Intravesical Oxybutynin for Children With Poorly Compliant Neurogenic Bladder: A Systematic Review

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Purpose: Children with neurogenic bladder and poor bladder compliance are usually treated with bladder catheterization and oral anticholinergic medication. They may become nonresponders to the drug or present with severe side effects. We evaluated the effectiveness and tolerability of intravesical oxybutynin in children with poorly compliant neurogenic bladder.
Materials and Methods: We conducted a search of MEDLINE®, EMBASE®, CINAHL®, SciELO, dissertations/theses in ProQuest®, LILACS, the Cochrane Library, protocol registries and the gray literature. Two reviewers independently assessed study quality and extracted data.
Results: Eight studies (2 prospective, 6 retrospective) assessed the effectiveness and side effects of intravesical oxybutynin in children with neurogenic bladder. A total of 297 children started treatment, of whom 22% (66 patients) discontinued therapy, with 9% (28) quitting due to systemic side effects. Mean change in bladder compliance (primary outcome) was reported in only 2 studies (+7.4 and +7.5 ml/cm H_2O). The pooled mean change in pressure at maximum bladder capacity was −16.4 cm H_2O (95% CI −22.8 to −10.0). Incontinence improved significantly in most studies, with "dry and improved" rates ranging from 61% to 83%. The funnel plot of pressure at maximum bladder capacity suggested no publication bias.
Conclusions: Adjunctive intravesical oxybutynin therapy increased mean maximum bladder capacity and decreased bladder pressure in children with neurogenic bladder. However, identified studies offered a low level of evidence, with most being poorly reported retrospective case series with potential biases. Although the incidence of side effects was lower with the intravesical route, side effects are still possible and should be discussed with patients and families. The evidence available is insufficient to recommend this therapy. Research of more sound study design such as a randomized controlled trial should be conducted to assess the efficacy and side effects of intravesical oxybutynin in children.

Key Words: administration, intravesical; child; oxybutynin; review literature as topic; urinary bladder, neurogenic

Children with various types of lesions in the spinal cord can present with neurogenic bladder, a condition in which the bladder partly or completely loses its ability to store urine and to void at low pressure. A poorly compliant bladder may cause urinary incontinence, which impacts negatively on quality of life.[1] In the long term a high pressure neurogenic bladder poses risks to the kidneys.

Children with neurogenic bladder are usually treated with intermittent bladder catheterization and oral anticholinergic drugs, with oxybutynin being the most commonly used. A number of these children may become nonresponders to the drug, or may present with significant side effects such as dry mouth, facial flushing, dizziness and constipation. To overcome these problems, an alternative regimen is the combination of intravesical and oral oxybutynin, which can improve effectiveness while minimizing side effects. Transcutaneous use of oxybutynin is an alternative way of delivering the drug, and it also decreases undesired anticholinergic effects.

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Objectives and Outcomes

The objective of this review was to evaluate the effectiveness and safety of intravesical oxybutynin in children younger than 18 years with poorly compliant neurogenic bladder who had an unsatisfactory response to oral oxybutynin (became refractory to oral oxybutynin or discontinued the oral drug due to side effects). The primary outcome was bladder compliance. Secondary outcomes were MBC, detrusor pressure at MBC, DLPP, neurogenic detrusor overactivity, UTI, episodes of urinary incontinence and side effects (dry mouth, blurred vision, dizziness, constipation).

Eligibility Criteria

Studies were considered relevant if they met the following inclusion criteria. Study design included RCTs, nonrandomized controlled trials, quasi-experimental studies and noncomparative case series. Participants included children younger than 18 years with poorly compliant neurogenic bladder that was refractory to oral oxybutynin or who had experienced severe side effects. Interventions included oxybutynin instilled into the bladder, with or without oral oxybutynin. Exclusion criteria consisted of case-control studies, age 18 years or older, intravesical treatment using a drug other than oxybutynin and animal studies.

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Search Strategy for Identification of Studies

The databases that were searched included MEDLINE (1966 to July 2007), EMBASE (1980 to week 39, 2007), the Cochrane Library (1981 to July 2007), CINAHL (1982 to July 2007), SciELO (1997 to July 2007), ProQuest Nursing and Allied Health Source (1961 to July 2007) and LILACS (1982 to July 2007). The search was restricted to articles published in English. Search strategy consisted of the search terms 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.rn.; 7) (oxibutinin or oxybutinin).mp.; 8) or/5-7; 9) Administration, Intravesical/; 10) intravesical.tw.; 11) 8 and (9 or 10); and 12) 4 and 11.

