VOIDING DYSFUNCTION

ALPHA BLOCKER THERAPY FOR CHILDREN WITH DYSFUNCTIONAL VOIDING AND URINARY RETENTION

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ABSTRACT

Purpose: Alpha blocker therapy has been successfully used to decrease residual urine in children with complex neuropathic and nonneuropathic voiding dysfunction. We evaluated the safety and efficacy of using selective alpha blocker therapy for children with uncomplicated voiding dysfunction and underlying poor bladder emptying.

Materials and Methods: A total of 55 patients with a mean age of 7.9 years presented with symptoms of urinary incontinence, urgency and urinary tract infection. All patients had increased post-void residual (PVR) on bladder ultrasound, with a mean residual volume of 65 ml (22% of age expected capacity). All patients were treated with doxazosin, a selective α-1 adrenergic antagonist, at dosages of 0.5 mg to 2.0 mg daily. Of the patients 38 were treated at presentation with a regimen of anticholinergics, timed voiding and antibiotic prophylaxis before initiating alpha blocker therapy. Patients were reevaluated with post-void ultrasound of the bladder 6 weeks after initiating alpha blocker therapy.

Results: After starting doxazosin average PVR decreased to 8 ml (p<0.0001), representing an 88% reduction in residual urine (or reduction to only 2.7% of age expected bladder capacity). Medication was discontinued in 2 patients due to minor side effects.

Conclusions: Selective alpha blocker therapy appears to be effective for improving bladder emptying in children with an overactive bladder, wetting, recurrent infection and increased PVR urine. This therapy may be used as either a replacement or in addition to biofeedback in patients with urinary retention. Further investigation, including a prospective randomized trial of alpha blocker therapy in children with urinary tract dysfunction, is warranted based on the findings of our study.

Key Words: adrenergic alpha-antagonists, urinary incontinence, urinary retention

Daytime wetting due to uninhibited contractions from an overactive bladder is a common problem in the pediatric population. In a small subset of these patients voiding dysfunction will lead to chronic urinary retention which complicates routine therapy for the overactive bladder. Traditional therapy has involved retraining the pelvic floor muscles using a variety of behavioral therapies including biofeedback in an attempt to resolve the functional outlet obstruction caused by the underlying detrusor-sphincter dyssynergia.1–5 Although alpha blocker therapy has been widely used in adults with benign prostatic hyperplasia and outlet obstruction, there have been few reports demonstrating the safety efficacy of this therapy in the pediatric and adolescent population. We have previously demonstrated success using α-adrenergic blockade in children with severe neuropathic and nonneuropathic voiding dysfunction.6 Because of our success with this more complex group, we investigated whether alpha blocker therapy would benefit children with voiding dysfunction and underlying poor bladder emptying.

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All patients were started on doxazosin, a specific α-adrenergic antagonist. This medication is available in scored 1 mg tablets, allowing medication adjustment in 0.5 mg increments. Initial dose was 0.5 mg daily which was increased incrementally to a maximum of 2 mg daily until improved bladder emptying was documented. Families were instructed about common side effects including lightheadedness and postural hypotension. All families were instructed to have the blood pressure taken during the daytime at least twice a week after initiating therapy. Of the patients 36 were treated with 0.5 mg daily, 17 with 1 mg daily and 2 with 2 mg daily. Medication was continued until the urinary retention had improved or resolved. Most patients were treated with alpha blockers for at least 6 months. Parents were encouraged to give the medication before bedtime to minimize the potential of daytime postural hypotension. Patients were seen within 6 weeks of initiating therapy for post-void bladder ultrasound, and every 3 to 6 months thereafter. A voiding history and repeat urinalysis and culture were also obtained.

In addition to the doxazosin, all patients were treated with behavioral modification, including recommendations for timed voiding every 2 hours and a high fiber diet, and parents were given a dysfunctional elimination syndrome booklet. Of the patients 38 (69%) had undergone multiple therapies for several months but all had persistent poor bladder emptying before initiating doxazosin. Anticholinergic medications (either tolterodine or oxybutynin) were started in 47 of 55 patients for significant symptoms of uninhibited bladder contractions, and 34 were also started on antibiotic prophylaxis because of a history of recurrent urinary tract infection. PVR values before and after treatment were compared for statistical significance with Student’s paired t test using standard computer software.

RESULTS

Average pretreatment PVR was 65 ml and average PVR after starting doxazosin was 8 ml (p <0.0001). This was a reduction of average residual urine to 2.7% of age expected capacity (p <0.0001), representing an 88% reduction in the pretreatment post-void residual urine. There were 3 patients with no change in post-void residual after initiating therapy.

There was also improvement in diurnal incontinence in 35 of the 42 children (83%), and urgency improved in 28 of 40 (70%). On questioning, the parents believed that there was notable improvement in the initial symptoms in 35 of the 55 children (64%), supporting the finding that all measured parameters improved following alpha blocker therapy (see figure). Two patients stopped the alpha blocker because of side effects that were attributed to the doxazosin. One patient had a questionable recurrence of a previously documented heart murmur during an emergency room visit for fever, and the medication was stopped. The other patient had mild dizziness during the daytime which completely resolved after discontinuing the alpha blocker. None of the patients had worsening incontinence after initiating doxazosin therapy.

DISCUSSION

This study adds further support for the use of alpha blocker therapy in children with increased post-void residuals and voiding dysfunction. Many of these children have complex voiding histories with a combination of inability to store urine due to the overactive bladder and uninhibited contractions, and poor emptying due to an inability to relax the pelvic floor musculature during voiding. The traditional approach has been to treat these patients with multimodal therapy using anticholinergic medication to suppress uninhibited contractions and timed voiding during the daytime to allow the bladder to be emptied before these contractions. Recurrent infections have been suppressed with antibiotic prophylaxis. In refractory cases there have been several different options described, all aimed at relaxing the pelvic floor musculature using different techniques of biofeedback.

A limitation of our study is that patients were treated with multiple medical therapies, which might have also improved bladder emptying. The addition of anticholinergics to diminish uninhibited bladder contractions could potentially have decreased the pelvic floor dysynergia (the learned response of increasing the external sphincter tone during uninhibited contractions to avoid wetting) and improved bladder emptying. In addition, some of the patients were also treated for constipation and recurrent infection simultaneously with the alpha blocker therapy. Although all of these therapies would tend to improve emptying with time, we believe that the rapidity of improvement in residual urine favors initiation of the alpha blocker as the primary factor impacting bladder emptying. In addition, the majority of the patients (38 of 55) had been on multimodal therapy before initiation of alpha blocker therapy and still had poor bladder emptying.

Another limitation of our study is its nonrandomized nature. This is a pilot study to evaluate α-1 blocker therapy in children with voiding dysfunction and urinary retention. Our goal to characterize the safety and efficacy of alpha blocker therapy in children represents the first report that provides adequate preliminary data to support a prospective controlled randomized clinical trial of α-1 blocker therapy for children with voiding dysfunction and incomplete emptying. Prior studies with nonselective alpha blocker therapy have also shown similar favorable results but treatment was limited by significant side effects of the blockade, primarily orthostatic hypotension.

The exact mechanism and site of action for alpha blocker therapy in children with urinary retention remain in question. There are documented reports of α-1 adrenergic receptors at the bladder outlet and in the proximal urethra. Stimulation of the alpha receptors will result in smooth muscle contraction and increased outlet resistance. Alpha adrenergic blockade would theoretically result in smooth muscle relaxation at the base of the bladder and decreased outlet resistance in the proximal sphincter complex. This theory is somewhat different than the understood mechanism of biofeedback therapy, which targets the external sphincter, is...
under voluntary control and can be affected with behavioral modification.

A subset of patients with dysfunctional elimination present with an overactive bladder and when evaluated with a voiding cystourethrogram demonstrates a spinning-top urethra with bladder neck hypertrophy, a dilated urethra and evidence of narrowing at the external sphincter. These findings are thought to be due to a functional obstruction at the level of the external sphincter causing increased intraurethral pressure and eventual urethral dilatation. Therapies have all aimed at relaxing the bladder and the external sphincter to allow more complete emptying. The addition of alpha blocker therapy could potentially act synergistically to facilitate relaxation of the bladder and the external sphincter to allow more complete emptying. The addition of alpha blocker therapy could potentially allow improved funneling of the bladder outlet during voiding, resulting in a more rapid improvement in bladder emptying.

Our study adds further support to the evidence suggesting a role for alpha adrenergic blockade therapy in children with increased post-void residuals and an overactive bladder. The medication has been proven to be safe in children, and results in rapid and significant improvement in bladder emptying. The addition of this therapy early in management has the potential to eliminate the need for the more labor and time-intensive biofeedback in some patients. In refractory cases alpha blocker therapy may also still be useful as an adjunct to biofeedback therapy.

