by the Pressure at the TBC. The distribution of bladder compliance will be examined graphically by means of a histogram. As observed in the CHEO case-series, bladder compliance is expected to be skewed, and the log-transformation is likely to be approximately normally distributed.

Descriptive summaries of clinical characteristics of the participants at baseline will be computed. Dichotomous variables will be summarized using percentages, normally distributed continuous variables will be summarized using means together with standard deviations, and continuous variables that are not normally distributed will be summarized using medians together with 25th and 75th percentiles. The effect size estimate for the primary and secondary analyses will be reported with the 95% confidence interval.

4.3.14.a. Primary analysis

The Student's t-test for independent groups will be used to compare the bladder compliance outcome (continuous data) between the intervention and the control groups.

If necessary, log scale transformation will be used for the analysis of bladder compliance, our primary outcome.

4.3.14.b. Secondary analysis

Continuous variables for secondary outcomes such as TBC and detrusor pressure at the TBC will be checked for normality using histograms and then compared between study groups using Student's t-test (assuming a normal distribution of the scores; otherwise, logarithmic transformations will be performed on the data). Differences between the treatment and control group in the number of neurogenic detrusor overactivity episodes, UTIs, and episodes of urinary incontinence will be assessed using a Wilcoxon Mann Whitney test. Finally, chi-square tests (or Fisher's exact tests if necessary) will be used to compare the prevalence of upper urinary tract abnormalities, constipation, and systemic harm.

4.3.15. Exiting from the protocol

In the event of clinical deterioration in a patient that has been compliant with the treatment, this patient will be allowed to exit from the protocol. Persistent high bladder pressure may cause or worsen a pre-existent kidney dilatation, and can lead to a progressive renal and clinical deterioration. One of the following items will be considered signs of clinical deterioration:

New onset of renal dilatation on the ultrasound

Worsened of a previous kidney dilation

New onset or increase of serum creatinine and urea

Progressive increase of bladder pressure

The reasons for the protocol deviation and the new management elected should be reported. Patients with renal function deterioration or refractory high bladder pressure may need a bladder augmentation for control of the refractory high bladder pressure.

4.3.16. Data management

A research assistant, with experience in data entry, will input the data collected into the SSPS[®] software. All data will be compiled from the “data extraction forms” used by the assessors to collect information such as outcome measurements, harms reports, visual analogue scale grading severity of harm, etc. The trial data will have a security back up that will be stored in a safe location at the principal investigator’s office. The principal investigator will examine the data to assess for accuracy and completeness of the data entry before the analysis.

4.3.17. Proposed methods to prevent Bias

4.3.17.a. Randomization

Randomization is the main procedure used in this trial to avoid bias. It will protect the allocation process against investigators’ preferences, and avoids selection bias. It tends to produce groups that are similar with respect to risk factors, avoiding systematic difference in these factors between groups. It also guarantees that statistical tests will have valid significance levels, as discussed in section 4.3.12.a.

To ensure a reliable randomization process, it will be implemented through a central phone service operated by the trial’s statistician office, which will reveal the participant allocation upon the physician call. The trial statistician is the only person to

know the randomization sequence, and under no circumstances, will it be revealed until the follow up of the last participant has ended.

4.3.17.b. Blinding the outcome assessors to intervention assigned

Blinding to treatment groups, the nurse urodynamicist and the nurse who will interview about harms, is an attempt to avoid the introduction of biases. The knowledge of the treatment could introduce bias in the assessment of the outcomes, as discussed in section 4.3.13.

4.3.17.c. Blinding the trial statistician during the statistical analysis

The trial statistician will be blinded to the treatment each group is taking until the statistical analysis has been completed. It will protect the conducting and reporting of the statistical analysis to the statistician judgement about the treatment being tested, thus avoiding biased results.

4.3.17.d. Other biases

Other procedures were implement to avoid different types of biases. The different procedures implemented in an attempt to prevent bias are listed in table 4.2. Some of these preventive measures are restriction of risk factors to avoid introduction of bias in the trial design and conducting.

Table 4.2 Methods used to prevent biases in the design and conduct of the trial	
Method	How it could avoid bias
Exclusion bladder augment	Bladder augmentation increases absorption of the drug an leads to more systemic harm
Exclusion vesicoureteric reflux	The drug washes back to the kidney and loses contact with the bladder
Exclusion severe constipation	Constipation can worsen bladder dysfunction
Blind urodynamicist nurse	Avoid personal interference during the UDS
Standardization of UDS	Measurement bias, different techniques could lead to systematically different results in the measures
Use of ICC terminology in the UDS reports	Information bias, similar terms used with different meaning could lead to classification bias
Blind the nurse who interviews to assess harm	Avoids judgement or interpretation of patient's report of a harm or symptom

ICC: international continence society

4.4. Results

4.4.1. Flow of participants

To facilitate the reader's understanding of the trial design, conduct and flow of participants, the diagram recommended by the CONSORT Statement (113) will be used. (Appendix 4.9) This diagram outlines the 4 key levels of the RCT progression, namely enrolment of participants, allocation to groups, outcome follow up and statistical analysis.

A panoramic view of the trial development helps in discerning weaknesses and strengths of study design and conduct. The CONSORT flow chart displays the number of participants in the course of each phase of the trial, revealing possible distortions or imbalances. Information about the trial progress will be outlined, such as the number of participants assessed for eligibility, how many were included/excluded and why, the

number of participants randomized, the number of participants who were allocated to each group, etc.

The proportion of participants assessed for eligibility who were included or excluded informs as to whether the study sample represents the study population or not, and may address possible threats to external validity. It also provides more transparency about specific approaches such as intent-to-treat analysis, in which investigators include in the analysis all participants who were randomized, independent of whether they received or completed the intervention. The accuracy of the treatment effect estimate is related to the number of participants who were allocated to but did not receive an intervention.

4.4.2. Protocol deviations from study as planned and its reasons

Any deviation from this protocol and the reason for it will be reported. This includes changes that were not planned in any of the protocol steps such as the way that the intervention was delivered, assessment of follow up, data collection, method of analysis, etc. Any participant excluded after the randomization will be reported, the reason for this exclusion must be clear, and this information will appear on the flow diagram of participants of the trial.

4.4.3. Recruitment, baseline data and numbers analyzed

4.4.3.a. Recruitment

This section will summarize data on the screening process and recruitment of participants to the trial. Descriptive analysis will display information such as starting and

ending dates of each phase, the setting where it took place, median time of follow up, target rate of recruitment and actual numbers achieved.

4.4.3.b. Baseline data

Descriptive analysis of the baseline demographic and clinical characteristics for each group will be displayed in tables to facilitate the appraisal. These data include age, gender, weight, ambulatory status, neurological diagnosis and coexistent diseases. Continuous values will be reported as mean and standard deviation for normally distributed observations, and median and percentile range (25th and 75th percentile) for skewed distributions.(Ref 127 in CONSORT) Incidence of events such as urinary tract infection or constipation will be reported as true values and proportions.

Baseline characteristics of groups assessed in a RCT are not necessarily equal, and as discussed in section 4.3.12, randomization prevents selection bias but does not necessarily equally distribute participants' characteristics at baseline(113); which could be achieved by means of stratification and randomization within each stratum.(Machin 2004, p 24) Randomization assures that any difference found in the treatment effect between treatment and control groups is due to chance and not to investigator interference or other bias.(121)

In RCTs, statistical analysis to compare baseline characteristics of patients from each group, using tests such as ANOVA, is not appropriate and adjustments made based on differences found in this analysis may bias the result of the trial.(Ref 137 in CONSORT)

4.4.3.c. Numbers analyzed, intention-to-treat analysis and dropouts

To ensure transparency, the number of participants included in each group and the number of participants used in each analysis will be reported together with the total

number of events observed. The results will be reported in absolute numbers, and appropriate summary measures like relative risk or odds ratio for binary outcomes.

Intention-to-treat analysis

Intention-to-treat analysis was selected as the statistical strategy for this trial; thus every participant will be analyzed according to the allocated group whether they have been compliant with the intervention or not. Participants considered for this approach must have follow up information such as outcome assessment.