Specialized journals and relevant conference proceeding abstracts were hand searched. Reference lists of the retrieved articles were reviewed for additional relevant citations. Corresponding authors and drug industry representatives were contacted to obtain additional information. Two clinical trial registries were searched for studies on intravesical oxybutynin, namely "ClinicalTrials" (www.clinicaltrials.gov) and "Controlled-trials" (www.controlled-trials.com).

METHODS

All potentially relevant records were imported into an electronic database (RefWorks®). Two assessors screened the records independently to exclude those considered irrelevant. Full copies of potentially relevant records were obtained and a more focused screening excluded additional documents.

Assessment of Quality and Data Collection

Two reviewers independently assessed the quality of reports of the included studies. Noncomparative case series were evaluated using a quality assessment instrument developed for this study, including criteria used on previous published instruments.[2–4] A calibration exercise using 3 separate studies was conducted before quality assessment. Any unresolved disagreement between the reviewers was submitted to a third expert opinion and decided by consensus. This report follows the Quality of Reporting of Meta-Analyses statement guidance.[5] Authors were contacted to obtain missing information.

Assessment of Heterogeneity and Publication Bias

Heterogeneity was assessed graphically by examining the forest plot and statistically using the I^2 test.[6] We evaluated clinical heterogeneity by looking at parameters such as population characteristics and methods of administration of the intervention. Publication bias was assessed visually using a funnel plot.[7]

Data Analysis

Effectiveness was assessed based on the change in bladder compliance, MBC and detrusor pressure at MBC. Tolerability and side effects were evaluated as functions of compliance with treatment. Meta-analysis using weighted mean difference (random effects model) was conducted using Cochrane RevMan® software, version 4.2.

RESULTS

Literature Search

Electronic searching identified 739 records, of which 38 were identified for a closer examination after obtaining hard copies. Eight studies met the inclusion criteria and were included in this review (fig. 1).[8–15] The reasons for study exclusion were age older than 18 years (9 studies), language other than English (6), assessment of different outcomes (6), review or editorial articles (3) and failure to meet the inclusion criteria (6). The hand search of specialized journals, reference lists of the articles retrieved and protocol registries uncovered no study that met the inclusion criteria.

Study Characteristics and Quality Assessment

The general characteristics of the studies are outlined in table 1. Seven studies were retrieved from the journal literature and 1 was a thesis manuscript. No RCT was identified. Ferrara et al[14] compared intravesical to oral oxybutynin, and this was the only study using a comparison group. All 8 studies used the same inclusion criteria that were used for this review. Intervention, dose and means of administration were reported in detail in almost all studies. Although side effects were well reported, several articles did not include or were unclear about the results of primary and some secondary outcomes.

Population and Intervention Characteristics

A total of 297 children were treated with intravesical oxybutynin. Patient gender, age and clinical diagnoses are outlined in table 1. Participants included in the studies received a mean dose of 10 mg oxybutynin daily instilled into the bladder with a urethral catheter. The duration of treatment across studies varied from 3 to 36 months. Only Buyse[13] and Guerra[15] et al used a pharmacy prepared oxybutynin solution. In all other series patients used crushed pills diluted in sterile water.

Outcomes

Mean change in bladder compliance was reported by Ferrara[14] and Guerra[15] et al, and improved 88% and 260%, respectively. Mean change in bladder compliance was calculated for the study by Kaplinsky et al,[11] and improved 370% (table 2).

Most studies included pre-intervention and post-intervention mean values of MBC and pressure at MBC (table 3). There was moderate inconsistency across the studies for MBC (I^2 = 62%) and pressure at MBC (I^2 = 69%). The pooled mean difference for MBC showed an improvement of 78 ml (95% CI 55.7 to 103.7). The pooled mean difference for pressure at MBC demonstrated an improvement of −16 cm H_2O (95% CI −22.8 to −10.0, fig. 2).