CONCLUSIONS

Selective alpha blocker therapy appears to be effective for improving bladder emptying in pediatric patients presenting with primary symptoms of overactive bladder, recurrent infection and increased post-void residual urine. This therapy may be used as either replacement for or in addition to biofeedback in patients with urinary retention. Further investigations, including randomized prospective trials, are warranted to help define the role of alpha blocker therapy in children with urinary tract dysfunction.

REFERENCES


EDITORIAL COMMENT

Voiding dysfunction is commonly encountered in daily practice. Its etiology is multifactorial and consequently treatment must be multimodal with an emphasis placed on the dominant etiological factors. It is not surprising to see some patients respond to one form of therapy to which others may be frustratingly resistant.

The authors studied a group of patients with voiding dysfunction. They presented with the usual symptoms of incontinence, urgency and urinary tract infection. In addition all shared a high post-void residual urine (mean 22% of age expected capacity). Almost a third had vesicoureteral reflux and half were constipated. PVR was reduced to a mean of 2.7% of age expected capacity with alpha blockers while maintaining multimodal therapy including behavioral modification, anticholinergics and antibiotics as dictated by symptoms. Constipation was also treated. In addition to the statistically significant reduction of PVR, diurnal incontinence and urgency also improved. No mention is made of the occurrence of further episodes of urinary tract infection, reflux resolution or constipation status.

Although this study is a pilot and suffers from lack of randomization, it does make a strong case for advocating the use of alpha blockers in the presence of increased PVR. Effective and rapid diminution was noted in the majority of patients and the medication was well tolerated except in 2 patients.

The authors surmise that the up-regulation and increased toxicity of the proximal urethral sphincter may contribute to bladder overactivity. This theory is quite plausible if bladder neck overactivity may be considered as an integral part of detrusor overactivity albeit under the control of a different set of receptors. Although there are no alpha receptors in the external sphincter as such, they have been demonstrated in its blood vessels. Vasospasm of the external sphincter may stimulate it to contract. Thus, alpha blockers may also have an effect at the external sphincter level by improving its blood supply and allowing it to relax. The same goal may be achieved with biofeedback and pelvic floor rehabilitation, which however does not address the proximal urinary sphincter. The bottom line is that to achieve effective voiding, a synergistic balance must be obtained between the detrusor and both urinary sphincters. It appears from this study that alpha blockers have a place of choice in achieving this goal.

The authors recognize that further documentation of precise mechanisms and sites of action are necessary. Long-term safety in children must be established with alpha blockers as is the case with neurogenic bladders. Alpha blockers have a place of choice in achieving this goal.

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DISCUSSION

Dr. Seth Schulman. One of the problems with multimodal therapy is that it is hard to differentiate exactly which mode is the most effective. Why not consider a placebo versus doxazosin to know whether that really made the difference versus all of the other therapies that you offered?

Dr. Mark Cain. Two-thirds of the patients had received multimodal therapy for 6 to 12 weeks before adding the alpha blocker and still had significant residual urine that decreased significantly after alpha blocker therapy. With that good of a result, we began to use it initially to try to speed up the resolution of residual urine in these patients.

Mr. David Frank. Is this study scientific? There is no randomization, no controls or no double blinding.

Doctor Cain. I think it works.

Mr. Frank. I am not saying that it does not work but I am just saying how can you say scientifically that this is valid without doing it properly?

Doctor Cain. I think that it would be very hard to give somebody a placebo when you have already identified that this therapy is effective.

Mr. Frank. But the whole point about double-blind controlled clinical trials is that the patients do not know and then you can conclude that they do work. The trouble is that because you have not done this, the study is not scientifically valid.

Doctor Cain. I disagree because two-thirds of the patients received multimodal therapy, had residual urine and had persistent symptoms, and when doxazosin was added, the symptoms went away and so did the residual urine.

Mr. Frank. I think you are wrong.

Dr. Pat McKenna. We reported in a study last year that a little less than 1% of 170 patients had true bladder neck obstruction and responded unbelievably to alpha blockers. However, they make up less than 1% of the incontinence cases that we treat.

Dr. Yves Homsy. I have been using alpha blockers for about 7 years, and have found them to be quite benign provided you exert care in their use. I start by using a lot of bowel management and multimodal therapy first. As a criterion for the use of alpha blockers, I simply rely on post-void residuals. If they are increased, I would start with a low dose of doxazosin and incrementally increase it every 2 weeks to maximum tolerance. Most of my patients respond to 1 to 2 mg, although some patients have required up to 5 mg. I am able to wean patients off of the alpha blockers, which may vary from 6 months to a year, but I continue followup of post-void residuals and of course the way that they void. If PVR recurs, I go back to the constipation issue to determine if this was the initial cause. Very often kids sink back into their old habits because the constipation issue is not only chronic but it is also recurrent. We need to keep this fact in the back of our minds. So all I am saying really is that we have to include alpha blockers as part of multimodal therapy. Yes it is true that we do not have controlled studies as such, but we do not have to reinvent the wheel. Benign prostatic hyperplasia has definitely been treated successfully with alpha blockers. At least half of us in this room will probably be taking alpha blockers.
Purpose: We examined the symptoms of bladder-bowel dysfunction (i.e., severity of voiding dysfunction and stool consistency) and psychosocial difficulties in children presenting to the pediatric urology clinic for voiding dysfunction and to the pediatric gastroenterology clinic for functional constipation.

Materials and Methods: Parents of children seen at the gastroenterology clinic were recruited during the outpatient clinic appointment, and parents of children seen at the urology clinic were randomly selected from the research database and matched to the gastroenterology sample based on age and gender of the child. All parents completed the Dysfunctional Voiding Scoring System, Bristol Stool Form Scale, Pediatric Symptom Checklist, and Parenting Stress Index—Short Form, which assessed severity of voiding dysfunction, stool consistency, level of psychosocial difficulties, and level of parenting stress, respectively.

Results: Children seen at the urology and gastroenterology clinics did not differ significantly on any of the measures, indicating that the severity of their bladder-bowel dysfunction is similar. However, they had significantly more severe voiding dysfunction, more constipated stool, and more psychosocial difficulties than historical healthy controls. Additionally, level of parenting stress was significantly correlated with patient level of psychosocial difficulties and severity of voiding dysfunction.

Conclusions: Patients with bladder and bowel dysfunction represent a homogeneous group that would potentially benefit from a multidisciplinary treatment approach involving urology, gastroenterology, and psychology professionals.

Key Words: Combined modality therapy, constipation, urinary incontinence

VOIDING dysfunction comprises almost 40% of referrals to pediatric urologists, while bowel dysfunction leading to functional constipation accounts for approximately 25% to 30% of referrals to pediatric gastroenterologists. While previous reports have indicated significant overlap in these conditions in primary care settings, with 24% of children with functional fecal retention also reporting daytime incontinence, the prevalence of these comorbid conditions is higher at tertiary care centers. It was recently reported that 47% of patients seen at a pediatric urology clinic for lower urinary tract symptoms also met criteria for functional constipation. Children presenting with a combination of bladder and bowel disturbances are now classified as having bladder-bowel dysfunction. Acknowledging the importance of assessing bowel habits in children presenting with lower
urinary tract symptoms, the Standardization Committee of the International Children’s Continence Society recently published guidelines for the management of functional constipation in children with urinary symptoms.5

In addition to an overlap in symptoms of bladder and bowel dysfunction, children seen for conditions such as voiding dysfunction and functional constipation are at increased risk for psychosocial problems. For example children with daytime incontinence have been rated by their parents as having higher levels of attentional problems and more oppositional behavior than those without daytime wetting.6 Recently we reported that children seen at a pediatric urology clinic for voiding dysfunction were 1.53 times more likely than children seen in primary care settings to exhibit clinically significant levels of psychosocial difficulties.7 Among children presenting to an outpatient GI clinic for functional constipation behavioral problems were identified in 37%, with significant numbers exhibiting internalizing and externalizing behaviors.8

We examined the similarities and differences between groups of children referred to our pediatric urology clinic for voiding dysfunction and children referred to our pediatric GI clinic for functional constipation. We compared the groups in terms of severity of voiding symptoms, stool consistency and level of psychosocial difficulties to determine whether the groups are sufficiently similar to warrant multidisciplinary care from a urologist, gastroenterologist and psychologist.

METHODS

After obtaining institutional review board approval parents of children seen for functional constipation at the GI clinic were recruited during regular outpatient clinic appointments. After data collection at the GI clinic was completed a comparison group from the urology clinic was obtained from the research database. Parents of urology patients were selected randomly based on their child with voiding dysfunction being an age and gender match to the children seen at the GI clinic. Additionally, historical control data were obtained from studies using the PSC, DVSS and BSFS in healthy children.1,9,10

Parents completed the PSC, a brief 35-item screening tool for psychosocial difficulties in children. The parent rates each item on a 3-point scale ranging from “never” to “often.” Examples of items include “fidgety, unable to sit still” and “feels sad, unhappy.” Items are summed to create a total score, with higher scores being indicative of more problems. Previous research has identified total cutoff scores of 24 for children 4 to 5 years old,11 and 28 for children 6 to 16 years old.12 It is recommended that patients with a positive score (at or above the cutoff) be referred for further evaluation by a mental health professional. The PSC is valid and reliable,9 and has been validated for use in samples of children with GI disorders,13 and those with voiding dysfunction and/or enuresis.14

The DVSS is a 10-item standardized measure that objectively assesses the severity of dysfunctional voiding symptoms.1 This measure is completed by the child and his/her caregiver. Symptoms are rated on a 4-point scale ranging from “almost never” to “almost every time,” and then “yes” or “no” for the presence of a significant life stressor (eg new baby, abuse, home problems, etc). Examples of the items include “When I have to pee, I cannot wait” and “I have had wet clothes or underwear during the day.” The items are summed to create a total score, with higher scores indicative of more severe voiding dysfunction.