Dropouts

Dropouts from the trial, with incomplete follow up, will not be analyzed under the label of intention-to-treat analysis; this approach will only be applied to participants for whom follow up data is available. Dropout and missing data were discussed in section 4.3.9.d.

One must be sure that the total number of participants used for analysis in each group, the denominators, are correctly accounted for and that all outcome results are recorded, especially for binary outcomes. This denominator may vary amongst outcome assessments, but it is important to know the total number of participants who experienced an event and the total number of participants assessed for each specific outcome. Only then can relative risks and odds ratios be derived. Thus, results will be reported in absolute values, together with summaries such as relative risk or risk difference.

The inclusion in the analysis of all participants allocated to each group, whether or not they received the intervention assigned, is of utter importance. Excluding these participants from analysis would result in bias and overestimation of the treatment effect. Intention-to-treat analysis accounts for deviations from the protocol and gives a more accurate estimate of treatment effect.

4.4.4 Outcomes and estimation

The measures of treatment effect within each group (pre- versus post-intervention) for all outcomes analyzed in this trial will be reported. The effect size between groups will be followed by its 95% confidence interval (precision).

4.4.4.a. Primary outcome

Bladder compliance, which is a continuous variable and our primary outcome, will be assessed at baseline, 45 days, 3 and 6 months of follow up. Summary of treatment effect and precision for bladder compliance in each group will be displayed in a table. The effect size, which is calculated as the difference in means' changes between the intervention and control group, will be reported with 95% confidence interval.

4.4.4.b. Secondary outcomes

Secondary outcomes that are measured as continuous variables will be handled in the same manner as the primary outcome. The treatment effect for binary outcomes such as hydronephrosis and constipation will be reported as the proportion of participants presenting with the event. The measured effect size, the difference between the incidence of the event in the intervention and control groups, will be reported as the relative risk and the 95% confidence interval.

4.4.5. Subgroup analysis and adjusted analysis

4.4.5.a. Subgroup analysis

Although no differences were found between the outcomes of ambulatory and wheel chair bound patients in the review of CHEO's experience presented in chapter 2 of this thesis, it is worthwhile to do a subgroup analysis of the outcomes of ambulatory

participants versus wheel chair bound participants. As this is a pre-planned analysis, the level of confidence for this analysis will be 95 %, with alpha 0.05, two-sided tests.

Rationale for subgroup analysis: The rationale for this subgroup analysis is the hypothesis that “ambulatory patients have a better response to the intervention compared to wheel chair bound patients.”

As previously discussed, ambulatory children with neurogenic bladders tend to be more active and have more frequent bowel movements compared to those children who are wheel chair bound. The immobilization experienced by non-ambulatory patients is a risk factor for intestinal constipation.(107) It is known that intestinal constipation can impair bladder function, and it is one of the most important risk factors for dysfunctional bladder behaviour in neurologically normal patients.(106) Thus, it is hypothesized that the subgroup of ambulatory patients will have a better response to intravesical oxybutynin.

4.4.5.b. Adjusted analysis

No adjustment in the analysis is planned, since stratification by age was used for the randomization and it will control for this possible confounder. A “restriction” strategy was also used in an attempt to avoid introduction of other potential confounders.

Rationale for not doing adjustment in the analysis: During the planning phase, several factors were identified that could potentially introduce bias in the results of this trial. In an effort to avoid these potential biases, a restriction approach was used. These factors are listed amongst the exclusion criteria and are discussed in section 4.3.6.d. To name some, patients older than 18 years of age, previous bladder augmentation, severe constipation and concomitant use of another anticholinergic drug, were excluded.

4.4.6 Harms

The number and the proportion of participants who experienced harm in each group will be reported in a table. In the case of participants presenting with the same harm more than once, the frequency of the event will be reported. In case of therapy discontinuation, the reason for it should be clear. As previously mentioned, the most common harms with this drug are those secondary to the anticholinergic effect of the oxybutynin, such as dry mouth, facial flush, blurred vision, dizziness, intolerance of heat, and constipation. Participants will be asked to report immediately any occurrence of harm rather than wait until the next follow up visit. As suggested by Pocock, participant/parents will be supplied with a checklist containing the possible harms, and an open-ended question asking if the participant had any unexpected symptom or harm.(Pocock 1983, p 44)(22) They will be asked to note and check in the box the symptoms they experienced.(Appendix 4.10) Although there is a chance of overestimating the harms with this approach, because some participants may feel influenced by the list of symptoms, it may reduce recall bias. The same assessment will be done for the control group, and the incidence of harms in both groups will be compared.

4.4.6.a. Quantifying the intensity of the harm

A visual analogue scale will be used to quantify the intensity of harms from the participant's perspective.(Appendix 4.11) The participants will be asked to mark on a scale from zero to ten the intensity of the harm they experienced. The minimum, "0" is defined as a very mild harm causing no change in normal life activities, "5" is a moderately uncomfortable harm that does not affect normal life activities, and "10" is an extremely severe harm incompatible with normal life activities. For participants less than

7 years of age, their parents will be asked to answer as proxy, and to mark on the visual analogue scale the intensity of the harm the child experienced, in their opinion.

4.4.6.b. Rationale for harm assessment

This trial will assess efficacy and safety of oxybutynin. Therefore it is important to record and report harms associated with the intervention being investigated. Harms may be associated with the intervention and be a determinant of the compliance with the treatment. Occurrence of harm can reduce the willingness of the participant to comply with the intervention or to stay in the trial. However, harm might be totally unrelated to the intervention, and could be associated with the condition itself. In the report of the main harms, those associated with the condition and those that are related to the intervention will be discerned.

4.5. Data and safety monitoring committee and interim analysis

4.5.1. Data and safety monitoring committee (DSMC)

An independent team of professionals not involved in the trial will make up the DSMC. This committee will monitor the trial progression with regards to safety variables, and should be informed by the investigators of any issue related to harm or patient safety. The composition and responsibilities of the DSMC is listed in table 4.3. An independent statistician will conduct the interim statistical analysis and provide the feedback to DSMC regarding whether the trial should continue. The O'Brien and Fleming boundaries (Jenisson 2000, p 32) will be used as a guideline for premature stopping of the trial, and the members of the DSMC will be responsible for the decision whether or not the trial should stop prematurely upon receiving the independent statistician's recommendation.

Table 4.3 Composition and responsibilities of the DSMC

Composition		Responsibilities	Meetings
DSMC (independent members not involved in the trial)	Statistician (1)	Review periodically the collected data on patient safety	Every 6 months , or as often as necessary
	Clinical epidemiologists (1)	Advise the steering committee in case of continuation, interruptions or modification of the trial	
	Trial methodologist (1)		
	(blinded to the patients' identities and group assignments)	Members should have no financial or material interests in the trial	
		Should guard trials' information with confidentiality	

4.5.2. Interim analysis

An independent statistician, not involved in the trial and blinded to patients' identities and group assignments, will conduct the interim analysis. One interim analysis is planned, which will be performed after the 143nd (50% of the total sample) participant has completed the follow up period. The interim analysis will focus on the primary outcome, difference in bladder compliance between the group taking high dose oral oxybutynin and the group using intravesical oxybutynin. A statistical analysis of the principal safety data will be conducted (i.e., anticholinergic harms, constipation, complications with bladder catheterizations).

