Efficacy of Combined Anticholinergic Treatment and Behavioral Modification as a First Line Treatment for Nonneurogenic and Nonanatomical Voiding Dysfunction in Children: A Randomized Controlled Trial

S. Ayan, K. Topsakal, G. Gokce and E. Y. Gultekin

From the Department of Urology, Cumhuriyet University School of Medicine, Sivas, Turkey

Purpose: This randomized blinded clinical study was designed to compare the efficacy of tolterodine treatment combined with behavioral modification, behavioral modification alone and behavioral modification plus placebo in children with nonneurogenic, nonanatomical voiding dysfunction.

Materials and Methods: A total of 72 children meeting inclusion criteria were randomly allocated to 1 of 3 groups. One group received tolterodine (1 mg twice daily) along with behavioral modification, 1 received behavioral modification only and 1 received placebo with behavioral modification. A dysfunctional voiding scoring system questionnaire was completed for all patients at the beginning of the study, and at 1 and 3 months of treatment.

Results: A total of 71 patients were evaluated. The groups did not differ with respect to age, gender and symptom score before study enrolment ($p > 0.05$). Repeated calculations of symptom scores at 1 month of the treatment revealed a significant decrease in symptoms in all 3 groups, with a significant decrease in patients receiving tolterodine. In addition, at month 3 the symptom score of the tolterodine group was significantly lower compared to month 1, while scores remained steady in the behavioral modification and behavioral modification plus placebo groups.

Conclusions: Tolterodine combined with behavioral modification for voiding dysfunction in children without neurological or anatomical abnormality can be recommended as a first line treatment before invasive evaluation.

Key Words: urination disorders, behavior therapy, cholinergic antagonists, tolterodine, pediatrics

Voiding dysfunction is one of the most frequently seen clinical entities in pediatric urology.[1] Symptoms include daytime and nighttime wetness, urgency, frequency or infrequency, constipation or fecal incontinence, and UTI.[2] Although there is no consensus regarding the diagnostic features, or the ideal methods of detecting and monitoring voiding dysfunction, a history, physical examination, voiding diaries and uroflowmetry curves with detection of post-void residual volume are the most accurate methods of diagnosis.[3] Many recent studies have shown that routine urodynamics, radiological evaluation and cystoscopy do not change therapy or influence final outcome in the majority of children with voiding dysfunction.[4,5] Anticholinergic medication and strict behavioral modification are the cornerstones of treatment for functional voiding disorders and incontinence.[1,6] Tolterodine is an anticholinergic that has been widely used in the treatment of incontinence and overactive bladder in the adult population. In addition, it has been found to be effective and safe with reportedly fewer adverse effects compared to oxybutynin in recent pediatric series.[7–11]

In a recent study we demonstrated that the use of tolterodine combined with behavioral modification for dysfunctional voiding in children without neurological or anatomical abnormality can be recommended as a first line treatment before invasive evaluation.[12] The results of that study may be criticized because behavioral modification alone provided considerable improvement in this population of children. In the present study of children with voiding dysfunction without obvious anatomical or neurogenic problems we compared the effectiveness of antimuscarinic treatment combined with behavioral modification, behavioral modification only and behavioral modification plus placebo.

PATIENTS AND METHODS

For sample size determination an average difference of 5 points in symptom score (dysfunctional voiding scoring system) was defined as clinically relevant (see Appendix).[6] It was expected that 95% of the calculated scores would range between 6 and 20, resulting in a standard deviation of 2. A total sample size of 60 patients (20 in each arm of the study) was calculated to be necessary to detect a 5-point reduction in symptom score with a power of 80% and an alpha error of 5%. It was assumed that the study dropout rate would be about 15%, and, therefore, a total sample of 72 children (36 girls and 36 boys) meeting the inclusion criteria were recruited and randomly allocated to 1 of 3 groups (table 1). Voiding dysfunction was defined as incontinence, frequency, urgency or obstructive symptoms with or without recurrent nonfebrile urinary tract infection in the absence of an obvious anatomical or neurogenic cause. A total of 72 children 4 to 12 years old presented with these features and had symp-

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TABLE 1. *Age and gender rates by treatment group*

	Group 1	Group 2	Group 3
No. pts	3	20	20
Mean yrs age ± SD*	9.09 ± 2.59	8.65 ± 2.30	8.25 ± 1.86
No. gender (%):			
Male†	15 (48.4)	13 (65)	8 (40)
Female‡	16 (51.6)	7 (35)	12 (60)

* F = 8.21, p = 0.444.
† p = 0.270.
‡ Chi-square = 2.61.

TABLE 2. *Presenting symptoms and associated complaints*

Symptoms	No. Pts
Diurnal enuresis	35
Nocturnal enuresis	27
Frequency/urgency	45
Constipation and/or encopresis	22
History of afebrile UTI	41
Giggle incontinence	2

tom scores of 6 (girls) or 9 (boys) or greater. One patient in the tolterodine group was excluded because of edema in the hands and feet within 3 days of beginning treatment.

