Long-term effect of conservative treatment versus low threshold endoscopic desobstruction on urine incontinence and urgency in boys with persistent overactive bladder symptoms: A cohort study

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AIMS: To assess the long-term effects of two treatment strategies (low threshold endoscopic desobstruction vs. conservative treatment) on urinary incontinence (UI) and urgency-frequency in boys.

METHODS: Boys with persistent overactive bladder symptoms treated in two tertiary referral centers between 2006 and 2009 were included. Treatment strategy in center 1 was urethrocystoscopy (UCS) and in case of obstruction urethral desobstruction and in center 2 conservative. The primary outcome was time to being dry during daytime, secondary outcomes were being dry both day and night and presence of urgency-frequency, using the “provisional” International Consultation on Incontinence Questionnaires Children’s Lower Urinary Tract Symptoms (LUTS) questionnaire.

RESULTS: Median age at start of treatment was 8.0 (IQR 6.4-9.4) years in center 1 and 8.4 (IQR 6.0-10.1) years in center 2. At baseline daytime incontinence was present in 100/104 children (96%, center 1) and 37/44 (84%, center 2). In center 1, UCS was performed in 98 (93%) boys, with desobstruction in 93 (88%), while in center 2 these numbers were 16 (36%), and 5 (11%). There were no differences between groups after a mean follow-up of 5 years concerning dryness at daytime (HR 0.86, 0.56-1.30), dryness day and night (HR 0.72, 0.51-1.14), and presence of urgency-frequency (HR 0.67, 0.38-1.25).

CONCLUSIONS: The benefit of a strategy including low-threshold UCS and endoscopic desobstruction in boys with urge incontinence and suspected infravesical obstruction to prevent LUTS and incontinence on the longer term could not be confirmed.

KEYWORDS
boys, endoscopic treatment, long-term effect, overactive bladder, urethral obstruction

1 INTRODUCTION

Overactive bladder (OAB) complaints with or without daytime incontinence in boys are bothersome. Although reported prevalence varies and have been shown to decline with age urinary incontinence (UI) remains in some boys despite conservative treatment, causing great distress and embarrassment.
Idiopathic detrusor overactivity may be the primary cause of persistent OAB. Alternatively, there is some animal experimental and clinical evidence that a functional or anatomic infravesical obstruction may cause detrusor overactivity.\textsuperscript{3,4} Therefore, treatment of boys with OAB can focus on either treatment of the OAB or on detection and desobstruction in case of anatomic obstruction of the urethra. Since, no consensus has been reached with regard to the importance of (relatively mild) urethral obstructions in boys presenting with persistent OAB, treatment protocols differ between hospitals. In some, low-threshold urethrocystoscopy (UCS) is part of the treatment strategy when infravesical obstruction is likely or cannot be ruled out and in others UCS is not standard in the treatment strategy of boys with persistent OAB. We hypothesized that low-threshold endoscopic desobstruction added to conservative treatment would be more effective than conservative therapy alone.

The purpose of this study is to investigate whether endoscopic desobstruction contributes to a decrease in voiding complaints in terms of UI and lower urinary tract symptoms (LUTS) later in childhood.

2 | MATERIALS AND METHODS

2.1 | Study population

We performed a follow-up study comparing boys referred with persistent OAB between 2006 and 2009 to two Dutch tertiary referral centers, the Wilhelmina Children's Hospital in Utrecht (center 1), and the Sophia Children's Hospital in Rotterdam (center 2). IRB approval for this study was obtained from both institutions. Importantly, in these two centers a clearly distinct treatment strategy has been used since 1980. All patients had a standard intake consisting of voiding and defecation history, physical examination with neurological examination (with special attention to the lumbosacral region), ultrasound (US) of upper and lower urinary tract and uroflowmetry with US measurements of residual urine.