4.5.2.a. Guidelines to stop the trial and Safety profile of oxybutynin

Guidelines to stop the trial: The O'Brien and Fleming's criteria will be used for the sequential test, and according to this criteria it will be applied an alpha 0.005 for the interim analysis and a significance level of 0.048 for the final analysis at the end of the study.(122) This analysis will monitor whether there is an exaggerated superiority in the primary outcome favouring one of the groups, or if there is an unexpected high rate of

harm. This trial is powered to detect a superiority of 20% in the treatment group over the control group, and the goal is to enroll 286 participants. Harms will be assessed through a checklist filled by participants/family and at interviews with the clinical nurse during follow up visits. Patients will quantify the intensity of the harm in a visual analogue scale. The principal investigator will be responsible to empower the person responsible for the data organization, who will prepare the reports of the accumulated safety and efficacy data, and make them available to the independent statistician to conduct the interim analysis.(Machin 2004, pp 31-32)

Safety profile of oxybutynin: Due to the nature of the disease and the low harm profile of oxybutynin, it is not expected that the disease or the medication used in this trial will cause death or significant injury. Oxybutynin is a drug that is widely used in children. It was approved in the US in 1975, and in 1980 Moisey and colleagues published one of the first papers describing its use in urology.(18) Although the anticholinergic effect can cause harm (123-126), oxybutynin has a quite good safety profile and in the cases of more significant harm reported in the literature, the symptoms subsided completely after the drug had been discontinued.(26,38,127,128) It is not anticipated that serious harms will ensue with the dose used in this trial. Oxybutynin used intravesically was first described in 1989 by Brendler (35), and since then experience has been accumulating in the literature. In the CHEO's experience with intravesical oxybutynin reported in chapter 2, there was no significant harm with this route of administration at the proposed dose of 15 mg/day.

4.5.2.b. Impact in the sample size calculation

To account for the interim analysis and to maintain the 80% statistical power, the constant factor 1.008 (O'Brien and Fleming) was used in the determination of the group

sizes (two side test).(Jenisson 2000, p 30) This provision has been factored in the sample size calculation and is describe in section 4.3.11.

Rationale of interim analysis: A planned interim analysis is usually performed for one of the following reasons: ethical, scientific, financial or administrative. Ethical and scientific reasons to conduct an interim analysis are generally supported by the same rationale.

As interim analysis increases the chance of finding a difference between groups, when in fact this difference does not exist (type I error) (Spilker 1991, p 494), the alpha value for the interim analyses should be adjusted to maintain the whole-study confidence level of 95% (alpha 0.05). Using O'Brien and Fleming's criteria is a conservative approach; the chance of finding significant results are very small at the beginning of the study and increase at subsequent analyses, since as the trial accumulates more participants the power to find differences increases.

There is a debate about the appropriateness of the interim statistical analysis, how it should be done and its impact over the trial development. Some authors argue that if the results coming out from these analyses are not well handled, external pressure over the investigators may impact in the conduct of the trial.(122) Data monitoring committees should have ethical and appropriate conduct when they need to make their results of interim analysis public, avoiding inappropriate repercussion on the trial. Although some committee reports may ask for the interruption of a trial, others will just suggest corrections in the design or conduct. However, the result of the analysis may trigger all kinds of external judgements and actions toward the investigators, who may precipitously make wrong decisions. Monitoring committees have an important invested responsibility, they should act firmly but conscientiously, and be aware of "when" and

“to whom” disclosure should be made of the results of partial analyses of a trial that is still going on. In a double-blind study, it is inappropriate for the monitoring committee to give the partial results to the investigators conducting the trial, which could bias his/her approach to the participants.(Spilker 1991, p 492)

One should be wary with trials that stop earlier than the planned time. There is some evidence that randomized trials stopped early for benefit tend to show larger treatment effects. In a systematic review of RCTs that stopped early for benefit, Montori et al reported an estimated median RR of 0.53 (IQR, 0.28-0.66) amongst 126 RCTs with dichotomous outcomes.(129)

4.6. Ethical considerations

This protocol was prepared in accordance with ethical principles and respecting the standards of the declaration of Helsinki.(87) This study will be submitted for approval to the CHEO Research Ethics Board. The randomization process will ensure an equal chance for every participant to receive either one of the interventions, thereby respecting the participant’s right to equal access to treatment. The oral treatment with oxybutynin offered to the control group is a standard treatment for this condition. The participants or their parents have the right to enter the study, to refuse or to drop out at any time, with no consequence for the treatment received at this hospital. No surgical or anaesthetic procedure is needed for this therapy. The risks are minimal, and are mainly associated with the bladder catheterization, that most of the participants are currently using in any case.

Healthy volunteers typically receive no medical benefit from medical trials, so it is reasonable and ethically acceptable that they receive financial compensation for the

risk of harm they are taking.(Spilker 1992, p 150) The amount of money paid should not be excessive such that it may compel the participant to stay on the trial, even when he/she is experiencing severe harm. This trial will enrol no healthy volunteers, and no financial or material gain will be offered to participants or to investigators.

Chapter 5 – Overview

5.1. A condition with a major impact on quality of life

Neurogenic bladder is a term used for a bladder dysfunction caused by a neurological condition, in which the bladder loses its physiological ability to store or void urine under voluntary control. It generates high pressure inside the bladder that can cause urinary incontinence and/or damage to the kidneys. This dysfunction may also lead to an important physical and social limitation, impairing the quality of life of these children. The most common cause of neurogenic bladder in children is congenital spinal dysraphism, which has an incidence of 1 in 1000 births in the United States.(23) The morbidity associated with spinal dysraphism can vary from a mild form, in which the patient is ambulatory and has most of the cognitive functions preserved, to a severe form with paralysis, orthopedic problems, hydrocephalus and cognitive deficit. The urinary tract is one of the most common sites of morbidity in these children, and high bladder pressure is the most common cause. At least 25% of the clinical problems seen in paediatric urology are the result of a neurological condition that causes dysfunctional behaviour of the lower urinary tract.(Campbell 2002, p 2234)

The urological care of patients with neurogenic bladder typically relies on bladder catheterizations, a technique introduced by Lapedes in the 1970's, which ensures adequate urine drainage, control of the bladder pressure and avoids urinary incontinence.(1) When the catheterizations are not sufficient to decrease bladder pressure, an oral anticholinergic drug is also used. If the anticholinergic drug fails to control bladder pressure, the next option is bladder augmentation, which is a major surgery with potential risk of morbidity. Intravesical oxybutynin is an alternative

treatment for children with neurogenic bladders who are not responding to the standard therapy. It may delay or obviate the need for a bladder augmentation, and thereby improve the quality of life for these children who have been burdened with this chronic pathology.

5.2. What can we conclude from this thesis?

This was a systematic review of the available evidence of intravesical oxybutynin therapy in children with neurogenic bladder. It suggested that this therapy is effective; however there was no controlled study of sound design assessing efficacy. Based on this research, the level of evidence to support this therapy in children is very low. Excluding the CHEO case series, the systematic review showed that the first study was published in 1991 and the last two were published in 1998 and 2001. A few other studies evaluated intravesical oxybutynin in children, but they used different endpoints such as pharmacological outcomes, incontinence only, or harms; they were excluded from this review, and the reasons were discussed in chapter 3. The CHEO case series suggests effectiveness, however like the other studies, it was a retrospective review, had a weak design and low level of evidence. Neither published RCTs nor registry of study protocols assessing the efficacy of this intervention in children were found.

5.3. An important issue for the national health care system

A multidisciplinary health-care team is essential for the management of these patients, and this condition demands a considerable expenditure from the health care system. The Ontario Ministry of Health and health care decision-makers in Canada need to create policies to optimize their investment in health care. Clinical research and

evidence-based medicine should guide these health care policies. Due to the relevance of this condition, a nation-wide agenda for research in “spinal cord malformation and neurogenic bladder in children” seems appropriate. This initiative should receive governmental and academic support. Moreover, to generate evidence-based medicine, it is also important to involve private institutions that fund studies in children. Finally, it is of vital importance that after this knowledge has been generated, a structured strategy of knowledge transfer and dissemination spread these findings amongst health care professionals.

5.4. What came up from this study in terms of clinical care?

Physicians and health professionals involved in the care of patients with spina bifida and neurogenic bladder should be aware of this potentially morbid threat to the kidneys. Close follow up of the renal function and kidney status should be done routinely. Special attention should be paid to incontinence and urinary infection management, which impact highly the quality of life.