Ferrara[14] and Guerra[15] et al reported on DLPP, and both groups found statistically significant improvements. Detrusor neurogenic overactivity improved in 33% to 77% of the patients across studies. Detrusor-sphincter dyssynergia was

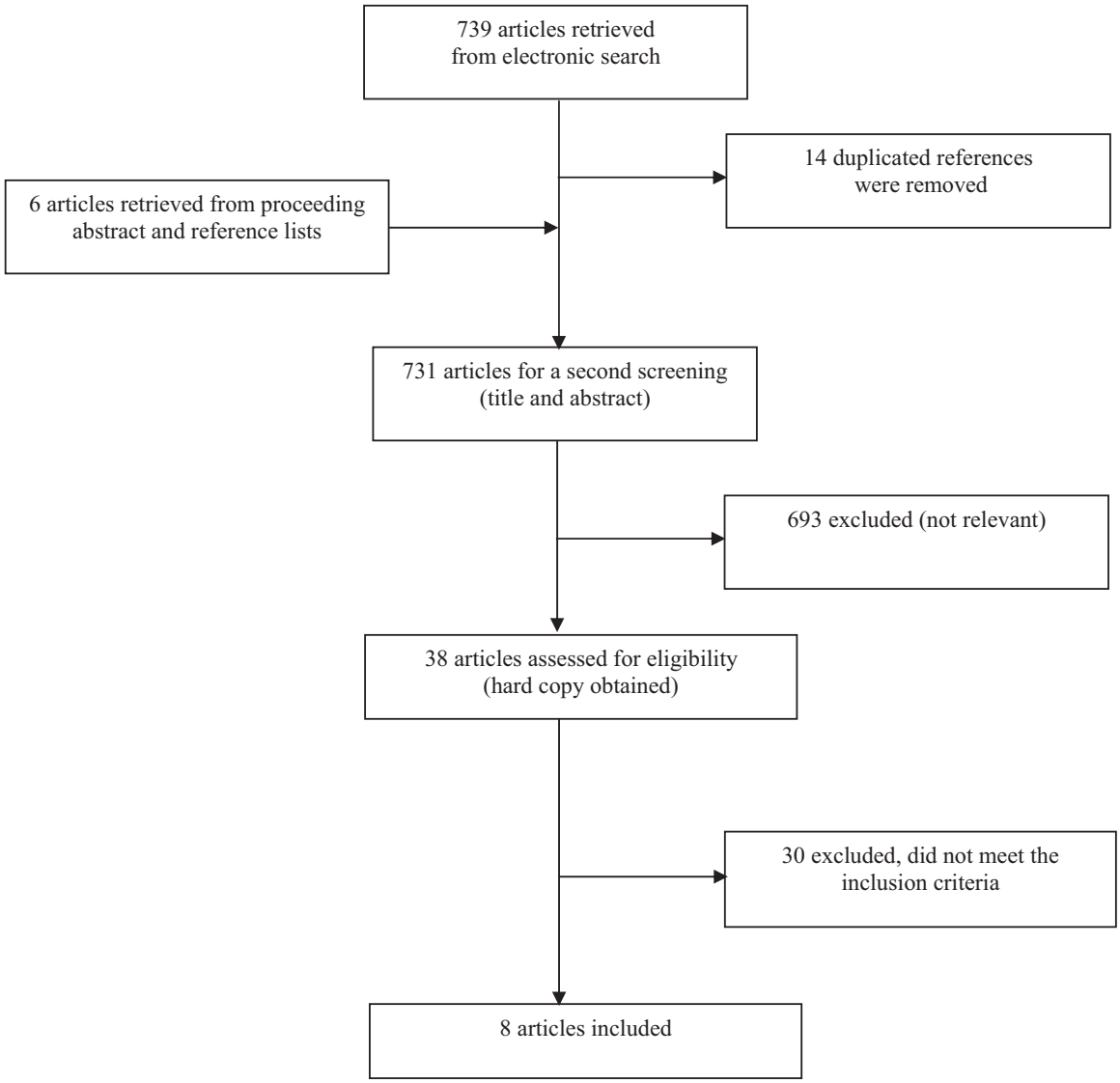

FIG. 1. Quality of Reporting of Meta-Analyses flow chart of excluded and included articles

addressed only by Buyse et al, who observed the condition in 11 children but did not report the change after treatment.[13] Incontinence and improvement in UTI are outlined in table 4. The percentage of patients "continent and improved" after treatment ranged from 36% to 83%.

The most commonly reported side effects were those secondary to the anticholinergic effect on the muscarinic receptors, namely dry mouth, facial flushing, constipation, blurred vision and orthostatic hypotension or dizziness (table 5). Constipation secondary to or worsened by intravesical oxybutynin was not reported as a common occurrence in most studies.