In center 1, boys with OAB in whom infravesical obstruction was likely or could not be ruled out because of presence of signs suggestive of urethral obstruction, UCS, and eventual desobstruction was part of the treatment strategy. Infravesical obstruction was suspected in case of a weak stream, straining, a plateau shaped uroflowmetry, and/or urodynamically high-voiding pressures (>55 cm H\textsubscript{2}O).

Besides UCS, most patients were also treated conservatively consisting of alarm clock therapy, antimuscarinics, urotherapy, or a combination of these. In center 2, most patients were treated conservatively also consisting of alarm clock therapy, antimuscarinics, urotherapy, or a combination of these. UCS was not part of the standard treatment strategy and was only performed when there was a clear indication of urethral obstruction based on plateau shaped uroflowmetry and urodynamic study. The two treatment strategies were clearly distinct with respect to the low threshold performance of UCS and eventual desobstruction in center 1 and high-threshold performance of UCS in center 2.

2.2 | Cohort selection

In both centers, boys treated for OAB between 2006 and 2009 were retrieved using the hospital diagnosis code registration database. To be included, patients with persistent OAB had to be treated conservatively for at least 1 year before referral to one of the two tertiary centers. We excluded patients with conservative therapy <12 months, monosymptomatic nocturnal incontinence, neurogenic bladder disorders, congenital anomalies of the penis (e.g., hypospadias or epispadias), previous UCS, other urologic surgery (e.g., ureteral reimplantation, pyeloplasty), and syndromal disorders and/or mental retardation. Follow-up information from the patients was obtained by contacting parents. Parents were asked by telephone to participate and to sign and return the informed consent form.

2.3 | Patient characteristics and initial treatment

Clinical information was obtained by reviewing hospital records: age, date of first UTI, preoperative diagnostic tests (radiologic imaging), (non) surgical treatment, and post operative complications according to the Clavien Classification of Surgical Complications (CCSC) were recorded. Furthermore, performance of UCS and presence of urethral obstruction was scored retrospectively based on the surgery reports.

2.4 | Outcomes

Parents were asked to fill in a Dutch translation of the “provisional” ICIQ-CLUTS (International Consultation on Incontinence Questionnaire—Children's LUTS) questionnaire, a questionnaire screening for LUTS in children a questionnaire based on the Utrecht Wilhelmina Children's Hospital questionnaire for micturition complaints, and a 24 h frequency voiding chart (FVC).

Our primary outcome measure was being dry at daytime. Secondary outcome measures were being dry day and night and urgency-frequency. Being dry at daytime was defined as no incontinence during daytime and being dry day and night as no incontinence during day and night. Presence of urgency-frequency was defined as either a micturition frequency more than seven times a day and/or urge to go to the toilet most of the time or always. Definitions conform the standards recommended by the International Children's Continence
Society were used except where specifically noted. Information on the primary and secondary outcome was collected through the "provisional" ICIQ-CLUTS questionnaire, the first validated questionnaire to screen for paediatric LUTS developed by the International Conference on Incontinence Questionnaire (ICIQ) Committee (www.ics.org). We applied the definitions recommended by the ICCS, except where specifically noted.

2.5 | Data analysis

Data are presented as medians with interquartile ranges (IQR). Categorized data were analyzed using the chi-square test; continuous data were analyzed using the Mann–Whitney U-test. Cox proportional hazards analysis was used to estimate the relation between the treatment strategies and time-to-being dry. To control for confounding, daytime incontinence status at baseline was included as a covariate in the Cox regression models. In a separate analysis, we performed an analysis in a sub cohort that was matched for age at treatment and age at the moment the questionnaire was filled in to control for dissimilarities (different follow-up time) in the distribution of prognostic patient characteristics between the two centers. Results are presented as hazard ratios with corresponding 95% confidence intervals.