Recommendations for health care practitioners

- UDS, ultrasound and renal function should be obtained as baseline measurements, and should be repeated at least yearly in children with neurogenic bladder. If risk factors for renal deterioration are detected, they should be repeated more frequently.
- CIC and oral anticholinergic medication should be used for inadequate voiding, incontinence or high bladder pressure.

- In cases refractory to clinical treatment, and before opting for bladder augmentation, paediatric urologists should rely on the findings of this review to decide if it is appropriate to use intravesical oxybutynin.

5.5. What research needs are identified by this study?

The result of this research indicates the necessity of a study of sound design examining the use of intravesical oxybutynin in children. Considering the importance of this medical condition in paediatrics and the impact of its management on the health care system, a well designed RCT should be undertaken. Besides the involvement of the health care professionals, this trial should include a team of an experienced trialist, clinical epidemiologist, trial statistician and information specialist.

Recommendations for researchers

Specific recommendations to assess the epidemiology and morbidity of paediatric neurogenic bladder, and to assess efficacy of this alternative treatment

- That a large clinical trial should be conducted to assess the efficacy and safety of intravesical oxybutynin in children with neurogenic bladder.
- That the incidence of paediatric neurogenic bladder with unsatisfactory response to standard treatment (CIC and oral anticholinergic medication) be closely monitored in patients followed in urology clinics.
- That urology clinics should implement surveillance to study the epidemiology and incidence of surgical bladder augmentation and renal failure, the two major parameters of urological deterioration.
- In the case of the proposed trial demonstrating efficacy and safety of intravesical oxybutynin, a knowledge transfer and dissemination program should be

implemented to make these results widely available to physicians and health care practitioners.

- Centres should conduct a surveillance program after 3 years of implementation of this therapy, to detect if there is a reduction in the number of bladder augmentation surgeries and/or patients with renal failures associated with paediatric neurogenic bladder.

Appendixes

Appendix 2.1 Data collection form

Study: Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial

Number:	
Name:	
Neuro diagnosis (MM, LM, SCI, TC):	
Age:	Date of Birth:
Sex:	Ambulatory status:

Status of urinary function prior to intravesical oxybutynin:

Incontinence	CIC	Antibiotics	#UTI/6mo	Constipation	Cecostomy

Treatment with oral oxybutynin:

Start Date	mg/day	Harm	Which?	Weight Kg

Urodynamics before treatment:

Date	TBC	P at TBC	B.Compliance	Overactivity	DLPP

Treatment with intravesical oxybutynin:

Start Date	mg/day	Reason for IV oxybutynin		Oral oxybutynin associated	
		Harm w/oral	No response	y/n	Dose

Status of urinary function after intravesical oxybutynin:

Incontinence	CIC	Antibiotics	#UTI/6m	Constipation	Cecostomy

Urodynamics after treatment

Date	TBC	P at TBC	B.Compliance	Overactivity	DLPP

Harm assessment

Dry mouth:
Facial flush:
Heat intolerance:
Dizziness:
Blurred vision:

Constipation:
Headache:
Bad dream/insomnia:

Upper tract assessment before

	Ultrasound	Hydro
	Date	y/n
Before		
After		

MM: myelomeningocele, LM: lipomyelomeningocele, SCI: spinal cord injury, TC: tethered cord

Appendix 3.1 Intervention, assessments and outcomes

1. Description of the intervention

Oxybutynin is an anticholinergic drug used to improve bladder compliance in children with poorly compliant neurogenic bladders. In place of or in combination with oral dosing, intravesical administration may improve clinical response and reduce harms. Oxybutynin is delivered intravesically as a solution in sterile water, using a plastic sterile catheter which is inserted into the bladder through the urethra.¹¹ It is injected into the bladder two or three times a day (0.4 mg/kg/day), just after the patient has completely emptied his/her bladder. These patients are already on a bladder catheterization regimen, so patients and parents usually have no resistance to this additional therapy.¹⁴

Patients with neurogenic bladders commonly use catheterization to empty their bladders three to five times daily. This "clean intermittent catheterization technique" requires adequate hand washing and appropriate hygiene of the penis or vulva before the procedure, but does not require sterile gloves.

2. Assessments

2.1. Baseline assessment

- Medical history and physical examination, including medications, allergies, urologic symptoms and infections, and surgical history (i.e. cecostomy tube for bowel irrigation, bladder augmentation, etc).
- Patient demographics (birth date, sex)
- Neurological diagnosis (i.e. spina bifida, spinal cord injury, etc.)
- Treatment with oral oxybutynin:
 - Duration of pre-trial treatment (months)
 - Dosage of oral medication (mg/kg/24 hr)

Harms (constipation, dry mouth, blurred vision, orthostatic hypotension),
whether treatment was stopped or reduced, and if so why

- Previous treatment with intravesical oxybutynin?

Reason for using intravesical oxybutynin

Duration of intravesical treatment (months)

Dosage of intravesical medication (mg/kg/24 hr)

Harms (constipation, dry mouth, blurred vision, orthostatic hypotension),
whether treatment was stopped, and if so why.

2.2. Outcome assessments at baseline and follow-ups

- Urodynamic study (UDS) to evaluate the bladder compliance, total bladder capacity, pressure at total bladder capacity, detrusor leak point pressure, presence and intensity of detrusor overactivity, and pelvic floor electromyograph pattern
- Ultrasound to assess the bladder and kidney status (presence of hydronephrosis or ureteral dilation)
- Plain X -ray of the abdomen to assess constipation
- Catheterization calendar: Written record of five days bladder catheterization frequency, volume drained and incontinence episodes
- Stool calendar recording the intestinal function - frequency of bowel movements, characteristics of the stool and soiling episodes

3. Outcomes definitions and unit of measurements

3.1. Primary outcome

- Bladder compliance - measured in mL/cmH₂O

(Ratio of “volume-change/pressure-change” that is measured at TBC during UDS)

3.2. Secondary outcomes

- Total Bladder Capacity (TBC) – measured in mL
(Maximum bladder volume before the patient refers to pain or starts to leak urine while the bladder is being filled during UDS)
- Detrusor pressure at the TBC – measured in cmH₂O
(The difference between the intravesical and intra-rectal pressure measured at the TBC during UDS)
- Detrusor leak point pressure (DLPP) – measured in cmH₂O
(Detrusor pressure of an involuntary urine leak during UDS)
- Neurogenic detrusor overactivity – measured in cmH₂O and number of events
(Involuntary bladder contractions during the filling phase of the UDS)
- Urinary tract infections (UTIs)– measured as the number of events
(Monthly frequency of UTIs clinically confirmed and with positive urine culture)
- Episodes of urinary incontinence – measured as number of events
(monthly frequency of daytime wetting accidents)
- Upper urinary tract abnormalities – measured as dichotomous outcome (yes/no)
(Presence of dilation of the kidney on the ultrasound)

3.3. Harms

- Constipation – measured as dichotomous outcome (yes/no)
(Absence of bowel movement for more than 3 days)

- Systemic harm – measured as dichotomous outcome (yes/no)

(Dry mouth, facial flushing, blurred vision, orthostatic hypotension)

- Dropping out of the study, and reason why – measured as percentage

(Whether the patient refuses to continue clinical follow up)

Appendix 3.2 Search Strategy for Embase

EMBASE Search

1. neurogenic bladder.mp. or Neurogenic Bladder/
2. Neurogenic Bladder/
3. limit 2 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
4. OXYBUTYNIN/ve [Intravesical Drug Administration]
5. 3 and 4
6. 2 and 4
7. oxybutynin.mp. or OXYBUTYNIN/
8. intravesical.mp.
9. 7 and 8
10. 3 and 8
11. 8 and 2
12. 2 and 7
13. 12 and 8

Appendix 3.3 Quality Assessment Check list

Systematic Review - Intravesical Oxybutynin

ID number: _____ Reviewer: _____

Title: _____

Authors: _____

Journal: _____

Date Publication: _____ Source (*Database, proceeding, etc*): _____

Language: _____

	Yes	Unclear	No	n/a*
• Nature of the question: Clearly stated question of assessment of effectiveness	_____	_____	_____	_____
• Study design: Evaluation of the effectiveness of the intravesical oxybutynin in children with neurogenic bladder.	_____	_____	_____	_____
• Study design threshold:				
○ Inclusion criteria:	Yes	Unclear	No	n/a
Randomized controlled trials.	_____	_____	_____	_____
Non-randomized controlled trials.	_____	_____	_____	_____
Quasi-experimental clinical trials.	_____	_____	_____	_____
Before-and-after design	_____	_____	_____	_____
○ Exclusion criteria:				
Case-control study.	_____	_____	_____	_____
Cohort studies.	_____	_____	_____	_____

* n/a: not applicable

Generic quality items checklist:

	Yes	Unclear	No	n/a
Was adequate generation of random sequence for allocation patient for intervention? (<i>Computer or Random Tables generating random numbers</i>)	_____	_____	_____	_____

	Yes	Unclear	No	n/a
Was adequate concealment of allocation used? (<i>Well-designed method to prevent knowledge of the allocation</i>)	_____	_____	_____	_____

sequence to clinicians, staff and patient, e.g.: web based or centralized randomization)

Was **blinding** done adequately?