A total of 297 children were initially treated with intravesical oxybutynin, of whom 22% (66) discontinued treatment, leaving 231 patients for analysis. Side effects were responsible for 9% of the discontinuations (28 patients), and the most common effects were those secondary to anticholinergic effects. "Other causes" were responsible for 13% of the withdrawals (38 patients), with the most frequent being inconvenience of the procedure, including crushing the oxybutynin pills to prepare the solution. Among the 66 patients who discontinued therapy, side effects and "other causes" were responsible for 42% (28 patients) and 58% (38) of the discontinuations, respectively. A graphical assessment of publication bias revealed little asymmetry when examining pressure at MBC (data not shown).

DISCUSSION

Most studies failed to include data on bladder compliance. Since it was largely unreported, no inference could be made about the effectiveness of this intervention based on bladder compliance. However, since pressure at MBC is an important clinical indicator of kidney safety,[16] it was elected as the outcome for the assessment of effectiveness, and the pooled estimate demonstrated a statistically significant improvement of –16 cm H_2O. This improvement may be a result of the antimuscarinic action on the cholinergic receptors and the local analgesic effect on the sensitive C fiber afferents in the detrusor.[17]

In general, a marked improvement in urinary incontinence was reported, with most studies having high "dry and

TABLE 1. *Population demographics, clinical diagnosis and intervention characteristics*

	Greenfield and Fera[8]	Connor et al[9]	Kasabian et al[10]	Kaplinsky et al[11]	Painter et al[12]	Buyse et al[13]	Ferrara et al[14]	Guerra et al[15]
Sex:								
M	7	9	Not reported	15	18	6	Not reported	31
F	3	4	—	13	12	9	—	31
Mean yrs age (range)	Not reported (4–18)	8.7 (1–18)	7.7 (4–12)	Not reported (3–18)	8.6 (1–17)	6.1 (0.3–14)	4.2 (0.25–10)	9.5 (2–17)
No. clinical diagnosis:								
Myelomeningocele	9	28	11	27	42	12	101	47
Imperforate anus	1	0	0	1	0	0	0	0
Lipomyelomeningocele	0	0	0	0	0	1	0	6
Caudal dysplasia	0	0	0	0	0	1	0	1
Spinal cord injury	0	0	0	0	0	1	0	2
Sacral agenesis	0	0	0	0	0	0	0	2
VATER syndrome*	0	0	0	0	0	0	0	1
Tethered cord	0	0	0	0	0	0	0	1
Myelitis	0	0	0	0	0	0	0	1
Trisomy	0	0	0	0	0	0	0	1
Assessment objective†	Effectiveness	Continence, effectiveness, bladder compliance	Effectiveness	Unclear (effectiveness, long term)	Long-term effect on MBC, pressure at MBC, continence	Effectiveness, harms, treatment compliance	Harms/efficacy between oral/ intravesical oxybutynin	Effectiveness, harms
Study group (intravesical oxybutynin):								
No. pts	10	28	11	28	42	15	67	62
Dose	10 mg/day	10 mg/day	10–20 mg/ day	10 mg/day	10 mg/day	0.2 kg/day	0.1–0.2 kg/day	10 mg/day
Time left in bladder	Until next CIC	Not reported	30–180 Mins	Until next CIC	Until next CIC	Not reported	Not reported	Until next CIC
Control group (oral oxybutynin):								
No. pts.	0	0	0	0	0	0	34	0
Dose	—	—	—	—	—	—	0.1–0.2 mg/kg/ day	—
Treatment duration (mos)	3	6.5	6	35	13	24	36	6

* Vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.
† Effectiveness was measured as maximum bladder capacity and pressure at maximum bladder capacity.

improved" rates. Urinary continence improves quality of life in patients with neurogenic bladder.[18] However, this perspective was not addressed by the studies.

Although the optimum dose for intravesical instillation has not been determined, published studies suggest that an oral dose of 0.2 mg/kg daily can be safely used intravesically.[19,20] Haferkamp et al reported improved urodynamics and urinary continence as the intravesical dose was increased from 0.3 to 0.9 mg/kg daily, with no significant increase in side effects.[21] Most studies in this review used 0.2 mg/kg daily (average 10 mg daily), and recommended leaving the drug in the bladder until the "next catheterization" or "3 to 4 hours." However, this approach does not appear to influence the effectiveness (or reported side effects) of the drug.[22] There was no specific recommendation for the timing of followup urodynamics. At our institution we routinely use 0.2 to 0.3 mg/kg daily intravesically, divided into 2 or 3 instillations, and urodynamics are repeated at least 3 months after starting this regimen.