3 | RESULTS

3.1 | Patient characteristics

Of 228 boys treated for persistent OAB complaints from 2006 to 2009 in center 1, 194 (85%) could be traced, 173 (76%) consented to participate, and 105 (46%) patients returned the questionnaires. Of all 86 boys treated for persistent OAB between 2006 and 2009 in center 2, 68 (79%) could be traced, 62 (72%) consented to participate and 44 (51%) patients returned the questionnaires. In total, 149 patients were included: 105 from center 1 and 44 from center 2. UCS was performed in 98 (93%) patients in center 1 with desobstruction in 93 (88%). In center 2, UCS was performed in 16 (36%) boys, with desobstruction in 5 (11%). Thus, not only did we observe a higher percentage of boys subjected to cystoscopy in center 1 compared to center 2 (93% vs. 36%), but also a higher percentage of valves was diagnosed and treated in center 1 compared to center 2 in the boys who underwent cystoscopy (88% vs. 11%). The median age at the start of treatment was 8.0 (IQR 6.4-9.4) years in center 1 and 8.5 (IQR 6.5-10.2) years in center 2. At baseline, any daytime incontinence was present in 101 (96%) patients of center 1 and 37 (84%) patients of center 2. Daytime incontinence was present ≥7 times a week in 70/105 (67%) patients in center 1 compared to center 2 (93% vs. 36%), but also a higher percentage of valves was diagnosed and treated in center 1 compared to center 2 in the boys who underwent cystoscopy in center 1 compared to center 2 (93% vs. 36%). In center 2, UCS was performed in 16 (36%) boys, with desobstruction in 5 (11%). Thus, not only did we observe a higher percentage of boys subjected to cystoscopy in center 1 compared to center 2 (93% vs. 36%), but also a higher percentage of valves was diagnosed and treated in center 1 compared to center 2 in the boys who underwent cystoscopy (88% vs. 11%). The median age at the start of treatment was 8.0 (IQR 6.4-9.4) years in center 1 and 8.5 (IQR 6.5-10.2) years in center 2. At baseline, any daytime incontinence was present in 101 (96%) patients of center 1 and 37 (84%) patients of center 2; daytime incontinence was present ≥7 times a week in 70/105 (67%) patients in center 1 and in 23/44 (52%) patients in center 2. Night-time incontinence was present in 81 (77%) and 40 (91%) of patients in center 1 and 2, respectively. Few clinically important differences existed between patients treated in center 1 and 2. Age at follow-up tended to be higher (0.8 year) and follow-up time was longer in center 2 (1.0 year) (Table 1).

3.2 | Subgroup patient characteristics: wet during daytime at start of treatment

A total of 138 patients were wet during daytime at the start of treatment; 101 patients in center 1 and 37 in center 2. The median age at the start of treatment was 7.8 (IQR 6.4-9.4) years in center 1 and 7.2 (IQR 5.9-10.1) years in center 2. Age at follow-up was 12.7 (IQR 10.8-14.1) in center 1 and 13.1 (IQR 12.0-15.0) in center 2. Of those with any daytime incontinence, daytime incontinence was present ≥7 times a week in 70/101 (69%) patients in center 1 and in 23/37 (62%) patients in center 2.
At the end of follow-up (after a mean duration of follow-up of 4.5 and 5.8 years in centers 1 and 2, respectively), the primary endpoint being dry at daytime was met in 63 out of 101 (62%) patients with daytime incontinence at the start of treatment in center 1 and in 25 out of 37 (67%) of boys with daytime incontinence at the start of treatment in center 2; hazard ratio (HR) 0.86 [0.56-1.30]. The matched cohort included 44 subjects of each center. Within this cohort, centers were comparable with respect to age at baseline (8.2 year center 1, 8.4 year center 2) and age at follow-up (13.3 year center 1, 13.5 year center 2) (Table 2). The abovementioned results for the primary outcome were confirmed in the matched cohort: (HR 0.80 [0.49-1.30]).