The BSFS is a standardized and validated measure of stool consistency originally developed for use in adults, although it has been validated for use in children as well.10 The BSFS is a 7-item scale that includes images and descriptions of stool ranging from “type 1: separate hard lumps, like nuts (hard to pass)” to “type 7: watery, no solid pieces, entirely liquid.” The BSFS is significantly correlated with whole gut transit time in children, and it has been approved for use in research to differentiate between functional defecation disorders.10 Lower BSFS scores are indicative of more constipated stool.

The PSI-SF is a 36-item standardized measure of parenting stress that uses a 5-point scale ranging from “strongly agree” to “strongly disagree.”15 Examples of items include “my child is not able to do as much as I expected” and “I feel trapped by my responsibilities as a parent.” Higher PSI-SF scores indicate greater parenting stress, with a clinical cutoff score of 91. The PSI-SF shows high internal consistency (α = 0.92), and its validity has been established in parents of children with chronic medical conditions such as diabetes and asthma.15–17

Descriptive statistics were calculated to characterize the sample. Chi-square analyses and independent t-tests were calculated to examine potential differences between the groups regarding parent gender and race/ethnicity, and to confirm that the sample was successfully matched for child age and gender. To determine whether the urology and GI groups differed from each other on level of voiding dysfunction, stool consistency or level of psychosocial difficulties, 1-way ANCOVAs (urology vs GI, while controlling for race and laxative use) were conducted with the total scores from the DVSS and PSC, and the BSFS score as the dependent variables in separate analyses. Since there were no significant differences between the urology and GI groups, they were collapsed into 1 group and single sample t-tests were conducted to compare the urology/GI group to historical controls on the DVSS total score, BSFS and PSC total score. Finally, the percentages of children who met the cutoff score on the PSC were compared between the urology and GI groups, and between the combined urology and GI group and the historical controls using chi-square analysis. Exploratory analyses were conducted to examine the relationship between level of parenting stress and patient symptoms of voiding dysfunction and psychosocial difficulties in a subset of parents who completed the PSI-SF. All analyses were conducted with SPSS,® version 20.
RESULTS
Participants included a total of 120 parents of children 4 to 16 years old seen at either the urology (60 patients) or GI (60 clinic. The urology group included 45 mothers (75.0%) and 15 fathers (25.0%), while the GI group consisted of 48 mothers (80.0%), 11 fathers (18.3%) and 1 grandmother (1.7%) who had primary custody of the child. Chi-square analyses indicated that the groups did not differ significantly regarding parent gender ($p = 0.375$).

With regard to the children, there were 33 boys (55.0%) and 27 girls (45.0%) in each group, and the groups did not differ significantly regarding age, indicating that the groups were successfully matched for child age and gender. For comparison of racial/ethnic composition of the groups using chi-square analysis (ie to control for small cell counts), race/ethnicity was collapsed into 3 categories, namely white, black and other (table 1). The groups differed significantly regarding race/ethnicity, with white parents being overrepresented in the GI group and black parents being overrepresented in the urology group. As such, race was entered as a covariate in all between group analyses.

Urology vs GI Group
With regard to patient total DVSS score, results of the 1-way ANCOVA (urology vs GI) while controlling for race were not significant, indicating that the groups did not differ significantly on severity of voiding dysfunction (table 2). The 1-way ANCOVA comparing BSFS (urology vs GI) while controlling for race and laxative use was not significant, indicating that the groups did not differ significantly regarding stool consistency. Finally, the ANCOVA conducted to compare the groups (urology vs GI) while controlling for race on level of total PSC score was not significant, indicating that the groups did not differ significantly regarding severity of voiding symptoms, stool consistency and psychosocial difficulties.

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<tr>
<th>Table 1. Demographic characteristics</th>
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<tr>
<td>Urology Clinic</td>
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<tr>
<td>No. parent gender:</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>No. child gender:</td>
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<tr>
<td>Female</td>
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<tr>
<td>Mean ± SD age (yrs)</td>
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<tr>
<td>No. race (%):</td>
</tr>
<tr>
<td>White</td>
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<tr>
<td>Black</td>
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<tr>
<td>Other</td>
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for voiding dysfunction and children seen at the GI clinic for functional constipation had similar levels of symptoms of voiding dysfunction, stool consistency and psychosocial difficulties.

Combined Urology/GI Group vs Historical Healthy Controls
The single sample t-test comparing the urology/GI sample to historical healthy controls on the DVSS total score was significant, indicating that the urology/GI group had significantly more symptoms of voiding dysfunction than the control group (table 3). Similarly the single sample t-test that compared the Bristol Stool Scale scores of the urology/GI group to historical healthy controls was significant, indicating that the urology/GI group had a significantly lower Bristol Stool score (ie more constipated stool) than the controls. Regarding psychosocial problems, the single sample t-test comparing total PSC scores between the urology/GI group and historical healthy controls was significant, indicating that the urology/GI group had significantly more psychosocial difficulties than the control group. Finally, compared to children in the control group, a significantly higher proportion of children in the urology/GI group met the clinical cutoff on the PSC.

Exploratory Analyses—Parenting Stress
The ANCOVA comparing level of parenting stress in parents from the GI and urology clinics while controlling for race was not significant ($p = 0.869$). As such, the parents were collapsed into a single group. Level of parenting stress was significantly related to patient overall psychosocial difficulties ($p <0.001$) as well as to level of symptoms of voiding dysfunction ($r^2 = 0.29$, $p = 0.012$), such that parents who reported higher levels of stress had children with higher levels of psychosocial difficulties and more severe symptoms of voiding dysfunction.

DISCUSSION
Children referred to the pediatric urology clinic for voiding dysfunction and children referred to the pediatric GI clinic for functional constipation appear to represent a homogeneous group in terms of severity of voiding symptoms, stool consistency
and psychosocial difficulties. Additionally, their parents report similar levels of parenting stress, with higher levels of parenting stress being related to more severe symptoms of voiding dysfunction. Previous recommendations have been made with regard to the importance of urology clinicians conducting a thorough assessment of bowel habits in children presenting with lower urinary tract symptoms, in addition to psychosocial screening of children with urinary and/or fecal incontinence. The findings from the current study suggest that children seen at GI clinics for functional constipation should also be assessed for lower urinary tract symptoms and psychosocial difficulties.

While the underlying physiology of bladder-bowel dysfunction is not completely understood, there is consistent evidence that bladder and bowel disorders are related through neurological connections and overlapping roles of the pelvic floor muscles during voiding and defecation. The International Children’s Continence Society recommends that initial treatment for bladder-bowel dysfunction in children be focused on constipation and/or fecal incontinence, using a 4-step process that includes education, disimpaction, prevention of reaccumulation and followup. These guidelines are supported by evidence from studies that have demonstrated improvements in urinary symptoms, including a reduction in urinary tract infections and decreases in daytime and nighttime incontinence, after successful treatment of constipation. Other therapeutic modalities that have been effective in treating bladder and bowel disorders involve education, behavioral modification and animated biofeedback.

Previously it has been documented that when children present with urinary symptoms, parents do not typically report constipation, as they often do not view it as a clinical symptom. This finding is consistent with our experience at the urology clinic. Additionally our GI colleagues have reported that patients seen at their clinic for constipation do not usually report urinary symptoms unless specifically questioned by the clinician. These clinical observations suggest that although patients may have symptoms of bladder and bowel dysfunction, referrals are differentially made to the pediatric urology or GI clinic based on the child and parental primary complaint of either urinary or bowel symptoms.

A study of primary care physician referrals to pediatric specialists identified urology as the fifth most common surgical specialty referral and GI as the fifth most common medical specialty referral, with 7% and 8% of children being referred, respectively. Additionally mental health referrals are quite common, with most children being referred to psychologists for behavioral problems. Overall behavioral problems, urological signs and symptoms, and abdominal pain (which may be indicative of constipation) are all in the top 25 conditions most commonly referred to specialty care. Notably children with bladder-bowel dysfunction exhibit urinary symptoms and constipation, and are at increased risk for behavioral problems. As such, they could potentially be referred to up to 3 specialists, which could result in different management and treatment of the conditions, higher health care costs, and more burden on the child and family secondary to multiple outpatient appointments. The development of a multidisciplinary clinic that includes pediatric urologists, gastroenterologists and psychologists will allow children with bladder-bowel dysfunction to be treated in a more holistic manner, such that their urinary, GI and psychological symptoms can all be targeted simultaneously.