Six of the 8 studies reviewed (75%) used intravesical oxybutynin in the form of diluted crushed pills in sterile water. However, "inconvenience of the procedure" was indicated in 4 studies as being the cause of dropout from the treatment, and it was responsible for 68% of all dropouts (26 of 38) not related to side effects. Although not on the market, the prepared solution (154 mEq/l purified oxybutynin and sodium chloride dissolved in sterile water, 5 mg/5 ml and pH 5.85) used by Buyse[13] and Guerra[15] et al makes the process

TABLE 2. *Bladder compliance change after treatment with intravesical oxybutynin*

References	Before Treatment (mean ml/cm H_2O ± SD)	After Treatment (mean ml/cm H_2O ± SD)	Change (mean ml/cm H_2O ± SD)	% Mean Change
Greenfield and Fera[8]	Not reported	Not reported	Not reported	Not reported
Connor et al[9,*]	Not reported	Not reported	Not reported	Not reported
Kasabian et al[10]	Not reported	Not reported	Not reported	Not reported
Kaplinsky et al[11]	2.0	9.4	7.4	370
Painter et al[12]	Not reported	Not reported	Not reported	Not reported
Buyse et al[13]	Not reported	Not reported	Not reported	Not reported
Ferrara et al[14]	8.5 ± 6.1	16.0 ± 11.0	7.5	88
Control group (oral oxybutynin)	8.1 ± 6.3	14.8 ± 11.6	6.7	83
Guerra et al[15]	5.3 ± 3.7	19.3 ± 45.1	13.8 ± 44.65	260

* Of 13 patients 12 had improvement but no values were given.

TABLE 3. *Changes in MBC and pressure at MBC after treatment with intravesical oxybutynin*

References	Before Treatment	After Treatment	Mean Change	% Mean Change
	Max bladder capacity (mean ml ± SD)			
Greenfield and Fera[8]	Not reported	Not reported	10–140	11–335
Connor et al[9]	Not reported	Not reported	Not reported	41
Kasabian et al[10]	159.3 ± 113.4	246.0 ± 128.70	86.7 ± 19.7	54.4
Kaplinsky et al[11]	99.7 ± 85.5	199.6 ± 97.3	99.9 ± 25.7	100.0
Painter et al[12]	209.0 ± 103.0	282.0 ± 148.0	73.0 ± 28.5	34.9
Buyse et al[13]	114.0 ± 54.7	214.0 ± 78.1	100.0 ± 25.7	87.7
Ferrara et al[14]	132.0 ± 103.0	226.0 ± 118.0	94.0 ± 12.7	71.2
Control group (oral oxybutynin)	128.0 ± 107.0	214.0 ± 110.0	86.0 ± 15.7	67.2
Guerra et al[15]	200.5 ± 100.5	243.6 ± 118.9	43.1 ± 10.7	21.5
	Pressure at max bladder capacity (mean cm H_2O ± SD)			
Greenfield and Fera[8]	Not reported	Not reported	−15–−75	−33–−66
Connor et al[9]	Not reported	Not reported	Not reported	−47
Kasabian et al[10]	47.3 ± 22.5	36.6 ± 21.4	−10.7 ± 6.25	−22.6
Kaplinsky et al[11]	60.1 ± 31.8	35.6 ± 20.0	−24.4 ± 6.31	−31
Painter et al[12]	63.0 ± 24.0	56.0 ± 31.0	−7.0 ± 2.84	−11.1
Buyse et al[13]	57.0 ± 25.6	30.8 ± 15.8	−26.2 ± 6.75	−46.0
Ferrara et al[14]	53.0 ± 30.0	34.0 ± 11.0	−19.0 ± 2.4	−35.8
Control group (oral oxybutynin)	49.0 ± 28.0	30.0 ± 13.0	−19.0 ± 2.9	38.8
Guerra et al[15]	47.7 ± 25.6	34.4 ± 22.9	−13.3 ± 3.5	−29.1

easier and more convenient. This solution can be readily prepared in pharmacies, and it may enhance compliance with treatment. The concern that the glucose contained in the syrup form of oxybutynin available for oral use may promote bacterial growth and infection led some centers to use crushed pill.[8] However, the pharmacy prepared solution is easier to use and is sugar-free.