Secondary outcomes

Dry both day and night was reported in 78 out of 105 (74%) in center 1 and in 36 out of 44 (82%) of boys in center 2; HR 0.72, 0.51-1.14. Presence of secondary outcome urgency was reported in 38 (36%) of patients treated in center 1 and 15 (34%) of patients treated in center 2. Cox regression analysis HR 0.67 (0.38-1.25) (Table 2).

Frequency voiding chart

A total of 74 patients completed a 24 h FVC, 58 of center 1 and 16 of center 2. No significant differences were found comparing outcomes of FVCs of both groups. Median values of 24 h voided volumes were: total: 1130 mL (IQR 935-1467) and 1100 mL (960-1565), average voided volume 170 mL [IQR 135-216], and 166 mL [IQR 134-240]. The median micturition frequency was 7 [IQR 6-8] in both groups. Eighteen patients (31%) in center 1 reported incontinence versus 2 (12%) in center 2 (Table 3).

DISCUSSION

The main purpose of this paper was to compare two different treatment strategies for boys with persistent OAB symptoms despite conservative treatment. Our analysis shows that on average 5 years after treatment, there was no advantage of the more invasive approach of center 1 which involves cystoscopy in 93% of the patients followed by valve ablation in 88%, compared to the conservative approach of center 2.
involving cystoscopy in 36% and valve ablation in 11%. Idiopathic detrusor overactivity can be the primary cause of persistent OAB complaints. It is hypothesized that a functional or anatomic infravesical obstruction may be the underlying cause of persistent OAB with or without UI. Proving that a (subtle) obstruction plays a significant role in OAB complaints is difficult, but when it does, complaints might resolve after deobstructive treatment and bladder dysfunction at later age may be prevented.

This study is unique because two treatment strategies in two different centers were compared to gain more insight into the effect of a treatment strategy aimed at detecting and deobstructing subtle urethral anomalies to improve OAB complaints in terms of micturition symptoms and UI at follow-up. Our data show that, there was no significant difference with regard to our primary (dry at daytime) and secondary outcomes (dry both day and night and urgency) between both centers at on average 5 years after treatment. It is known that age plays a significant role in the natural course of becoming dry. More precisely, there are thoughts that frontal lobe maturation plays a major role in controlling micturition. Using functional magnetic resonance imaging (fMRI), some studies have reported alterations in several brain functions in patients with urgency and urgency incontinence.

The European Bladder Dysfunction Study showed that besides cognitive treatment, time was the key to success in treatment of OAB in most patients. Testosterone in puberty is responsible for growth of the penis and urethra and may play a role in becoming dry. Age is one of the most important predictors of continence during childhood. Children in center 2, however, were on average almost 1 year older at follow-up compared to the children in center 1, which may bias a direct comparison between centers. To adjust for this potential bias, we took age as the basis (time axis) of our Cox regression model. Results of this analysis were consistent with a separate analysis in which we analyzed subsets of children who were matched according to age at start of treatment and age at the moment the questionnaire was filled in, to adjust for dissimilarities in the distribution of prognostic patient characteristics and follow-up time between the two groups. Other potential confounders (e.g., in center 1 there were relatively more boys who had daytime incontinence) were controlled for in multivariate Cox regression analysis, which did not materially change the results. Nevertheless, results could still be biased due to unmeasured confounders. However, since the most important predictors of daytime continence were controlled for, we consider the potential for such confounding small. Furthermore, in spite of the relatively small number of patients in this study, the estimator of the effect is sufficiently precise to produce reliable outcomes. Although results are similar for both groups, it should be noted that a considerable part of boys in both groups remained incontinent in spite of long-term treatment. Persistence of incontinence despite intensive treatment is consistent with earlier studies. Furthermore, we also found persistence of urgency symptoms in a significant part of the boys at follow-up in both groups. An explanation of persistent incontinence and urgency might be that bladder dysfunction in these boys was not caused by an anatomic infravesical obstruction but rather by a functional obstruction or that there was idiopathic OAB syndrome. Persistence of symptoms might also be caused by irreversible change in bladder function due to anatomic obstruction, lasting after elimination of the obstruction.