The current findings should be interpreted in light of some limitations. The study is cross-sectional in nature and no temporal relationships could be identified. Future prospective studies should collect longitudinal data on children with bladder-bowel dysfunction to examine changes in urinary, bowel and psychological symptoms throughout treatment. The current sample was collected from outpatient clinics at a single institution, which may limit the generalizability of the findings. However, the current sample is diverse in terms of racial/ethnic breakdown. The use of historical data as a comparison control group threatens internal validity, and inclusion of a peer control group will strengthen future studies. Finally, shared method variance may be a problem, given that although the children were involved in completing the DVSS and the BSFS, ultimately all of the measures were completed by the parents.

**CONCLUSIONS**

Children referred to urology clinics for voiding dysfunction and to GI clinics for constipation have a similar degree of bladder and bowel dysfunction and psychosocial problems. Thus, they appear to

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<tr>
<th>Urology/GI Sample</th>
<th>Historical Healthy Controls (reference)</th>
<th>p Value</th>
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<tr>
<td>Mean ± SD DVSS total score</td>
<td>9.29 ± 4.92</td>
<td>4.54 ± 3.71 (Farhat et al)</td>
</tr>
<tr>
<td>Mean ± SD Bristol Stool Scale score</td>
<td>3.54 ± 1.31</td>
<td>4.20 ± 0.50 (Russo et al)</td>
</tr>
<tr>
<td>Mean ± SD PSC total problems</td>
<td>17.48 ± 11.22</td>
<td>15.10 ± 10.00 (Jelinek et al)</td>
</tr>
<tr>
<td>No. meeting PSC cutoff/total No. (%)</td>
<td>24/111 (21.60)</td>
<td>2,657/21,065 (12.60; Jelinek et al)</td>
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represent a homogeneous group. In addition, they have significantly more symptoms of voiding dysfunction, more constipated stools and more psychological difficulties than healthy children. Based on these findings, it is suggested that they would benefit from multidisciplinary care that includes a urologist, gastroenterologist and psychologist. Importantly the inclusion of treatment modalities that affect bladder and bowel dysfunction, such as education, behavioral modification and biofeedback, should be integral aspects of care. It is recommended that clinical data be collected longitudinally for purposes of potentially creating a multidisciplinary clinic for these patients.

REFERENCES


Evaluation of Constipation by Abdominal Radiographs Correlated with Treatment Outcome in Children with Dysfunctional Elimination

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OBJECTIVES
To analyze the utility of assessing degree of constipation by abdominal radiograph (KUB) in relation to symptoms and urodynamic data in children with dysfunctional elimination.

METHODS
A retrospective review of children with concomitant constipation and daytime incontinence was performed. Inclusion required at least two consecutive visits with KUB and noninvasive uroflowmetry. Patients were excluded for anticholinergic medication use or neurogenic or anatomic abnormalities. Rectal fecal quantification and presence of stool throughout the colon was assessed on KUB and categorized as “empty,” “normal amount of stool,” or “fecal distention of rectum (FDR).”

RESULTS
Twenty-six patients met inclusion requirements (6 boys, 20 girls; average age, 7.7 ± 2.2 years). The average time between the initial and subsequent visit was 12.5 ± 7.8 weeks. Initial KUB revealed FDR in 17. No statistical significance was found between FDR on initial or final KUB and outcome of wetting symptoms, nor could a relationship between FDR uroflow parameters at either visit be demonstrated.

CONCLUSIONS
No correlation between any uroflowmetry parameter and the presence of FDR at the initial or final visits could be demonstrated. Similarly, no statistical significance between FDR on final or initial KUB and outcome of wetting symptoms was established.

Dysfunctional elimination syndrome describes children with concomitant bowel and bladder symptoms. Management of constipation in these children is imperative because this often confers an improvement in related conditions, including urinary tract infections (UTIs) and daytime incontinence. Children presenting with urinary incontinence, frequency, or urgency are generally recommended to begin conservative treatment, including the use of bladder diaries, timed voiding, and laxatives. Bowel habits are reviewed in conjunction with urinary habits to determine the possibility of constipation. Clinical assessment involves a history and physical examination, along with noninvasive uroflowmetry and residual urine quantification by bladder ultrasound scan. Abdominal radiographs (KUBs) may also be used to visually evaluate the amount of stool in the rectum and colon.

Although constipation is a common problem among children, it is not well understood and is difficult to diagnose objectively. Current definitions of constipation are somewhat vague and not universally standardized. Diagnosis often is based on subjective findings alone, including the parent’s and/or child’s report of the nature and frequency of stooling. Various methods have been developed to assess constipation objectively, including whole gut transit time, mean daily stool weight, daily KUBs, and digital examination of the rectum. These measures are generally not preferred because they are either time consuming or invasive. Radiographs have been used to visually assess constipation and have been valued because they are an inexpensive and quick method to obtain objective data.

Several scoring systems to assess fecal retention on KUB have been proposed. However, there is currently no common system for assessing degree of constipation on KUB, and the utility of using KUBs in this manner has not been determined. This study analyzed the association between the amount of stool in the rectum identified on KUB and the degree of daytime incontinence as...
assessed subjectively by symptoms and objectively by uroflow parameters and postvoid residual volume (PVR).

MATERIAL AND METHODS

An institutional review board–approved retrospective review of patient records with diagnoses of urinary incontinence, frequency, and/or daytime incontinence seen between 1999 and 2004 at the Pediatric Urology Clinic at the Children’s Hospital of Iowa was performed to identify patients with dysfunctional elimination. Inclusion required KUB and uroflowmetry at both the initial and subsequent follow-up visit. Analysis was limited to the initial and first follow-up visit to minimize the impact of confounding variables on outcome that increase with time. Patients were excluded from study if neurogenic or anatomic abnormalities were present. Children prescribed anticholinergic medication to treat daytime incontinence were excluded.

A history was obtained to document constipation symptoms as well as the child’s wetting severity, frequency, and duration. Children were considered to have constipation if the frequency of bowel movements was less than every other day, if the stool was hard or difficult to pass, or if there were stool accidents or fecal smearing of the undergarments. Recommendations for treating constipation included increased fluid intake and dietary fiber levels, use of over-the-counter laxatives, and/or polyethylene glycol 3350 (Miralax; Braintree Laboratories, Braintree, Mass), as previously reported. Treatment of incontinence included education and timed voiding every 2 to 3 hours.

Children were evaluated by physical examination, noninvasive uroflowmetry, and KUB. To conduct the noninvasive uroflowmetry, children were asked to wait until they felt at least a strong desire, if not an urgent need, to void. Maximum flow rate, average flow rate, and voided volume were recorded. Noninvasive ultrasound bladder scanning (BladderScan BV1 2500; Verathon, Bothell, Wash) was used to determine PVR volume. This volume and the voided volume were each expressed as a percentage of predicted bladder capacity (PBC) based on the patient’s age. The formula $PBC = (age + 2) \times (30 \text{ mL})$ was used to calculate age-expected bladder capacity.

Fecal load was categorized on KUB by two pediatric urologists in a blinded fashion. The amount of stool in the rectum was classified as empty, normal amount of stool, or fecal distention of the rectum (FDR). Fecal distention of the rectum was diagnosed when the width of the stool-filled rectum was greater than half of the width of the true pelvis. Presence of stool throughout the entire colon was also noted on the KUB. Changes in the readings were categorized as worse, unchanged, or improved according to the amount of stool in the colon and rectum. When a difference existed between KUB classifications, the radiographs were reviewed together and a consensus was determined. There was a difference noted in classification of rectal stool between the two urologists on the initial and final KUB in 27% and 15% (kappa coefficient $= 0.46$ [95% CI 0.11, 0.80] and 0.67 [0.39, 0.95]), respectively. No statistical difference was noted when subsequently using either individual findings or consensus findings, and all data and statistics noted here reflect the consensus findings of the two physicians.

The association between clinical and demographic variables and FDR as seen on KUB was tested with the chi-square or Fisher’s exact test for categoric variables and Wilcoxon rank-sum test for continuous and ordinal variables. The association between KUB findings and uroflowmetry values was tested with one-way analysis of variance.

| Table 1. KUB findings at initial and final visits |
|-------------------|---------|---------|
| Finding            | Initial Visit (n) | Final Visit (n) |
| FDR and stool throughout colon | 13 | 5 |
| FDR and normal/empty colon | 4 | 3 |
| Normal/empty rectum and colon | 6 | 8 |
| Normal/empty rectum + stool throughout colon | 3 | 10 |

KUB = abdominal radiograph; FDR = fecal distention of the rectum.

