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Use of baclofen in children with dysfunctional voiding: a preliminary report

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Introduction The aims of the present study were to examine the effectiveness and safety of baclofen in children with dysfunctional voiding (DV).

Material and methods Thirty children with primary DV were enrolled. Patients underwent history taking, complete physical examination, urine analysis and culture, ultrasonography of the urinary system, a uroflowmetry study and post urine residue analysis. The Dysfunctional Voiding Symptom Score (DVSS) questionnaire was completed and other related symptoms were recorded. Oral baclofen was started for the study group at a dose of 1 mg/kg in 3 divided doses. Ultrasonography, a uroflowmetry study and questionnaire were repeated 3 months later.

Results We observed a mean decrease of 14.67 ml in post void residual urine (PVRU) after 3 months. After usage of baclofen, increase in Qmax (5.74), increase in mean flow rate (8.2 vs. 11.3), and an average decrease of 12.3 in the DVSS questionnaire ($p < 0.001$) were also observed. The number of voluntary voiding and wetting episodes were significantly decreased after treatment with baclofen ($p = 0.001$). Three main complaints of the patients were urgency ($p = 0.001$), dysuria ($p = 0.004$) and straining ($p = 0.004$) and all were significantly decreased after medical therapy with baclofen.

Conclusions Baclofen may be useful in treatment of pediatric dysfunctional voiding. It was well tolerated among our patients with a remarkable reduction in their symptoms.

Key Words: dysfunctional voiding ‹› baclofen ‹› children

INTRODUCTION

Dysfunctional voiding (DV) is a common clinical entity which is seen by approximately 40% of patients referring to pediatric urologists [1, 2]. The term of dysfunctional voiding is used according to the current International Children's Continence Society (ICCS) terminology guidelines which state that "children with dysfunctional voiding habitually contract the urethral sphincter during voiding" [3]. It is likely that the etiology is multifactorial and may include learned behavior perpetuation of infantile pattern, maturation delay or, to a lesser extent, genetic or congenital factors [3]. DV can result in various symptoms, including storage symptoms (frequency, urgency and urge incontinence) and emptying symptoms (decreased force of stream, hesitancy, need to strain and a feeling of incomplete bladder emptying) [4]. It might also be responsible for recurrent urinary tract infections (UTIs), acute or chronic urinary retention and in severe cases upper and lower urinary tract decompensation [4]. There are many published reports of DV in children [5]. Currently there is no standardized protocol for treatment of DV in children [3]. Some of these children can benefit from non-pharmacological therapy such as behavioral interventions and biofeedback.

Behavioral therapies usually comprise of educating children and their families, maintaining adequate fluid intake, voiding at regular intervals to avoid bladder overdistension, correcting toilet posture, and creating an optimal bowel empyting program [3, 6]. A typical treatment session might include a uroflowmetry study, ultrasonographic evaluation of postvoid

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residual urine volume, and a one-hour session with perineal patch electrodes for electromyography [7]. However, because all patients do not respond to non-pharmacological therapy, it is recommended as an adjuvant treatment. To our knowledge there is no approved pharmacological therapy for DV in children [3]. The two available targets for pharmacologic treatment of DV are the bladder body (such as with anticholinergic agents) and the bladder outlet [3]. Although antimuscarinic agents have been effective in treating detrusor overactivity, muscarinic and cholinergic agonists (e.g. betanechol) have not been demonstrated to be effective in the treatment of emptying problems in children with DV. Subsequently, for resolving this problem, research has focused on drugs that affect the bladder outlet. Although there are several reports of selective alpha-blocker therapy in children with incomplete bladder emptying, [8, 9] the use of alpha-blockers in children with lower urinary tract dysfunction has not been approved [3].

Another pharmacologic approach to facilitate bladder emptying is intravesical botulinum toxin injection. There are several successful outcomes with use of botulinum toxin to treat children with detrusor-external sphincter dyssynergia [10, 11]. There is a relationship between bladder and bowel dysfunction that affects the assessment and management of DV. Commonly, stool retention with or without fecal incontinence coexists with DV as a result of non-relaxation of the pelvic floor musculature [3].

Gamma-aminobutyric acid (GABA)-ergic neurons exert their effects on the bladder and urethra. GABA immunoreactive interneurons in the sacral spinal cord receive projections from the pontine micturition center to relax the external urethral sphincter [12, 13]. In concordance with this mechanism, intrathecal application of baclofen could be used to relax the urethral sphincter [4]. Interestingly, Miyazato et al., demonstrated that GABA, as an important inhibitory neurotransmitter in the central nervous system (CNS), has an important role in inhibitory regulation of bladder contractions [13, 14].

Therefore, baclofen as a GABA agonist drug exerts its clinical effect through the two aforementioned mechanisms.