Our study has several limitations. It is difficult to determine the lowest threshold of what can be considered a resectable fold or valve. In a previous study involving a panel of 25 pediatric urologists, we tried to find a diagnostic reference standard for posterior urethral valves. In that study, we concluded that when judging cystoscopy results, we found fair to good agreement among pediatric urologists regarding whether a urethral obstruction was present, but also that a true reference standard for urethral obstruction in boys does not seem to exist, and that clinical data and additional diagnostic procedures are needed for diagnosis in most cases. Since this is not a randomized trial, baseline differences between the two comparison groups may bias our findings (confounding). Also, although our interest lies in comparing two treatment strategies, we actually compared centers in which these strategies are implemented. Observed differences (or absence thereof) between centers can then be attributed to differences in the treatment strategy, but may also be the result of differences in other local protocols, expertise of the treating doctor, and care paths around UI. In this study, we compared two tertiary care hospitals, both with trained urotherapists, and therefore we assume that the observed difference in the outcome between centers can indeed be attributed to difference in treatment strategy. Furthermore, group sizes differed in the two centers: the number of treated boys was larger in center 1 than in center 2. However, the response rates were comparable for both centers.

The percentage of available (i.e., traced) parents and children who returned the questionnaires in our study (54.1% and 64.7%, respectively) is comparable to the mean cooperation rate using telephone sampling of 56.5% described by the large KIDSCREEN study. Reasons for not returning the questionnaires were mainly related to other priorities in the family, while the puberty phase of the boys might also have played a role. Particularly motivation to complete the FVC’s appeared to be missing, whereby both above mentioned factors played a major role.

We studied patient files retrospectively. In the files, we searched for short-term post procedural stricture or other complications. In our cohorts we studied the outcome 5 years after treatment by using questionnaires and frequency-volume charts. These questionnaires did not include questions about possible complications within 5 years of
follow-up. In a previous study with longer follow-up, we estimated that at least 4% of young adults over 18 years of age, may have developed urethral strictures after childhood transurethral desobstruction.11

Based on our study results, we can conclude that 5 years after treatment of boys with persistent OAB, there are no major differences in outcome (daytime incontinence, day and nighttime incontinence, or urgency) between a low threshold endoscopic desobstruction treatment strategy and a conservative treatment strategy. It should be emphasized that there may be subgroups in which a more invasive strategy is beneficial, but our study lacked power to detect clinically relevant subgroups. In addition, it cannot be ruled out that a more invasive strategy brings early relief, since we did not measure the short-term effect of the two strategies. Short term relief (6-16 months) after urethral desobstruction in incontinent boys refractory to conservative treatment has been shown in one study: 31% of boys were cured and 37% showed significant improvement.6 However, in that study, outcome was not measured with a standardized questionnaire and results were not compared with conservative treatment.6 Furthermore, although not significantly different statistically, the finding that 31% and 12% were incontinent at long-term follow-up in center 1 and center 2, respectively, argues against the more invasive approach used in center 1. Although it would have been interesting to be informed about the course between treatment and follow-up after 5 years, we deliberately have chosen to ask whether the child was dry and not how long the child was already dry, because of the high-risk of recall bias.12 Because the influence of time and any natural fluctuation in outcomes are not yet known, and because we have no insight in the benefit of urethral desobstruction in specific subgroups, further investigation is warranted.

5 | CONCLUSIONS

A benefit of endoscopic desobstruction in boys with urge incontinence and suspected infravesical obstruction to prevent LUTS and UI on the longer term could not be confirmed. It cannot be ruled out that a more invasive strategy brings early relief or that there may be a subgroup in which more invasive strategy is beneficial, our study could not confirm this. Regular follow-up evaluation of incontinence and urgency complaints until after puberty will hopefully clarify the real efficacy of treatment.

REFERENCES