RESULTS

Twenty-six patients (6 boys, 23%; 20 girls, 77%) met study requirements. Average age of the boys was 7.5 ± 1.4 years, the average age of the girls was 7.8 ± 2.4 years, and the overall average age was 7.7 ± 2.2 years. The average time between the first and second visit was 12.5 ± 7.8 weeks. The majority of patients (58%) started treatment with Miralax at the initial visit, whereas 19% were already using Miralax, and 23% were recommended to increase dietary fluid and fiber intake and/or use nonprescription stool softeners. By the second visit, 9 of 26 patients (35%) reported that constipation had resolved.

Table 1 lists KUB findings at the initial and final visits. Overall, 17 patients had FDR at the first visit, and only 8 patients had FDR at the final visit. Nine patients had a normal or empty rectum at the initial visit, compared with 18 patients at the final visit.

Table 2 displays uroflowmetry parameters for children grouped according to the presence or absence of FDR on KUB at the initial and final visits. Statistically, no correlation between any of the uroflowmetry parameters and the presence of FDR at the initial or final visits could be demonstrated. Similarly, no statistical significance between FDR on final or initial KUB and outcome of wetting symptoms was established (Table 3).

Of the 17 patients who had FDR at the initial visit, 12 did not have FDR at the final visit. Of these 12, 25% became dry, 17% had significant improvement in wetting symptoms, 25% had slight improvement in wetting symptoms, and 17% were unchanged from the initial visit (16% were missing adequate chart data for determination of wetting change). Five patients had FDR at both the initial and final visits, whereas 6 did not have FDR at either visit. Three patients who did not have FDR at the initial visit were categorized as having FDR at the final visit.

There was no difference in the mean age of children with or without FDR at the initial (6.9 ± 1.8 versus 8.1 ± 2.3 years; $P = 0.23$) or follow-up visit (7.9 ± 2.3 versus 8.1 ± 2.2 years; $P = 0.82$). Of 25 patients, 16 (64%) had a history of recurrent UTIs. Of those 16, 8 (50%) showed FDR on the initial KUB, which approached but did not meet statistical significance ($P = 0.09$). Of these same 16 patients with a history of multiple UTIs, 5 had FDR at the final visit. No correlation could be demonstrated between those with a history of UTIs and FDR at the final visit ($P = 1.0$). Similar to the
analysis of FDR, no statistical correlation was identified between those with stool throughout the colon and uroflowmetry parameters or symptomatic outcome or UTIs (data not shown).

**COMMENT**

Constipation is a common childhood problem, and there are a few theories to explain the mechanism between the effects of a large fecal load and daytime incontinence. A clinical diagnosis of constipation is generally made on the basis of a history of infrequent stools, painful stools, or fecal accidents. However, there is no strict definition of constipation, nor is there a reliable objective test to determine whether a child is constipated. Many clinicians use KUBs to visualize the amount of stool in the rectum and colon, though there is no standardized method for reading a KUB in this context. No previous study has demonstrated the utility of assessing the degree of constipation on KUBs in children with daytime incontinence or whether constipation visualized on KUB correlates with the degree of urinary incontinence or uroflowmetry parameters.

Children with constipation have been shown to have concomitant difficulties with UTIs, daytime incontinence, and vesicoureteral reflux. Cayan et al. also showed that there is a relationship between constipation and nocturnal enuresis. These investigators used plain films to detect fecal loading and determined that the sensitivity of grading plain films for fecal loading in children with nocturnal enuresis is 87.5%. Eight children in the study group showed fecal loading on plain films, 7 of whom had constipation. Our population consisted of 26 children who demonstrated clinical signs of constipation, and 17 of these showed fecal distention of the rectum on KUB. At the final visit, 9 children reported improvement in constipation symptoms, and none of these children showed FDR on KUB.

A study by Giramonti et al. evaluated constipation on KUB in 100 children with UTIs. They found a poor correlation between a history of constipation and fecal load on a single KUB. This group showed a tendency for children with a history of UTIs to have increased fecal loading on KUB (P = 0.11). This was similar to our finding when looking at those with a history of UTI and presence of FDR (P = 0.09).

Uroflowmetry is an accepted method to evaluate a child with daytime incontinence. Previous studies have shown that treating constipation improves daytime wetting and that persistent constipation is associated with decreased resolution of voiding symptoms. When testing for a correlation between uroflow values and the presence of FDR in a group of children with a history of incontinence and constipation, we could not demonstrate a significant correlation between objective uroflow parameters and the presence of FDR. One of the strengths of this study was evaluating children with serial uroflowmetry and KUBs. However, no correlation could be demonstrated between those with improvement on the KUB and improvement in either uroflow parameters or symptomatic outcome.

Although a correlation between the presence of FDR and severity of daytime incontinence as assessed by uroflowmetry or symptoms was not demonstrated, our findings do not refute the relationship between constipation and abnormal bladder function. The sample size was relatively small, and perhaps with larger numbers a weak relationship could have been proven. One beneficial reason for ordering a KUB in the assessment of constipation is to educate parents and demonstrate that their child is experiencing problems of constipation. Visualizing the amount of stool in the rectum and colon allows for some

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**Table 2. Uroflowmetry parameters in patients with or without FDR at initial and final visits**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial visit</th>
<th>No FDR</th>
<th>FDR</th>
<th>P value</th>
<th>Final visit</th>
<th>No FDR</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Flow Maximum (mL)</td>
<td>25.78 ± 16.95</td>
<td>19.99 ± 8.34</td>
<td>23.69 ± 11.11</td>
<td>0.55</td>
<td>25.86 ± 13.90</td>
<td>23.69 ± 11.11</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean Flow Average (mL)</td>
<td>11.12 ± 6.61</td>
<td>9.59 ± 3.64</td>
<td>11.28 ± 7.26</td>
<td>0.53</td>
<td>12.08 ± 7.34</td>
<td>12.08 ± 7.34</td>
<td>0.80</td>
</tr>
<tr>
<td>Average PVR as % of PBC</td>
<td>26.25 ± 20.85</td>
<td>35.08 ± 32.02</td>
<td>25.50 ± 28.40</td>
<td>0.55</td>
<td>19.04 ± 16.08</td>
<td>19.04 ± 16.08</td>
<td>0.91</td>
</tr>
<tr>
<td>Average Flow Volume as % of PBC</td>
<td>61.01 ± 27.23</td>
<td>58.24 ± 39.64</td>
<td>51.16 ± 23.48</td>
<td>0.73</td>
<td>59.64 ± 33.45</td>
<td>59.64 ± 33.45</td>
<td>0.98</td>
</tr>
</tbody>
</table>

FDR = fecal distention of the rectum; PVR = postvoid residual volume; PBC = predicted bladder capacity. Data are presented as mean ± standard deviation.

**Table 3. Final symptomatic outcome groups and percentage of those with FDR at initial and final visits**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dry (%)</th>
<th>Significantly Improved (%)</th>
<th>Slightly Improved (%)</th>
<th>No Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDR at initial visit</td>
<td>66</td>
<td>60</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>FDR at final visit</td>
<td>17</td>
<td>40</td>
<td>33</td>
<td>50</td>
</tr>
</tbody>
</table>

FDR = fecal distention of the rectum.
* Complete data available for 24 of 26 patients.
objective data showing increased fecal load. The difficulty comes in accurately and consistently assessing the degree of constipation on the KUB. A recent bowel movement may result in an empty rectum on KUB in an otherwise constipated child. Perhaps more KUBs are needed to analyze each patient, given the fluctuating nature of a child’s dietary and bowel habits. A limitation in our study was the lack of information about the timing of the most recent bowel movement before the KUB. Likewise, assessment of the presence of constipation clinically may need to be refined. Children who are not accurately diagnosed with constipation may not be expected to show typical radiographic findings of constipation if radiographic findings can be relied upon. Future studies might be strengthened by specific questionnaires to evaluate a child’s stooling habits.

**CONCLUSIONS**

No correlation between any of the uroflowmetry parameters and the presence of FDR at the initial or final visits could be demonstrated. Similarly, no statistical significance between FDR on final or initial KUB and outcome of wetting symptoms was established.

**References**

eğin dysfunction

IMPROVED UROFLOW PARAMETERS AND POST-VOID RESIDUAL FOLLOWING BIOFEEDBACK THERAPY IN PEDIATRIC PATIENTS WITH DYSFUNCTIONAL VOIDING DOES NOT CORRESPOND TO OUTCOME

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ABSTRACT

Purpose: We evaluated pediatric patients who were treated with biofeedback for dysfunctional voiding with respect to clinical outcome and objective changes in uroflow parameters and post-void residual.

Materials and Methods: We retrospectively reviewed 81 patients treated for dysfunctional voiding and/or urinary tract infections with biofeedback. Conservative management had previously failed in all patients. Uroflow data and symptoms were reviewed, and clinical outcomes were recorded. For analysis, patients were stratified by symptoms of incontinence or presence of urinary tract infections.