In children, baclofen is indicated for the symptomatic treatment of spasticity of cerebral origin, especially when due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease [15]. For treatment of external urethral sphincter spasticity, baclofen was initially administered in an intrathecal injection for paraplegic patients with dyssynergia [16]. Then, during a trial in women with DV, the beneficial effect of baclofen was confirmed [4]. To our knowledge there is no study addressing the efficacy of baclofen in treatment of DV in children. Therfore, based on previous experiences, we conducted a study to evaluate the safety and efficacy of baclofen in children with dysfunctional voiding.

MATERIAL AND METHODS

Between February 2014 and August 2015, 30 children with a primary diagnosis of dysfunctional voiding according to the International Children's Continence Society (ICCS) definition were enrolled in our study. These patients were treated by one pediatric urologist at our institution. The initial assessment included a complete history and physical examination, urine analysis and culture, urinary tract ultrasonography with determination of post void residual urine (PVRU) volume and uroflowmetry. Patients with active UTI were managed appropriately before initiation of baclofen. Exclusion criteria were known neuropathic bladder and/or any anatomical abnormality of the lower urinary tract. In all cases, behavior modification was initiated for 4 to 6 weeks (including routine hydration, voiding at regular intervals, avoiding bladder overdistension and regular bowel program avoiding constipation and when these modalities failed or resulted in only slight improvement, medical therapy with baclofen was initiated. At least 3 months follow-up was required for inclusion in the study. Duration of medical treatment with baclofen was 3 months. For determination of treatment efficacy, each patient completed a questionnaire that was designed according to the dysfunctional voiding scoring system (DVSS) by Farhat et al [1]. In this system, 10 quantitative and qualitative parameters were translated into age appropriate questions for children. The questions were about urinary symptoms such as urinary incontinence, voiding habits, urgency, posturing, bowel habits and stressful life conditions. The 10 questions were assigned scores of 0 to 3 according to responding to the questionnaire. The responses were weighted equally giving a maximum possible score of 30. The optimal cutoff score was 6.02 for females and 9.02 for males [1]. This questionnaire was completed before treatment with baclofen and after treatment at the first and third month follow-up. Parents were asked to quantitate the number of frequency or voluntary voiding and wetting episodes and about signs such as urgency, straining and dysuria. For evaluation of associated bowel dysfunction, we used the Bristol stool chart [3]. Urinary frequency was defined as voluntary voiding more than 7 times per day with normal fluid intake [17]. After initial assessment, oral baclofen was begun for the patients with a dose

of 1 mg/kg in 3 divided doses (Baclofen tablets BP 10 mg, 2016). The DVSS questionnaire was completed again at one and three months after starting baclofen for each patient. Urinary tract ultrasonography and uroflowmetry was repeated after three months of medication. The number of voluntary voiding and wetting episodes and data about urgency, straining and dysuria was recorded again after three months of medication. Compliance was defined as good: child always taking the medication, fair: child taking the medication most of the time, and poor: child would not take the medication.

The Medical Ethical Committee of the University approved the study protocol, and informed consent was obtained from all patient's parents. The statistical analysis was performed using the Wilcoxon signed ranks test, paired t-test and McNemar's test. Values of $p < 0.05$ were considered as statistically significant.

RESULTS

A total of 40 children (22 girls and 18 boys) were evaluated for the study of whom 30 (16 girls and 14 boys) were enrolled. Ten children were eliminated from the study due to inadequate follow-up. The mean age of patients was 6.65 ±2.18. Presenting symptoms and associated complaints are summarized in Table 1. Evaluation of residual urine (RU) volume before and after treatment with baclofen showed that in 22 cases PVRU decreased and remained the same in 8 cases. The mean decrease in PVRU was 14.67 ml with confidence interval (CI) 95% (521–24.12) and standard deviation (SD) 4.62, so baclofen is effective in decreasing PVRU in children ($p = 0.004$). Maximum flow rate (Qmax) increased after baclofen therapy in 29 cases, the average rate of increase in Qmax was 5.74 with SE standard error (SE) 1.29 and CI 95% (3.11–8.37), so baclofen is a good drug when considering this variable ($p = 0.001$).