(Clinicians, staff, patients and outcome analyzers)

Was a priori **sample size calculation** adequately done?

Yes Unclear No n/a

The description of **withdraw/dropout** was adequately done? (Number and reason of the participants withdraw from both groups)

Did the analysis include “**intend-to-treat**” analysis?

(Intention-to-treat analysis - includes all dropped out/withdraw in the calculation)

Did they inform the type of **statistical tests** used?

Did they inform “**p values**” of the tests?

Specific quality items checklist:

Yes Unclear No

Population

Did they use correct inclusion/exclusion criteria?

Children < 18 yrs age with neurogenic poorly compliant bladder?

Intervention

Yes Unclear No

Did they describe how to perform the treatment?

(Use of catheter, crushing the pills or pharmacy-prepared solution)

Did they inform the dose of oxybutynin used?

Outcome

Primary:

Yes Unclear No

Did they give the baseline and post measures of Bladder Compliance?

Secondary:

Yes Unclear No

Did they give the baseline and post-treat. measures of:

Total bladder Capacity:

Pressure at total bladder capacity:

Neurogenic detrusor overactivity, inhibited contraction, hyperreflexia

or instability:	___	_____	___
DSD (<i>Detrusor sphincter dyssynergy</i>)	___	_____	___
Urinary incontinence?	___	_____	___

Harms:	Yes	Unclear	No
Did they give information about?			
Harms in general (<i>Dry mouth, blurred vision, constipation, orthostatic hypotension</i>):	___	_____	___
Was there withdraw due to harms:	___	_____	___

Appendix 3.4 Data-extraction Form

Systematic Review - Intravesical Oxybutynin

ID number: _____ Reviewer: _____

Title: _____

Authors: _____

Journal: _____

Date Publication: _____ Language: _____

Source data base: _____

1. Study design	(Check one)
RCT	<input type="checkbox"/>
Non-RCT	<input type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Before-and-after	<input type="checkbox"/>
Case-control	<input type="checkbox"/>
Cohort Observational	<input type="checkbox"/>

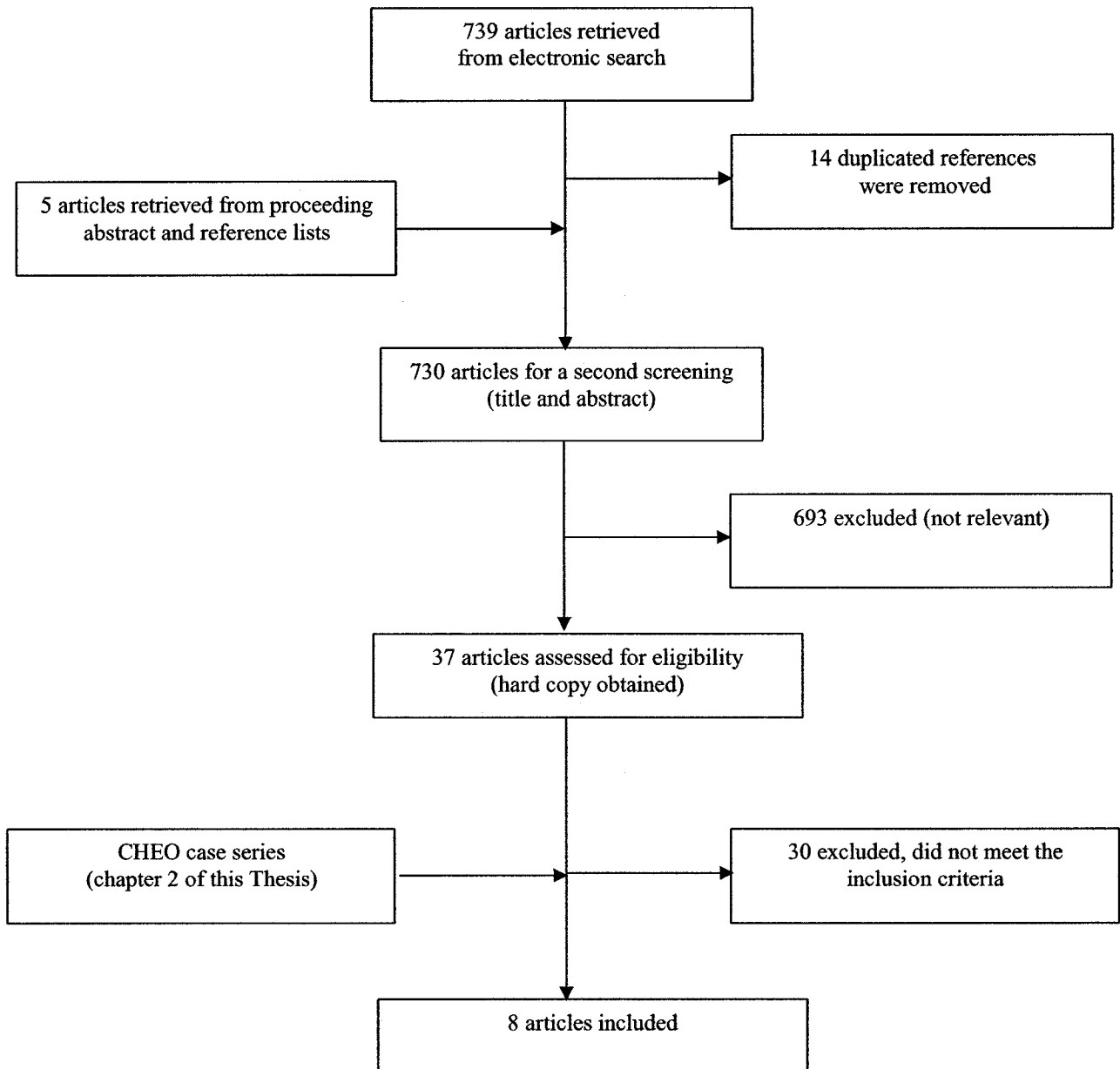
2. Population:	Yes	Unclear	No
Is it less than 18 years of age?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Is it clear that they have neurogenic bladder?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Neurological diagnosis and "n" of children (i.e. :MM :3, SCI:2, Myelitis: 2 etc)	<input type="checkbox"/>		

3. Intervention:					
Treatment group:	Yes	Unclear	No	Length in months	Dose (mg/day)
Intravesical Oxybutynin					
Oral oxybutynin					
Crushed pills or solution?					
	Yes	Unclear	No		
Control group is:					
Non-treatment					
Different treatment (which?)					
Different dose (which?)					
Other treatment (Specify):					