Results: Of 73 patients with incontinence 22 (30%) became dry, 36 (49%) had improvement and 15 (21%) reported no change following biofeedback. In 39 (78%) of 50 patients with recurrent urinary tract infections resolved. Overall, there was a significant (p < 0.002) increase in peak flow and average flow rate, and a significant decrease in post-void residual and post-void residual as a percent of predicted bladder capacity. There was no significant change in voided volume following biofeedback. Overall, there was no significant difference in uroflow parameters and post-void residual following biofeedback between patients with incontinence or infections, except for a higher maximum flow rate in patients who continued to have infections.

Conclusions: Treatment of children with pelvic floor muscle biofeedback is associated with improved urinary continence and decreased urinary tract infections in the majority. It results in improvement in uroflow curves and parameters, and a decreased post-void residual. Posttreatment results of these parameters did not correlate with improvement in continence and urinary tract infections.

Key Words: biofeedback, outcome assessment, urinary tract infections, incontinence

Children with dysfunctional voiding, defined as contraction of the pelvic floor muscles during voiding, often present with incontinence and/or recurrent urinary tract infections (UTIs). Dysfunctional voiding can be a difficult problem for physicians to treat, and biofeedback has been used when conservative therapy fails. Biofeedback is a treatment process that uses electronic instruments to measure, record and display information about bodily processes. The information that is gleaned allows a patient to become aware of and gain control over these bodily processes. Biofeedback has been studied in the treatment of dysfunctional voiding. Noninvasive urodynamic studies such as uroflowmetry, pelvic floor electromyography (EMG), and ultrasonographically measured post-void residual (PVR) help diagnose dysfunctional voiding. Subjective improvement in the shape of uroflow curves has been reported following biofeedback. However, most studies do not include these findings nor have changes in the uroflow parameters been previously reported to our knowledge. We reviewed pediatric patients treated with biofeedback for dysfunctional voiding with respect to clinical outcome and objective changes in uroflow parameters and PVR.

MATERIALS AND METHODS

We retrospectively reviewed 81 consecutive patients treated with biofeedback for dysfunctional voiding since establishing a treatment program at our institution in 1999. All patients underwent complete evaluations, including history, physical examination, uroflow with EMG and PVR measurements. Presence of recurrent urinary tract infections and urinary incontinence was noted. The diagnosis of dysfunctional voiding was based on symptoms and results of noninvasive urodynamic studies. In select patients renal ultrasound and a voiding cystourethrogram were performed as indicated. Patients were excluded from analysis if neurogenic bladder dysfunction or anatomic abnormalities (eg ureterocele, posterior urethral valves, etc) were present. All patients were initially treated and failed to gain continence despite conservative therapy, including a regimen of timed voiding and hydration, and in select patients treatment of constipation and/or anticholinergics. In patients with recurrent UTIs prophylactic antibiotics were given as indicated.
Noninvasive urodynamic results were recorded before and after biofeedback therapy. Children were asked to wait until they felt an urgency to void. If small volumes were voided they were asked to repeat the test. Maximum flow rate (Qmax), average flow rate (Qave), voided volume and PVR were recorded. The PVR and voided volume (Vol) were also expressed as a percent of predicted bladder capacity (Pbc) based on patient age. The formula bc = (age + 2) × 30 was used to calculate the age expected bladder capacity in milliliters. EMG activity was defined as either present or absent during voiding. The shape of the uroflow curve was recorded (parabolic, interrupted or flattened). For analysis, parabolic shaped uroflow curves were considered normal while flattened and interrupted uroflow curves were considered abnormal.

Biofeedback sessions were performed under the supervision of a pediatric nurse practitioner (MAB). Sessions were typically 2 hours long, and during each visit symptoms were reviewed and any changes documented. Pelvic floor training was done using commercially available interactive videogame biofeedback (Multitrace 2 and Biointeractor Plus v4.0, Stens Corp., San Rafael, California). Patients also underwent uroflow and EMG studies with real time visual display of results. The post-void residual was recorded by ultrasound (BladderScan BVI 2500+ Diagnostic Ultrasound Corp., Redmond, Washington). The number of sessions performed varied according to improvement using clinical and urodynamic data as part of the assessment.

Outcomes of biofeedback therapy in patients with incontinence were defined as “dry” if incontinence resolved, “improved” if there was greater then 50% reduction in the number of wetting episodes per week or “no change.” Subjective improvement in frequency and urgency was recorded. In patients with recurrent urinary tract infections success was defined as resolution during followup but did not require patients to cease prophylactic antibiotic therapy. Patient age, sex, number of biofeedback sessions and time of followup were recorded.

Data were evaluated using computer software (SAS Institute, Cary, North Carolina) and, when appropriate, data are reported as mean ± standard error with p < 0.05 considered statistically significant. Square root of the value was used for data that were not normally distributed. The uroflow results were stratified into groups based on outcome for incontinence and recurrent urinary tract infections, and compared.

**RESULTS**

We treated 65 females and 16 males with biofeedback for dysfunctional voiding. Mean patient age was 8.2 years (range 4 to 17), mean number of treatment sessions was 5.9 (2 to 16) and mean followup after the last biofeedback session was 9.4 months (1 to 29). Urinary incontinence was present in 73 of 81 (90%) patients, recurrent urinary tract infections in 50 (61.7%) and both in 45 (55.5%). Of the 73 patients with incontinence 22 (30%) became dry, 36 (49%) improved and 15 (21%) had no change after biofeedback. Of the 50 patients treated for recurrent UTIs 39 (78%) had resolution and 11 (22%) continued to have infections. There was no significant difference in sex, age, number of biofeedback sessions and time of followup with regard to outcome for the treatment of incontinence or resolution of urinary tract infections.

Noninvasive urodynamic studies showed significant improvement following biofeedback (table 1). There was a significant increase in the Qmax and Qave, and a significant decrease in the PVR and PbcPVR after biofeedback therapy. There was no difference in voided volume or PbcVol. The shape of the uroflow curve was abnormal (flattened or interrupted) in 72 of the 81 (89%) patients, and 76 (94%) had EMG activity during voiding. Following biofeedback 25 of the 81 (31%) patients had an abnormal uroflow curve (p < 0.001) and only 21 (26%) had EMG activity during voiding (p < 0.001).

The uroflow results for patients with urinary incontinence were then stratified into 3 groups based on response to biofeedback (table 2). The trends for all groups in general were similar to the results for the patients overall. There was an increase in Qmax (significant for the improved group) and Qave (significant for the improved group), and a decrease in Pvr and PbcPVR (significant for the dry and improved groups). There was no difference in the voided volume or PbcVol. When the results of the post-biofeedback uroflow data were compared among the 3 outcome groups, there was no significant difference for any of the parameters. There was no difference in the percentage of patients in the 3 groups with an abnormal or parabolic shaped uroflow curve (p = 0.13). There was also no difference in the percentage of patients with or without EMG activity during voiding for the outcome groups (p = 0.07).

The uroflow data for patients who presented with recurrent urinary tract infections were stratified into those who were cured versus those with persistent infections after biofeedback (in table 3). Again the trends were similar to the results for the patients overall, with an increase in Qmax and Qave (significant for the cured group), and a decrease in the PVR and PbcPVR (significant for the cured and recurrent groups). There was no difference in voided volume or PbcVol. When the results of the post-biofeedback uroflow data were compared between the 2 outcome groups, there was no significant difference for the uroflow parameters, except for Qmax, which was lower in the cured group (23.8 ± 2.1 vs 30.5 ± 3.0 ml/sec, p = 0.04). There was no difference in the percentage of patients with abnormal or parabolic shaped uroflow curve for the 2 groups (p = 0.20), and no difference in the percentage of patients with or without EMG activity during voiding for the outcome groups (p = 0.54). Before biofeedback 42 of the 50 (84%) patients were on prophylactic antibiotics for recurrent UTIs and 22 (52%) stopped them after biofeedback, of whom 16 were considered cured (73%). Of 20 patients who continued on prophylactic antibiotics after biofeedback 15 (75%) were considered cured.

**DISCUSSION**

Children with dysfunctional voiding, defined as inappropriate relaxation of the pelvic floor/external sphincter, in whom conservative management fails have been shown on several previous studies to benefit from biofeedback thera-

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**Table 1. Overall uroflow results for patients before and after biofeedback**

<table>
<thead>
<tr>
<th>Uroflow Variable</th>
<th>Before Biofeedback</th>
<th>After Biofeedback</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Qmax ± SD (ml/sec)</td>
<td>21.0 ± 1.2</td>
<td>24.8 ± 1.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean Qave ± SD (ml/sec)</td>
<td>9.1 ± 0.6</td>
<td>12.0 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median ml PVR (25th-75th percentile)</td>
<td>75 (36–135)</td>
<td>34 (10–64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median % PbcPVR (25th-75th percentile)</td>
<td>26 (12–43)</td>
<td>15 (9–26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median ml Vol (25th-75th percentile)</td>
<td>157 (88–247)</td>
<td>151 (119–216)</td>
<td>0.38</td>
</tr>
<tr>
<td>Median % PbcVol (25th-75th percentile)</td>
<td>53.9 ± 3.1</td>
<td>57.1 ± 2.9</td>
<td>0.39</td>
</tr>
<tr>
<td>No. EMG activity (%)</td>
<td>76/81 (94)</td>
<td>21/31 (68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. abnormal uroflow curve (%)</td>
<td>72/81 (91)</td>
<td>25/81 (31)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
The diagnosis of dysfunctional voiding can be made with noninvasive urodynamic studies. Uroflow curves such as staccato, interrupted or flattened patterns can indicate intermittent or continuous pelvic floor muscle activity during voiding. Pelvic floor surface electromyography can be used to detect muscular activity during voiding. There are obvious possible inaccuracies to using surface EMG electrodes versus needle electrodes to isolate the muscle contraction of the external urinary sphincter but we believe that this would make biofeedback too traumatic to justify their routine use.