Mean flow rate increased from 8.2 (prior baclofen) to 11.3 (post baclofen) with a mean difference of 3.1 and SE 0.48 and CI 95% (2.11–4.08) and this change was statistically significant ($p = 0.001$). The number of voluntary voiding episodes significantly decreased after treatment with baclofen ($p = 0.001$), the mean rate of reduction in voluntary voiding was 4.07 with SE 0.7 and CI 95% (2.64–5.49). Wetting episodes decreased with a mean difference of 3.33, SE 0.45 and CI 95% (2.41–4.26) after treatment with baclofen ($p = 0.001$). The three main complaints of the patients were urgency ($p = 0.001$), dysuria ($p = 0.004$) and straining ($p = 0.004$) and these significantly decreased after medical therapy with baclofen. Before treatment, 56.7% of patients had urgency and after treatment in 10% urgency was positive (46.7% reduction). Straining was seen in 43.3% of children before baclofen and in 13.3% after baclofen (30% reduction). The rate of dysuria before treatment was 36.7% and after treatment with baclofen was 6.7% (30% reduction). In evaluation of voiding pattern, before treatment, 21 patients had staccato flow pattern and after treatment with baclofen, 19 (90%) patients showed change in voiding pattern towards the normal bell shape and this change was statistically significant ($p = 0.001$). In evaluation of DVSS, the score was significantly less after 3 months of baclofen therapy and this change was statistically significant ($p < 0.001$). This means that after 3 months, we recorded an average decrease in DVSS of about 12.3 (CI 9.11–15.49). In the evaluation of the stool Bristol score we had a mean increase in the score of about 2.33 three months after starting baclofen (SE 0.28 and CI 2.41–4.26), and this change was statistically significant ($p < 0.001$). Twelve patients reported side effects of baclofen in the present study; which were dizziness and fatigue in 5 patients and nausea and vomiting in 7 cases.

Table 1. *Summary of presenting symptoms in the patients who were included in the study*

Symptoms	No. (%)
Symptoms	20 (67%)
Dysuria	10 (33%)
Urgency	17 (57%)
Straining	13 (43%)
Diurnal/nocturnal enuresis	11 (37%)
History of urinary tract infections	7 (23%)

DISCUSSION

Dysfunctional voiding is an abnormality of bladder emptying in neurologically normal individuals in whom there is increased external sphincter activity during voluntary voiding [4]. Abnormal, slow urine flow rate and abnormally high post void residual urine volume are the basis of this diagnosis, which should be based on repeated measurements to confirm the abnormality [6]. In addition to conservative treatment, many drugs have been used such as bladder relaxants, anticholinergic drugs and alpha-adrenergic antagonists.

Urotherapy, referring to a non-surgical and non-pharmacological treatment, has been considered an effective treatment for DV even though there is no standardized protocol for this therapy [6]. Munding et al., in a 2001 pilot study in children with DV,

showed that tolterodine can be used with behavioral modifications to reduce wetting episodes without severe adverse events [18]. Danfeny et al. demonstrated that a 4-week course of baclofen significantly reduced the number of void/24 hr in women with DV [4]. In 2012, Chin and et al. showed that combined use of baclofen and antimuscarinic agents could reduce voiding difficulty in treating women with overactive bladder with abnormal voiding patterns [19]. Miyazato et al. explained that stimulation of the spinal GABA-ergic mechanism could be a good option for treatment of bladder contractions after spinal cord injury [14]. There is no study to address the efficacy of baclofen in treatment of DV in children. Therefore, based on previous experiences we conducted a study to evaluate the safety and efficacy of baclofen in children with dysfunctional voiding.

The data of the present study documented that baclofen can be a safe and effective drug for treatment of DV in children. Baclofen as a GABA agonist may exert its clinical effects through modulation of the aforementioned mechanism to reduce external urethral sphincter tone [12, 13]. In addition, it has been reported that detrusor overactivity can be reduced by baclofen [14].

In the present study, baclofen reduced residual urine volume, increased Qmax and mean flow rate, decreased straining during urination and improved the defecation pattern in children with DV which may be related to the effect of baclofen in reducing external urethral sphincter tone. In addition to the aforementioned effects, this study showed that using baclofen to treat children with DV can ameliorate symptoms such frequency, urgency, wetting and dysuria. Studies on rats by Pehrson [20] and Miyazato [14] showed that baclofen (given intrathecally), attenuated detrusor overactivity, suggesting that the inhibitory actions of GABA-B receptor agonists in the spinal cord may be useful for controlling micturation disorders caused by C-fiber activation in the urothelium and/or suburothelium [20]. So, baclofen may be useful in suppressing detrusor overactivity which is important in inducing symptoms such as frequency, urgency, wetting and dysuria. Another explanation for the ameliorating effect of baclofen might be due to lowering the residual urine and subsequent reduction of irritative symptoms. The adverse events attributable to baclofen were those associated with relaxation of the striated muscles and were generally transient and mild to moderate. In our study 12 patients had symptoms including dizziness and fatigue in 5 cases and nausea and vomiting in 7 cases which was well tolerated tolerated in all cases.

It should be mentioned that the usual method of uroflowmetry was applied to obtain the urine flow rate in the present study. It should be noted that Franco et al. explained the quantitative approach using a flow index that could provide better results than the present system of grading flow curves [21].

Our study had certain limitations. Firstly, the sample size was small and secondly the results of the study may be affected by previous behavioral therapy. Further evaluation of this medication in controlled clinical trials with longer follow-up of patients with and without behavioral and biofeedback therapy is necessary to confirm its efficacy in the pediatric population.

CONCLUSIONS

Baclofen, a potent GABA-ergic agonist significantly reduced the obstructive and irritative symptoms of DV in children and was well tolerated, thus, dysfunctional voiding can be treated by baclofen with good results in children.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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