4. Outcomes:					
Primary:					
	Mean improvement			Variability (SD, SE, 95%CI)	
Bladder Compliance	mL/cmH2O		%		
Secondary:					
	Mean improvement			Variability (SD, SE, 95%CI)	
Total bladder Capacity:	ml		%		
Pressure at total bladder capacity:	cm/H2O		%		
	Improvement		n/N (%)	Not Reported	
Overactive bladder, hyperreflexia, inhibited contraction or instability:	Yes	No			
DSD (Det. sphincter dyssynergy):	Yes	No			
Urinary incontinence improvement:	Yes	No			
(OR, RR, 95%CI, if used)					
Harms: (Surged or increased compared to baseline)				n/N (%)	Not reported
Constipation:			Yes	No	
Significant (Dry mouth, blurred vision, postural hypotension):			Yes	No	
Withdraw due to harms:			Yes	No	
Was any effect size summary measure used (Odds Ratio, Relative Risk, etc)?					
Which? _____ Specify value and 95% C.I.: _____					

Appendix 3.5 QUOROM flowchart

QUOROM flowchart outlining the excluded^d and included articles



^d The reasons for exclusions are outlined in section “3.7.1. Literature search”

Appendix 4.1 Screening record form

Study: Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial of efficacy and safety

Participant name: _____

Unique number: _____

Sex: M__ F__ Age (in years): _____

Race: 1- Caucasian 2- Black 3- Native 4- Asian

Neurologic diagnosis: _____

Ambulatory status: Ambulatory: 1 Wheel chair bound: 2

Urologic diagnosis: _____

Code: yes-1 no- 2 not evaluated- 3

Neurogenic bladder..... _____

Bladder compliance <10mL/cmH2O..... _____

Pressure at TBC >40cm/H2O _____

Is he/she taking oral oxybutynin?..... _____ For how long: _____

Dose of oral oxybutynin mg/day: _____

Has had harm?..... _____

What type of harm? _____

Taking any other anticholinergic..... _____ Which one? _____

Bladder augmentation..... _____

Severe vesico-ureteric reflux..... _____

Urethral stricture..... _____

Current UTI..... _____

Constipation (more than 3 days)..... _____

Emotional limitations _____

Hypersensitivity to oxybutynin..... _____

Medical conditions in which it would be unsafe to use an anti-cholinergic medication..... _____

The use of concomitant anticholinergic drugs that could confound the efficacy evaluation..... _____

The use of concomitant drugs that would be unsafe with an anti-cholinergic medication..... _____

Considered for recruitment:..... _____

Reason for exclusion: _____

Source: Spilker 1992, p 11.

Appendix 4.2 Invitation letter for participation in the trial

Dear (_____)/ (Parents of _____)

Ottawa, _____ 2006

The Division of Paediatric Urology at the Children's Hospital of Eastern Ontario is currently conducting a study on the treatment of children with neurogenic bladder. This study assesses the effect of the intravesical treatment with oxybutynin to improve bladder pressure in patients who are not adequately responding to oral oxybutynin. We identified in our records that (_____) is a potential candidate for this study and we are pleased to invite you/your child to come for visit at CHEO to receive information about this study. You/your child may get some benefit from this study, and it may benefit other children with this condition as well. Participation is voluntary and there is no obligation to enroll in this study. The paediatric urologists working at CHEO are involved in this study. We appreciate your consideration and ask you please to contact Michele Levassuer at (613) 7600 x 2403 who will arrange your visit.

Sincerely,

Dr. Luis Guerra
Coordinator of the study
Children's Hospital of Eastern Ontario

Appendix 4.3 Informed consent form

Study: Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial

Principal investigator: Dr Luis Guerra (Paediatric Urologist)

Co-Investigators: Dr Michael Leonard (Paediatric urologist)
Dr John Pike (Paediatric urologist)
Julie Milks, RN (Urodynamicist nurse)
Michele Levasseur, RN (Clinical nurse)
Nick Barrowman, PhD (Statistician)
David Moher, PhD (Clinical epidemiologist)

Contact person: Dr Luis Guerra Ph: (613) 737-7600 x1353
Michele Levasseur Ph: (613) 737-7600 x2341

Emergency contact: Dr Luis Guerra, or call CHEO phone (613) 737-7600 and please ask page the urologist on call (24 hours a day, seven days a week).

Name of the participant: _____

Date of birth (mm/dd/yyyy): _____ Age: _____ Sex: _____

Address: _____

Telephone: () _____

Introduction

You or your child have been invited to participate in this study that will test a treatment called “intravesical oxybutynin.” As you recall, you/your child have been taking oral oxybutynin for a period of time. This treatment may work well at the beginning but in some cases it may become ineffective with time. In this situation, we can try higher doses of oral oxybutynin.

An alternative to taking high doses of oxybutynin is to use the oxybutynin instilled directly inside the bladder, and we call this therapy “intravesical oxybutynin”. The reason to do this study is that we do not know if the intravesical oxybutynin treatment really works.

What is the purpose of the study?

The objective of this trial is to test how well intravesical oxybutynin works in decreasing bladder pressure inside your/your child’s bladder.

Who is conducting the study?

The group of paediatric urologists and clinical epidemiologists working at CHEO, and affiliated with the University of Ottawa is conducting this study. It is planned to be finished in 3 and half years. If you have any questions about the trial please call Dr Luis Guerra at (613) 737-7600 x1353.

What if I choose not to participate?

You have been invited to participate in this trial, but you do not need to accept if you not feel motivated to. The enrolment is voluntary and you should ask the investigators any question to help you decide. The quality and frequency of the care you/your child is receiving will absolutely not change based on this decision.

What if I change my mind after I have entered the trial?

If you choose to participate in this study, you are free to withdraw at any time if you change your mind. The access to CHEO’s services and quality of care will not change. Nobody will be “disappointed” with you. This is your decision and you can change your mind if you desire.

Scientific information about this trial

Neurogenic bladder is a condition in which the neurologic connections between the brain or spinal cord and the bladder are damaged. The bladder has basically two functions: to store a normal volume of urine at a low pressure, and to void the urine stored when the person feels that the bladder is full.

The treatment with oxybutynin aims to reduce the pressure inside the bladder and to increase the volume of urine the bladder is able to store. Oxybutynin is considered the best and most used drug for children with high-pressure neurogenic bladder.

What is randomization and why is it important in a trial?

Every time you want to evaluate if one treatment is better than another, you need to remove the interference of the person who is evaluating. Otherwise, the judgment may not be impartial. In a scientific study, the preferences of the investigators should not count, and nothing other than “chance” should interfere on the effect of treatment assigned to you. For this reason, the two treatments assessed in this study will be assigned for each patient “by chance”. Your doctor cannot choose the treatment, because

in doing that he could interfere in the results. This means that you have an equal but random chance of receiving a higher dose of oxybutynin or intravesical oxybutynin. If you are in the group receiving intravesical oxybutynin you will not take oral oxybutynin.

How the study is done?

Your doctor will inform you to which treatment you have been randomized. After you have been randomized to one of the two treatments, you will receive the information from your doctor and nurse. They will teach you how to do the treatment, and tell you about the follow up visits and the contact person to call if you have any concerns. The duration of the treatment is 6 months, and you will be asked to come to the urology clinic 3 times during this period, at 45 days, 3 and 6 months after the beginning of the treatment. The two exams that are necessary for this study are well known to you: an ultrasound of the abdomen and a urodynamics study will be done at the 3 and 6-month visit to clinic. You will be asked to fill a voiding and stooling calendar at home and to bring them to clinic. A list of possible side effects will be given to you, and we ask you to mark if you feel any of the listed symptoms.

Potential side effects or discomforts

The treatment with high dose of oral oxybutynin is the same that you/your child have been taking, and the only difference is that the dose will be higher. Some patients feel a dry mouth that does not get better after drinking water. This symptom usually improves with time. Other side effects are flushing of the cheeks, intolerance to heat (feeling tired on warm days}, or dizziness (feeling that you could faint). Intestinal constipation is another side effect that can happen with the use of oxybutynin. Bowel movements should be present every two to three days, and the stools should not be too hard or painful.