Length of treatment ranged from 3 to 36 months across the studies. Kaplinsky et al believe that the pharmacological effect is durable in patients with an initial response on urodynamics, and in their experience MBC markedly increases during extended followup.[11] On the other hand, Painter et al observed only a 53% durable long-term response.[12]

Neurogenic detrusor overactivity improved from 33% to 77% in the reviewed studies. 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 activation. Detrusor-sphincter dyssynergia and DLPP were addressed in only 1 and 2 studies, respectively, and there was insufficient information to draw conclusions.

It has been reported that oxybutynin has an anticholinergic effect on the intestinal muscle fibers,[23] and that this effect is also observed in patients with bladder augmented with gastrointestinal segments.[24] However, there are no clinical trials addressing this issue in children.

Our results indicate that 22% of the participants (66 of 297) discontinued intravesical therapy, with 9% (28) withdrawing secondary to systemic side effects. The incidence of side effects with the intravesical route was lower than the published incidence with oral administration, in keeping with the rationale for its use. Weese et al reported that the published incidence of significant side effects with oral therapy ranges from 57% to 94%.[25] N-desethyl oxybutynin is the first pass hepatic metabolite of oxybutynin, and it is associated with anticholinergic effects. Avoiding the oral route with drug absorption via the portal venous system decreases this problem. However, even when it is administered intravesically side effects are still possible, probably secondary to drug absorption through the bladder mucosa.[26]

Pharmacokinetic studies have revealed adequate plasma levels for different formulations of oxybutynin, and its plasma half-life is approximately 2 hours.[27] Amark et al reported that a mean intravesical dose of 0.1 mg/kg is associated with minimum plasma levels of 0.3 to 7.2 ng/ml for oxybutynin and 0.8 to 14 ng/ml for its metabolite N-desethyl oxybutynin.[19] However, there is no clear relationship be-

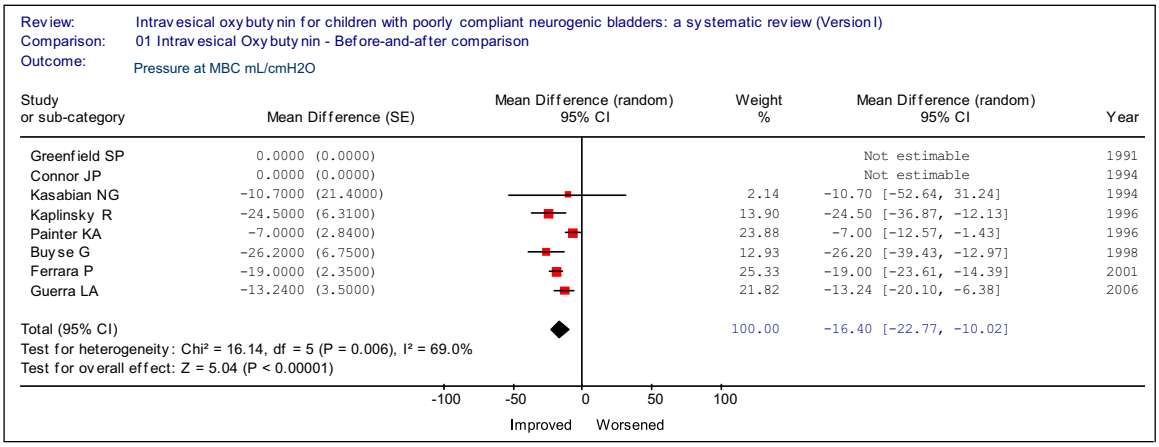

FIG. 2. Forest plot of change in pressure at maximum bladder capacity

TABLE 4. *Urinary incontinence and UTI changes after treatment with intravesical oxybutynin*

References	% Dry or Improved (No. pts/total No.)	Comments	UTI
Greenfield and Fera[8]	80 (8/10)	5 Pts (50%) became completely dry, 3 (30%) became dry during day	Not addressed
Connor et al[9]	61.5 (8/13)	5 Pts (38.5%) became dry, 3 (23%) reported reduction in pads	Not addressed
Kasabian et al[10]	83 (5/6)	5 Pts became continent, 1 (17%) still had minimal incontinence	Not addressed
Kaplinsky et al[11]	81 (17/21)	12 Pts (57%) became dry, 5 (24%) were dry only during day	Not addressed
Painter et al[12]	76 (22/29)	3 Pts (10%) became dry, 19 (66%) decreased pad use	Not addressed
Buyse et al[13]	61.5 (8/13)	8 Pts achieved "social continence" (not defined)	No UTI related to procedure but pretreatment and posttreatment changes were not reported
Ferrara et al[14]	Not reported	Continence was not addressed	69% Improvement in UTI episodes (70% oral, 68% intravesical treatment)
Guerra et al[15]	36 (17/47)	17 Pts became dry between bladder catheterizations ($p < 0.001$)	5 Pts with UTI (36%) had decreased episodes but difference was not significant ($p = 0.58$)