Our study is a retrospective review aimed at analyzing the changes in noninvasive uroflow and PVR results, and examines how they correspond to outcome. Prior studies have used uroflow evaluation as a diagnostic modality but only 1 study reported changes in parameters following biofeedback. Schulman et al reported that uroflow studies "normalized" in 30% to 94% of patients depending on the method of biofeedback used. There was no specific comment on how the results correlated with outcomes. Our data showed significant overall increases in Qmax and Qave, and decreases in PVR after biofeedback therapy. Uroflow curves became parabolic in 69% and EMG activity became absent in 74% of cases. There was no change in the voided volumes. Voided volume can affect Qmax and Qave. The lack of change in voided volume in our patients support our conclusion that the changes are due to improvement in voiding technique rather than voided volume. When stratified by outcome groups and comparing the results of individuals before and after biofeedback, there was significant improvement in PVR for the dry and improved category, and in the improved category for the maximum flow rate and average flow rate, while there was no improvement in the no change group for any of these parameters. This finding could indicate a correlation between improvement in uroflow parameters and PVR, and symptomatic improvement. However, when post-biofeedback results were compared among the dry, improved and no change groups the difference was not significant. In other words, although improvement was the greatest in patients who were dry or improved, when the groups were compared after treatment the uroflow results were similar among patients in all outcome groups and, thus, the results of the uroflow studies was not able to predict the outcome.

In patients with UTIs there was similar improvement in the uroflow and PVR results. When comparing the patients who were cured to those with recurrent UTI following biofeedback there was no significant difference in uroflow parameters and PVR, except that Qmax was higher in the patients who continued to have recurrent UTI. These findings are contradictory to what we had expected to find. Our hypothesis was that patients with the best symptomatic improvement would have better uroflow results than those with persistent symptoms. We had expected that patients with UTI resolution would have more normal uroflow results and lower PVRs. Our study shows that biofeedback improves the uroflow parameters and decreases PVR but these are clearly not the only influence on whether urinary incontinence improves or urinary tract infections resolve. Although the uroflow results may not predict clinical success, we continue to use these studies for diagnostic purposes, as an integral part of our biofeedback program and for monitoring progress during treatment.

In 79% of our patients urinary incontinence was cured or improved following biofeedback therapy, and 78% had resolution of recurrent UTIs. These results are comparable to prior reports. Three recent studies reported cure or improvement of urinary incontinence in 61% to 87% of patients treated. Schulman et al reported that with biofeedback recurrent urinary tract infections resolved in approximately 70% of patients. There were 28 patients with isolated urinary incontinence, and 5 with isolated UTIs, and their clinical outcomes after biofeedback were similar to those of patients with incontinence and UTIs. In our study the numbers in these isolated groups are too small for meaningful statistical analysis of uroflow data.

The limitation of our study and other studies is the lack of a control group and the failure to control for multimodal therapy. While biofeedback was being performed, patients were occasionally treated with anticholinergics, laxatives or prophylactic antibiotics. This problem was well documented by a recent review of publications regarding pediatric urinary incontinence.
incontinence which, after reviewing 943 studies, revealed that only 5 met the criteria of controlled trials comparing 2 or more modalities. Of these 5 trials no treatment demonstrated proven benefit. The followup is also short and, thus, there may be some improvements or relapses with time in those patients.

Incontinence is often categorized as either failure of bladder storage and/or emptying. Biofeedback is directed toward improving bladder ability to empty. Evaluation of bladder storage characteristics such as compliance and stability requires invasive urodynamics with cystometry. None of our patients had undergone invasive urodynamic studies before initiating biofeedback. The role of urodynamic studies in children with urinary incontinence due to dysfunctional voiding remains controversial due to the invasive nature of the study and difficulty with interpreting the results. We currently reserve invasive urodynamic studies for select patients in whom biofeedback therapy fails. Biofeedback seems to teach the child to void with a more normal flow pattern and improve voiding efficiency. Our data suggest that it can accomplish this in the absence of improving continence in some patients, the cause of which may be related to abnormal bladder storage or poor compliance with timed voiding. Herndon et al cited patient noncompliance with home exercises and a bladder capacity of less than 60% as independent predictors of failure of biofeedback. We found no difference in voided volumes of those patients who benefited or failed to improve following biofeedback therapy.

The reasons for failing biofeedback despite good improvement in urination pattern are probably related to the storage function of the bladder. The causes of these failures remain unknown but possibilities include detrusor instability or compliance changes due to chronic high pressure voiding. These changes could be potentially secondary to dysfunctional voiding. It remains possible that by improving voiding dynamics bladder storage will also be improved with longer followup as the bladder is rehabilitated.

CONCLUSIONS

Treatment of children with pelvic floor muscle biofeedback is associated with improved urinary continence and decreased urinary tract infections in the majority of patients. It results in improvement in uroflow curves and parameters, and a decreased post-void residual. The posttreatment results of these parameters did not correlate with improvement in continence and urine tract infections.

REFERENCES


DISCUSSION

Dr. George Klauber. Couldn’t the improvement that you saw in the patients just be due to the fact that attention was brought to the bladder, they probably emptied the rectum and they went to the toilet a little more frequently?

Dr. Josiah D. Nelson. The other patients had previously tried conservative therapy before biofeedback, and they did not improve. The improvement was seen after they had gone through all of their biofeedback sessions. However, you make a good point that we did not perform either a randomized or controlled study.

Dr. Mark Horowitz. Overall, 22% of your patients did not respond to biofeedback. With biofeedback, we know that even if we can get these children to relax the pelvic floor muscles, it may not translate into getting them dry because they have bladder instability. Were any of these patients taking anticholinergics?

Doctor Nelson. Of the patients enrolled in the study 44% were treated with anticholinergics before biofeedback, and most of them stayed on them throughout the sessions.

Doctor Horowitz. Including the 22% that did not do well with biofeedback?

Doctor Nelson. I am not certain.
THE THERAPEUTIC EFFICACY OF EXTENDED RELEASE OXYBUTYNIN CHLORIDE, AND IMMEDIATE RELEASE AND LONG ACTING TOLTERODINE TARTRATE IN CHILDREN WITH DIURNAL URINARY INCONTINENCE

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ABSTRACT

Purpose: We compare the tolerability and efficacy of extended release oxybutynin chloride, and immediate release and long acting tolterodine tartrate in children with nonneurogenic diurnal urinary incontinence and symptoms of overactive bladder.

Materials and Methods: Children with a history of diurnal urinary incontinence were arbitrarily assigned to extended release oxybutynin, immediate release tolterodine or long acting tolterodine. The dose was titrated until effective (onset of complete diurnal urinary continence), maximal recommended dosage was achieved or bothersome anticholinergic side effects developed. An independent observer recorded the dose used, anticholinergic side effects and efficacy of therapy (incidence of urinary frequency, urgency, posturing and urinary incontinence).

Results: The study included 86 girls and 46 boys. There were no statistically significant differences among the 3 treatment groups regarding the presence of peripheral or central nervous system anticholinergic side effects. Extended release oxybutynin and long acting tolterodine were significantly more effective at reducing daytime urinary incontinence than immediate release tolterodine (p < 0.01 and 0 < 0.05, respectively). Extended release oxybutynin was significantly more effective then long acting tolterodine for complete resolution of diurnal incontinence (p < 0.05).

Conclusions: Extended release oxybutynin and long acting tolterodine are more effective than immediate release tolterodine in decreasing diurnal urinary incontinence. Extended release oxybutynin chloride is more effective than either immediate or long acting tolterodine for control of daytime urinary incontinence and urinary frequency.

Key Words: pediatrics, urinary incontinence, enuresis, drug therapy

Diurnal urinary incontinence is a common condition in elementary school children. One or more symptoms of overactive bladder were reported in 26% of 7-year-olds, although most children had moderate urinary urgency as the only symptom. Diurnal incontinence was reported in 6.0% of girls and 3.5% of boys, and was usually combined with other symptoms of bladder overactivity. Specifically, urinary frequency, urgency and posturing were associated with urge and/or spontaneous incontinence. When pediatric patients with this voiding history are studied urodynamically approximately 80% demonstrate a reduced functional bladder capacity and/or detrusor hyperactivity. Left untreated, spontaneous resolution occurs in 25% to 30% of patients per year, which is similar to those with nocturnal enuresis. Although most children spontaneously outgrow diurnal urinary incontinence, it is often socially distressing, resulting in the need for the patient to modify behavior to accommodate the disability. Failure of the individual to modify behavior is currently hypothesized to be the chief cause of the Hinman-Allen syndrome (nonneurogenic neurogenic bladder).