If you/your child develop any serious problem you/your child will receive prompt and appropriate medical care at CHEO. If you/your child have any of these symptoms, you should indicate them on the form provided to you and make a phone call so that our nurse is aware (Michele Levasseur phone: (613) 737-7600 x2403). Note that most of these side effects are mild or moderate in intensity and generally subside with the discontinuation of the treatment. In the case of a severe symptom you should come to the emergency department of CHEO, inform the physician about the symptoms and ask him/her to contact the urologist on call. The paediatric urology division has coverage of the emergency department 24hs/7days. If you experience any problem with your bladder catheterization, you should contact Julie Milks at the urodynamic unit, phone: (613) 737 7600 x2450.

Potential benefits

It is difficult to anticipate if you/your child will benefit from this study. There are some published studies that suggest that intravesical oxybutynin could work in patients with neurogenic bladder, but they are not conclusive. The results of this trial will tell us if this treatment is effective.

Alternative treatments

When oxybutynin is not being effective in decreasing bladder pressure we can use another anticholinergic drug such as tolterodine. However, there are very few options of

anticholinergic drugs for children on the market, and oxybutynin is the most used and generally considered one of the most effective.

Confidentiality

All of the personal information collected in this trial will be confidential and only the investigators will have access to it. We will publish or release no information that discloses you/your child’s identity without your authorization. The trial records may be audited by the institutional review board (CHEO ethics committee) for the purpose of monitoring, but the auditors can release no information identifying you/your child. If someone external to the trial needs to examine the results, your/your child’s name and identity will not be revealed. The principal investigator will be responsible for keeping the trials records confidential.

Who is paying for this study?

This study is academic research of the Division of Paediatric Urology of CHEO, and we will receive no money or material benefits from this study. Our aim is to answer a question of which treatment is better for the condition you have.

Cost or financial compensation

There will be no cost or financial compensation for you/your child for participating in this study. The physicians and investigators work in this trial will receive no financial or material compensation either.

Consent

I acknowledge that I have read all the information above and that all the questions related to it were answered. I understood the nature of the intervention, how it will be done and the possible side effects. CHEO and the staff investigator will be promptly available for treatment of any complication that I/my child may have. I am aware of the alternative treatments for my/my child’s condition. I know that the participation in this trial is voluntary, and if at any point during the trial I/my child decides to withdraw, this will not change the quality or intensity of care that I and my family has received at CHEO. The records of the participants will be kept confidentially and no information disclosing my/my child’s identity will be done without my authorization, except if required by law.

I acknowledge that all necessary information, including that written in this consent, was explained to me/my child, and that it was sufficient for my decision. Patient/parents/investigators are satisfied that the necessary information was given to the child, who was able to understand it, and the child assents to participate in this study.

I received a copy of this informed consent.

_____	_____	_____
Participant/legal guardian – Print name	Signature	Date
_____	_____	_____
Witness – Print name	Signature	Date

Person who obtained the consent

Signature

Date

Appendix 4.4 Assent form

Study: Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial of efficacy and safety

Investigator

Dr Luis Guerra.

(Paediatric urologist - Children's Hospital of Eastern Ontario)

Phone: (613) 737-7600 x1353

Invitation

You are invited to participate in a study that your doctor and CHEO are doing. You don't need to participate if you do not want, and nobody will force you or will be upset if you decide not to participate. This study is about a new treatment.

Why are we doing this study?

Because sometimes, the medicine that you are taking to control your bladder does not work well. When the medicine does not work well, the pressure inside your bladder goes high and this is bad for the bladder. There is a different treatment but we are not sure if it works well. The study will help us to find if this treatment really works.

Who is doing the study?

Dr Luis Guerra is the principle investigator responsible for the study and he will work together with other physicians and nurses. If you have any question call him at (613) 737-7600 x1353

What if I decide not to participate?

You decide if you want to participate or not. Nobody will force you or will be upset if you decide not to participate. Your doctor and nurses will continue to take care of you and CHEO will continue to be your hospital. You should ask all your questions of your doctor and nurse before decide. Talk also to your parents and ask them what they think.

What if I change my mind?

If you decide to enter in the study and later on you change your mind, there is absolutely no problem. Your doctor and nurses will continue to take care of you. Nobody will be disappointed with you.

What is happening with my bladder?

You are taking a medication to control the pressure inside your bladder, but this pill has not worked well. We need to change your treatment. There is a new treatment, but we need to do this study to find out if this new treatment works well.

How the study is done?

There are two different treatments that we will use in this study. One treatment is a pill like the one your are taking now but a bit stronger, and the other one is a solution that is injected inside the bladder.

To inject the solution with the medication you will use the same catheter that you use to empty your bladder. Two times per day, after you have emptied your bladder, you will inject the solution with the medication.

Two exams are done during the study, ultrasound and urodynamics, those that you are used to do.

Is there any problem or risk with this treatment?

The risks with this treatment are very small. You have been using the same medicine used for the study, and we know that it did not make you feel sick. But if during the study you feel any discomfort or feel uneasy, you should tell your parents, and they can talk to us.

Will I get better taking the treatment of the study?

We cannot answer this question, and that is the reason we need to do the study. We want to know if you and children like you could get better with this treatment.

Can I have another different treatment?

Yes, there are few other medications that we could try, but the one that your are taking now is considered one of the best treatments.

Will I know which treatment is better?

Yes, you can ask your doctor at the end of the study and he will tell you which treatment worked better in this study.

Should I decide today?

No, you can decide when you feel that you understand. You should talk to your parents and ask their opinion.

Emergency contact: Dr Luis Guerra or the urologist on call,
Phone 7377600 x0 (24 hours a day, seven days a week)

I agree to participate in the study

Name of participant

Signature

Date

Appendix 4.5 General data form

Study: Intravesical oxybutynin for poorly compliant neurogenic bladder

Name:			
ID:	Date of visit:		Number of visit:
Age:	Sex:		Weight:
Neurologic diagnosis			
Urologic diagnosis			
Ambulatory status	Wheel chair bound		Ambulatory
Previous dose -oral oxybutynin	mg/day		mg/kg/day
Intervention randomized:	Intravesical oxybutynin		Oral oxybutynin
Dose during the trial:			
Compliance w/ intervention:	Yes	No	Percent of compliance:
Bowel movement-2 to 3 days	Yes	No	Doing bowel protocol?
Withdraw	Yes No Reason-		
Dropout	Yes No Reason-		
Complications:	Yes No Which?		
Comments:			
Assessor name and date:			

Please circle the options

Appendix 4.6 Data extraction form - Outcomes

**Study: Intravesical oxybutynin for poorly compliant neurogenic bladder
Randomized, controlled clinical trial**

Name:					
ID:					
Visit number:			Visit date:		
	Baseline		Follow up		
Outcomes	Value	Unit	Value	Unit	
Primary					
Bladder compliance		mL/cmH2O		mL/cmH2O	
Secondary					
TBC		cmH2O		cmH2O	
DPTBC		cmH2O		cmH2O	
DLPP		cmH2O		cmH2O	
	Number	Intensity	Number	Intensity	
Overactivity					
	Yes/No	# per month	Yes/No	# per month	
UTI					
Incontinence					
Hydronephrosis		N/A		N/A	
Comments					
Assessor name and date:					

Appendix 4.7 Data collection form - Harms

**Study: Intravesical oxybutynin for poorly compliant neurogenic bladder
Randomized, controlled clinical trial**

Name:				
ID:				
Visit number:			Visit date:	
Harms	Yes	No	Severity scale	Number per month
Dry mouth				
Facial flush				
Intolerance to heat				
Dizziness				
Blurred vision				
Constipation				
Headache				
Bad dreams/ difficulty sleeping				
	Yes	No	Reason	
Withdrawal				
Dropout				
Comments:				
Assessor name:				

Appendix 4.8 Urodynamics standardized technique

Study: Intravesical oxybutynin in children with poorly compliant neurogenic bladder: randomized, controlled, clinical trial of efficacy and safety

Definition

The urodynamics (UDS) provides a physiologic assessment of the bladder function. It evaluates the bladder ability to store and to empty urine, and the urethral sphincter function.

Machine: Dorado Urodynamics System from Laborie®

Setting

Setting For paediatric UDS, the setting is very important. The environment should be calm. Toys and movies usually make the child relaxed and compliant with the test. The staff should be well trained and friendly, and the child should be laid on his/her back.