tween plasma levels and their clinical effects. Massad et al compared intravesical to oral oxybutynin in 8 children and found a markedly higher plasma level with intravesical use after 3 hours of administration (14.4 vs 2.76 ng/ml).[26] Transdermal administration of oxybutynin reaches an average maximum plasma level concentration of 3 ng/ml for oxybutynin and 4 ng/ml for N-desethyl oxybutynin.[28]

Although the level of evidence in the literature is low, intravesical oxybutynin exhibits a decrease in detrusor activity, an increase in cystometric bladder capacity and a reduction in detrusor pressure in children with neurogenic bladder.[27] The funnel plot showed a symmetrical distribution around the mean effect, suggesting no publication bias. This surprising finding should be interpreted with caution. This finding may be the result of the small number of studies available to construct the funnel plot, so this interpretation should be tempered by its limitations. This series of studies may have a heterogeneous population, which could bias and threaten the external validity of the conclusions.

Since intravesical oxybutynin is relatively under studied in pediatric urology, the lack of experience with this therapy and the small number of published reports limit the available evidence. Thus, restricting 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 behavior and features, and they should not be analyzed together with adult cases. Although language restriction has been reported as not significantly changing the results of meta-analyses, it is a limitation of this review since, due to constraints of resources, 6 studies published in languages other than English were excluded.

CONCLUSIONS

This systematic review suggests that intravesical oxybutynin is a potential alternative treatment for children with neurogenic bladder refractory to oral oxybutynin therapy, and those who experience severe side effects with oral oxybutynin. In general, this therapy increases mean MBC and decreases pressure at MBC. However, the level of evidence of the studies is low. Therefore, based on the current collected information, there is insufficient evidence to recommend this therapy for children with neurogenic bladder. Research using a more sound study design, such as RCT, should be conducted to assess the efficacy of this intervention in children.

TABLE 5. *Incidence of side effects related to intravesical oxybutynin therapy*

References	Constipation	Systemic Side Effects
Greenfield and Fera[8]	Not reported	"No local or systemic side effect observed"
Connor et al[9]	None observed	1 Pt using home oxygen had significant decrease in partial tension of oxygen and withdrew, 1 had facial flushing, 1 had dry mouth, 1 had hematuria + UTI
Kasabian et al[10]	None observed	1 Pt had facial flushing, 1 had dry mouth, 1 had hematuria + UTI
Kaplinsky et al[11]	2 Pts had severe constipation but were also taking oral oxybutynin	7/21 Pts (33%) had anticholinergic side effects (dry mouth, dizziness, constipation, hyperactivity, seizures)
Painter et al[12]	Not reported	"No patient had systemic side effects"
Buyse et al[13]	None observed	7 Pts had intolerable side effects of oral oxybutynin which resolved in 3, 4 had only minimal facial flushing + xerostomia, 1 had transient supraventricular tachycardia that started shortly after beginning intravesical therapy but did not recur after reintroduction
Ferrara et al[14]	None observed	11 Pts in oral oxybutynin group (facial flushing in 4, facial flushing + fever in 2, dry mouth in 1, dry mouth + fever in 1, vomiting in 1, diplopia in 1, mydriasis-caumesthesia in 1) 6 Pts in intravesical oxybutynin group (facial flushing in 1, drowsiness + facial flushing in 2, cognitive effects such as attention deficit disorder/difficulty with basic math operations in 2, hallucinations in 1)
Guerra et al[15]	22 Pts had constipation before therapy, 26 had constipation after therapy (difference not significant)	Abdominal discomfort in 1 pt, difficulty with urethral catheterization with some bleeding in 2

Abbreviations and Acronyms

CIC = clean intermittent catheterization
DLPP = detrusor leak point pressure
MBC = maximum bladder capacity
RCT = randomized controlled trial
UTI = urinary tract infection

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