The Food and Drug Administration recently approved immediate release and long-acting tolterodine tartrate, and extended release oxybutynin chloride for the treatment of detrusor hyperactivity. There are conflicting reports regarding the efficacy and side effects of these medications in adults and minimal to no information comparing their efficacy in children. We directly compare the efficacy of these 2 drugs in the treatment of children with diurnal incontinence and a history consistent with an overactive bladder.

MATERIALS AND METHODS

We conducted an open label, parallel group, retrospective study of the efficacy and side effects of immediate release tolterodine, long acting tolterodine and extended release oxybutynin for the treatment of overactive bladder. The pharmaceutical companies manufacturing tolterodine and oxybutynin did not support this study in any way. All patients referred to our pediatric incontinence clinic with a history of diurnal urinary incontinence and symptoms of overactive bladder (urinary frequency, urgency, posturing associated with urge and/or spontaneous urinary incontinence) were eligible for the study. No patients were excluded from study due to previous treatment failure, constipation or coexisting nocturnal enuresis.

All study patients underwent a detailed medical and voiding history; physical examination with evaluation of the spine and sacral reflexes; urinalysis and urine culture; uroflow with pelvic floor patch electromyography; renal ultrasonography with pre-void and post-void bladder volumes and abdominal x-ray to evaluate the spine and fecal load. Voiding cystourethrography was performed on patients with a history of urinary tract infection or with an anatomical abnormality detected during the initial screening studies. All patients received detailed written and verbal instructions regarding

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timed voiding, dietary restrictions and treatment of underlying constipation, if present.

Patients included in the study were arbitrarily assigned to start on immediate release tolterodine, long acting tolterodine or extended release oxybutynin based on the formulary restrictions of their health plan, minimizing any drug selection bias. Medications were started at the lowest possible dose (2 mg. tolterodine and 5 mg. oxybutynin) and titrated according to response. Anticholinergic side effects were assessed by the study nurse and given a numerical value of 0—no side effects noted, 1—mild side effects noted by parents only, 2—moderate side effects noted by parents and the patient, and 3—severe side effects significant enough that parents/patient desired to discontinue the medication. The anticholinergic side effects were separated into peripheral effects (dry mouth, dry skin, skin flushing and constipation) and central nervous system effects (mood changes, irritability, sleepiness, sleeplessness and confusion). The patient and parent were asked to comment on each possible facet.

The study nurse assessed efficacy of therapy by reviewing the voiding diary of each patient. Voiding diaries were maintained for 1 to 2 weeks as a baseline before initiating medications. Patients and parents were asked to record the incidence of posturing, urinary frequency, nocturnal enuretic episodes, and the number and frequency of diurnal incontinence episodes. Efficacy for each symptom was categorized as 0—cured, complete resolution of all symptoms, 1—significantly improved, with minimal symptoms remaining, 2—decreased incidence of symptoms but symptoms still causing social distress and 3—No change or improvement in symptoms.

Statistical analysis was performed using the Pearson asymmetrical chi-square method. Cases were analyzed in bimodal (all tolterodine versus oxybutynin) and trimodal (immediate release tolterodine versus long acting tolterodine versus extended release oxybutynin) fashion, with p < 0.05 considered significant. It is noteworthy that all individuals included in the study had a verbal history of diurnal incontinence but only part of the patient population had a history of urgency, frequency, posturing and nocturnal enuresis. Therefore, we calculated symptomatic improvement using the number of patients with a documented symptom of interest as a denominator.

**RESULTS**

The study included 86 girls and 46 boys. Patients were equally distributed by age and sex among the treatment groups (table 1). There were no significant differences in the peripheral or central nervous system anticholinergic side effects among the treatment groups (table 2). Clinical symptomatology and therapeutic efficacy are summarized in table 3. Extended release oxybutynin was significantly better than immediate release tolterodine in the relief of urgency frequency (p < 0.01). Extended release oxybutynin and long acting tolterodine were significantly better than immediate release tolterodine in improving symptoms of diurnal incontinence and urinary frequency (p < 0.01 and p < 0.05, respectively). Extended release oxybutynin was significantly more effective than long acting tolterodine in completely resolving diurnal incontinence (p < 0.05).

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. Girls/No. Boys</th>
<th>Mean Yrs. Age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release tolterodine</td>
<td>32/16</td>
<td>9 (5-18)/9.1 (6-17)</td>
</tr>
<tr>
<td>Long acting tolterodine</td>
<td>10/12</td>
<td>10.4 (6-15)/7.5 (5-15)</td>
</tr>
<tr>
<td>Extended release oxybutynin</td>
<td>44/18</td>
<td>9.1 (5-18)/9.8 (6-18)</td>
</tr>
</tbody>
</table>

Diurnal urinary incontinence as a result of an overactive bladder is a condition frequently seen in school-aged children. Urinary symptomatology can cause significant social embarrassment and psychological distress. Although the vast majority of children outgrow this condition spontaneously, effective medical therapy can rapidly improve quality of life. If initial management with timed voiding, relaxation techniques and treatment of constipation fails to achieve adequate urinary control, pharmacological management may be considered. In such circumstances the goal is to use the medication with the greatest efficacy and fewest side effects.

Immediate and extended release tolterodine tartrate and extended release oxybutynin have been extensively studied in adults with overactive bladder. Tolterodine, a novel potent antimuscarinic agent, was developed for the treatment of urge urinary incontinence and other symptoms related to the overactive bladder. It was specifically developed to be selective for the bladder over other sites of cholinergic activity. Previous studies on the use of tolterodine have documented that this medication exerts a dose-dependent effect on bladder function in adults with detrusor hyperreflexia. A similar controversy exists regarding whether anticholinergic side effects are equivalent between the 2 medications or if tolterodine is truly better tolerated than oxybutynin.

In this study we compared and contrasted the ability of 2 forms of tolterodine (immediate and long acting) to that of extended release oxybutynin for pediatric diurnal urinary incontinence secondary to an overactive bladder. When initiating this study we had originally anticipated that tolterodine in either form would be more tolerable than extended release oxybutynin. This hypothesis was based on the fact that this drug had been specifically engineered to cause fewer anticholinergic side effects. Our study does not support this hypothesis since the clinically apparent anticholinergic side effects were similar among all 3 medications evaluated. The finding that tolterodine and extended release oxybutynin have a similar incidence of anticholinergic side effects has been previously seen in adults by Appel et al.

Long acting tolterodine (p < 0.05) and extended release oxybutynin (p < 0.01) were significantly more effective in improving diurnal urinary incontinence symptoms over the immediate release form of tolterodine. Extended release formulations of both drugs have been noted to improve the therapeutic efficacy and side effect profile by reducing the extent of drug peak and trough values in adults. Our study helps confirm that the therapeutic efficacy of these 2 anticholinergic medications is enhanced with the extended or long acting forms in pediatric patients as well. The finding that extended release oxybutynin was significantly more effective than tolterodine in resolving the symptoms of diurnal urinary incontinence and micturition frequency is also similar to that reported by Appel et al and associates in the management of urge incontinence in adults. Based on these data we recommend use of extended release anticholinergic medications over their immediate release forms for the treatment of pediatric patients with bladder overactivity. In addition, in a direct comparison between extended release oxybutynin and tolterodine, extended release oxybutynin was clinically more efficacious in the relief of symptoms for the pediatric overactive bladder.

There is potential for bias in our study design. Any conclusion regarding efficacy and safety may be seriously biased by the patients/nurses/physicians and parent knowledge of which treatment was given (open label). A
randomized double-blind trial is needed to avoid bias and account for placebo effect. Distribution of patients into the treatment arms was uneven. Although the number of patients treated in each arm was adequate for statistical analysis and supports the conclusions, including more patients in the long acting tolterodine arm might have resulted in different results. Finally, in our study patients and parents were asked to comment on each possible side effect. The study nurse actively solicited responses to the side effects. Active solicitation of side effects may lead to overreporting, and introduces the potential bias of the individual collecting the data.

**CONCLUSIONS**

For the treatment of pediatric diurnal urinary incontinence secondary to overactive bladder extended release forms of tolterodine and oxybutynin are well tolerated and significantly more efficacious than the immediate release form of tolterodine. In our experience the extended release form of oxybutynin chloride was significantly more effective than either immediate or extended release tolterodine for the control of daytime urinary incontinence and micturition frequency.

Dr. D. Husmann provided editorial assistance, and the Statistics Department of Mayo Clinic performed data analysis.

**REFERENCES**