All patients underwent a noninvasive evaluation consisting of history, urinalysis, renal and bladder ultrasound, and physical examination with specific emphasis on voiding pattern. Exclusion criteria were abnormality on renal ultrasound, large post-void residual volume, a history of febrile UTI, a history of failed therapy and positive neurological examination, including back lesions and abnormal voiding pattern. Residual urine less than 20 ml was accepted as insignificant. Informed consent was obtained from the parents.

All patients were trained in behavioral modification, including timed voiding, double voiding and relaxation of the pelvic floor during voiding. Anticholinergic treatment with tolterodine (1 mg twice daily) was started in group 1 and maintained for at least 3 months. No medication was administered to the children in group 2, who received behavioral modification training only. Children in group 3 were administered 0.5 mg glucose in 20 ml water once daily, along with behavioral modification training. Dysfunctional bowel elimination requiring a special diet and laxatives was defined by pebble-like hard stools for a majority of stools, or firm stools 2 or fewer times weekly. A total of 30 patients (17 girls and 13 boys) with dysfunctional bowel elimination were treated with a higher fiber diet and laxatives if necessary. At the study onset, and at 1 and 3 months of treatment a DVSS questionnaire was completed for all patients. Parents were asked to record the side effects during drug administration. We used SPSS® version 10.0 software, ANOVA, multivariate repeated measures of ANOVA with the Tukey test as a post hoc test, the smallest detectable difference, and Mann-Whitney U test and chi-square test were used to test the difference, with p values less than 0.05 considered statistically significant.

RESULTS

Patient age and gender distribution were similar between the groups (table 1). Presenting symptoms and associated complaints are outlined in table 2. The differences among symptom scores in the 3 groups before treatment were insignificant (fig. 1). Repeated calculations of symptom scores at 1 month of treatment revealed a significant decrease in all 3 groups. Decrease of symptom score was significantly greater in the tolterodine group compared to the other groups. At 3 months the symptom score of the tolterodine group was significantly lower compared to 1 month, while scores remained steady in the behavioral modification and behavioral modification plus placebo groups (fig. 1).

When boys and girls were grouped separately and decreases in symptom scores by gender were compared there was an insignificant difference between genders in the tolterodine group. Similarly, gender adjustment did not affect the statistical results in the other groups (fig. 2).

Mean scores for a subgroup of DVSS questions (numbers 1, 2, 6 and 7) related to detrusor overactivity were also significantly different at 1 month of treatment in the tolterodine group (8.90 vs 3.50, $p < 0.001$), while there was a nonsignificant difference in the behavioral modification group (7.60 vs 6.90, $p > 0.05$) and a slight but significant difference in the behavioral modification plus placebo group (9.40 vs 5.25, $p < 0.05$).

A total of 41 children had a history of afebrile UTIs. The numbers of patients with UTI at first enrollment were 5 among the tolterodine group, 7 of those receiving behavioral modification only and 3 of those receiving behavioral modification plus placebo. All children were monitored with urine culture performed monthly even if they were asymptomatic. New UTIs were documented in 6 patients in the tolterodine group, 5 of those receiving behavioral modification only and 7 of those receiving behavioral modification plus placebo. The difference in the UTI rates between the groups was insignificant. Children with UTI at first enrollment and during the study were treated appropriately and placed on antibiotic prophylaxis.

Tolterodine was discontinued in 1 girl in whom hand and foot edema developed. This patient was excluded from the

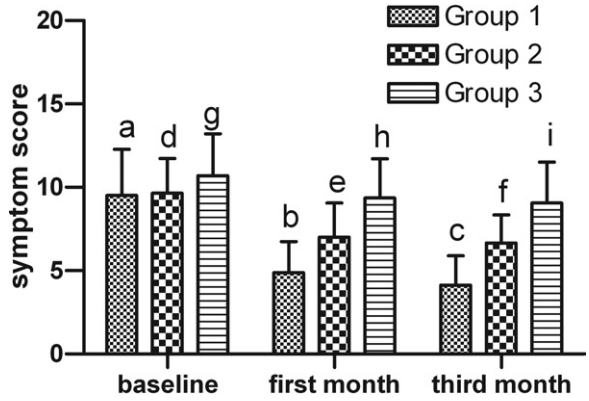

FIG. 1. Baseline and followup symptom scores in 3 treatment groups. Data are expressed as mean ± SD. *Group 1* (*a* to *c*), tolterodine plus behavioral modification. *Group 2* (*d* to *f*), behavioral modification only. *Group 3* (*g* to *i*), behavioral modification plus placebo. There were no significant differences between baseline mean scores (Fisher's F ratio = 1:45; p = 0.240). There were significant differences between a and b ($p < 0.05$), between d and e ($p < 0.05$), and between g and h ($p < 0.05$). Significant differences were also noted between b and e/h (Fisher's F ratio = 28:62, $p < 0.05$), and between b and c ($p < 0.05$). There were no significant differences between e and f, or h and i ($p > 0.05$). Significant difference was noted between c and f/i (Fisher's F ratio = 38:41; $p < 0.05$).