Catheterizations

Urethral: A small 2-channel urethral catheter (6 or 7 Fr) is inserted gently through the urethra using a lubricant. The younger the child the thinner the catheter used. Ideally, it should go smoothly without catches or bleeding. The bladder is emptied and the catheter could be fixed at the upper portion of the thigh.

Rectal: A 10 Fr plastic catheter is introduced 5 cm in the rectum. A water balloon or an open-end catheter can be used to monitor the abdominal pressure.

Electromyograph

Two skin electrodes are attached to the perineum at 3 and 9 o'clock position around the anus. A ground electrode is attached to the upper thigh. This device records the audio and graphical electrical activities of the pelvic floor muscles and estimates the activity of the external urethral sphincter. The urethral sphincter activity can be estimated during the filling and voiding phase of the UDS.

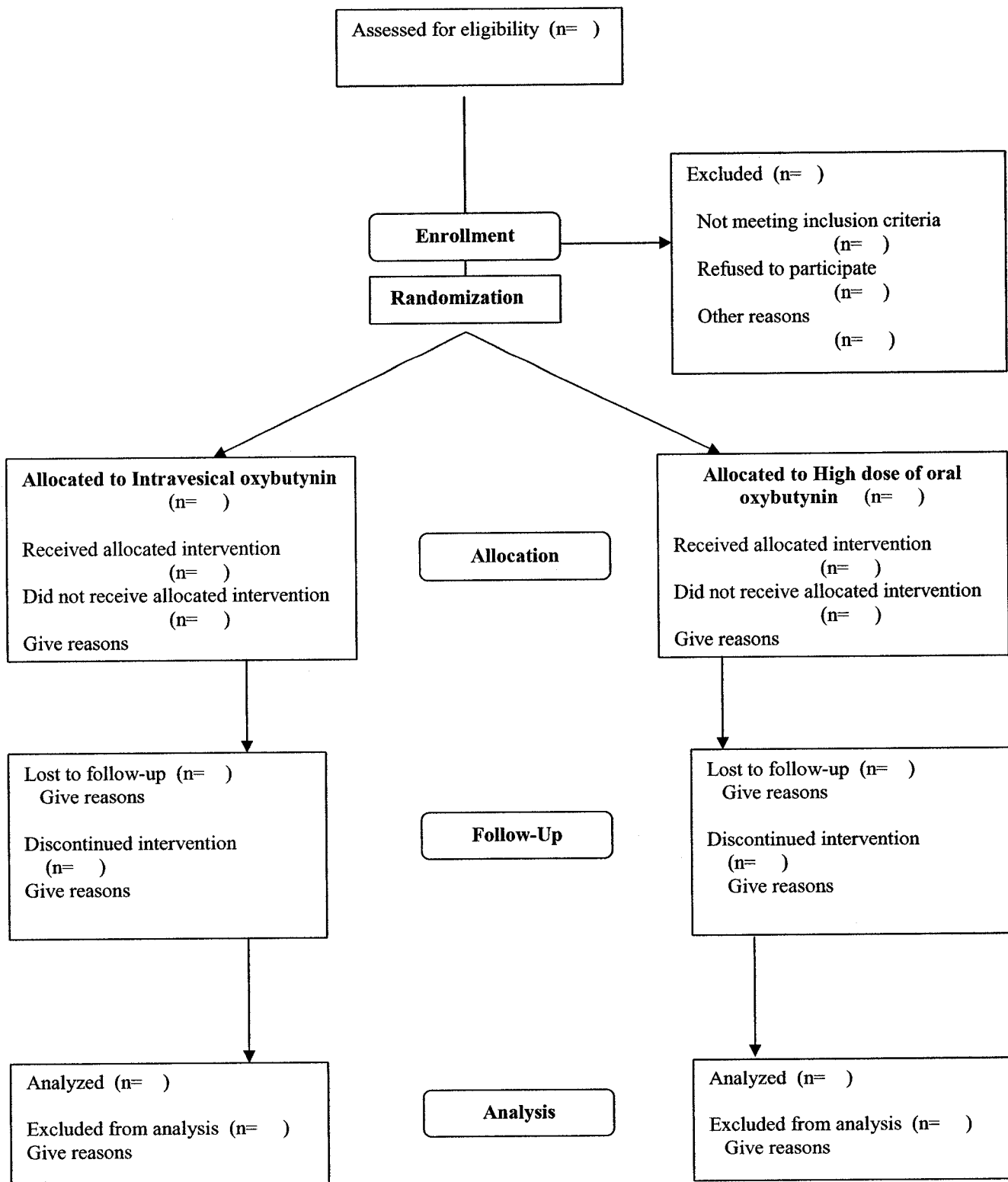
Filling phase

Ambient temperature or warm sterile water should be infused at a physiologic filling rate that is calculated by the formula: body weight in kg divided by 4, expressed in ml/minute.(40) Bladder storage function should be assessed with regards to bladder sensation, detrusor activity, bladder capacity and bladder compliance.(130)

Voiding phase (pressure-flow study)

For those children with neurogenic bladders, who are able to void spontaneously, a voiding phase of UDS can be obtained. This can be accomplished by means of a child with a full bladder voiding in a special toilet with an electronic scale collecting the urine. A graphic record will show the urine flow and detrusor pressure simultaneously, allowing the assessment of the voiding patterns. The electromyography records the urethral sphincter activity during the pressure-flow

Appendix 4.9 The Consort Flowchart



Appendix 4.10 Checklist of side effects (harms)

**Intravesical oxybutynin in children with poorly compliant neurogenic bladder:
randomized, controlled, clinical trial of efficacy and safety**

You should note that some symptoms you/your child may feel during the period of the treatment may not be related to the treatment itself, but it is important to mark them on this checklist. Mild uneasiness or vague symptoms that were present before the start of this treatment may not be related to the treatment as well but is important to let us know. Mark the date and time, each time you feel any of the symptoms, even if the same symptom recurs.

It is important to mark only the symptoms that you have had since last visit to clinic.

Dry mouth (persistent dry mouth not improving after a drink of water)	Yes	No
Dizziness (feeling that you would faint)	Yes	No
Blurred vision (sensation of weak visual accommodation)	Yes	No
Facial flushing (check reddishness)	Yes	No
Intolerance of heat (feeling extremely uneasy on hot days)	Yes	No
Constipation (more than 3 days without a bowel movement)	Yes	No
Headache	Yes	No
Unusual difficulty sleeping or bad dreams	Yes	No

Please mark below the dates and numbers of times you felt the above symptoms.

Date / time	Symptom
Please indicate here if you have had any other symptoms that were not on this list	

(Use extra page if necessary)

Appendix 4.11 Assessment of intensity of side effect (harm)

Visual analogue scale

Study: Intravesical oxybutynin for poorly compliant neurogenic bladder

You are participating in a study in which oxybutynin is used to treat neurogenic bladder with high pressure. We ask you to grade the severity of any possible side effects.

This scale is to tell us how intense or bad the side effect was. Please mark the number below for each side effect that you may feel as follows:

“0” A very mild symptom that did not disturb your normal activities such as going to School, play with friends, watch television, etc.

“5” Moderate symptom that disturbed your normal activities

“10” A symptom that was extremely severe and not compatible with normal life, usually bringing you to the emergency department of a hospital.

Note: “normal activity” means that you: go to school, play with your friends, do your homework, watch television, are happy and communicative.

Please circle the any number between “0” and “10” that reflects how bad (severe) the side effect was.

If you did not feel any of these side effects below, please leave them blank.

Dry mouth (persistent dry mouth not improving after a drink of water)

No 0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Facial flushing (flushing the cheeks)

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Intolerance to heat (feeling extremely uneasy on hot days)

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Dizziness (feeling that you would faint)

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Blurred vision (sensation of weak visual accommodation)

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Constipation (more than 3 days without a bowel movement)

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Headache

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

Bad dreams or difficulty falling asleep

0 1 2 3 4 5 6 7 8 9 10
Mild Moderate Severe

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