Treatment efficacy of tolterodine versus belladonna mixture in children with idiopathic overactive bladder

Zheming Xu, Dehua Wu, Chang Tao, Juan Zhou, Zhihui Zheng, Daxing Tang

ABSTRACT

Objectives  Children with symptoms of urinary urgency, frequency and incontinence are common in the clinic. The aim of the present study was to compare the tolerability and efficacy of tolterodine, a bladder-selective muscarinic receptor antagonist, with belladonna mixture, a traditional anticholinergic drug, in the treatment of idiopathic overactive bladder in children.

Methods  Children aged 5–10 years with a history of diurnal urgency, frequency and incontinence were randomly divided into two groups. Participants in group 1 were given tolterodine 1 mg twice a day for 14 days. If the results were found to be mildly ineffective, after the first 14 days of therapy, prolonged course with 2 mg twice a day was given. In group 2, the children were treated with belladonna mixture 5 mL twice a day for 14 days.

Anticholinergic side effects were recorded during the therapy and efficacy was evaluated with voiding diary recorded by the parents at the beginning and end of therapy.

Results  A total of 668 cases were included in this study and 334 for each 25 group (496 boys and 172 girls). Evident anticholinergic side effects which could cease the therapy, such as dry mouth, constipation, mood changes, irritability, and so on, exhibited only on 2% of participants in the tolterodine group but 69% in the belladonna mixture group (p<0.05). The symptoms of detrusor overactivity disappeared or significantly improved in 80% of children in the tolterodine group and 37% in the belladonna mixture group (p<0.05) group.

Conclusions  Tolterodine had better tolerability and efficacy than belladonna mixture in treating overactive bladder in children.

INTRODUCTION

School-year-old children with symptoms of daytime urinary urgency, frequency with/without wetness and incontinence are common in the clinic.1 Reports have shown that the symptoms of one or more overactive bladder (OAB) behaviors occur in 26% of 7-year-old children,2 and 80% of them demonstrate a reduced functional bladder capacity and/or detrusor overactivity.3 With 49 left untreated, spontaneous resolution occurs in 25%–30% of patients per year, which is similar to those with nocturnal enuresis.4 However, it is often socially and mentally distressing, resulting in the need for the patients to modify behavior to accommodate the disability. Failure to modify behavior is currently hypothesized to be the chief cause of the Hinman-Allen syndrome (non-neurogenic bladder).4,5 Therefore, these children need positive and effective medical interventions in which anticholinergic drugs and behavior therapies are commonly accepted right now. The aim of the present study was to compare the tolerability and efficacy of tolterodine, a bladder-selective muscarinic receptor antagonist, and belladonna mixture (a traditional anticholinergic drug which was commonly used in pediatric clinics in China) in children with detrusor overactivity.
METHODS
Between August 2004 and August 2018, children aged 5–10 years old with symptoms of urge incontinence suggestive of detrusor overactivity were included into this study. In this study, 668 children were randomly divided into two groups (496 boys and 172 girls, mean age 7 years, range 5–10 years). Eligible children were those with symptoms of urge incontinence suggestive of detrusor overactivity (1 diurnal incontinence episode or more days out of 7), which last more than 2 weeks. In group 1, the children (242 boys and 92 girls) start to take tolterodine 1 mg twice a day for 14 days. If the effect was mild or there was no effect after the first 14 days’ therapy, prolonged course with 2 mg twice a day was given for another 14 days. In group 2, the children (254 boys and 80 girls) were treated with belladonna mixture containing belladonna tincture and compound vitamin B solution 5 mL twice a day for 14 days. Pretreatment assessments were performed using physical examination, routine urine test, and ultrasound for postvoid residual (PVR) volume. Patients were excluded if they had urinary tract infection, urinary tract malformation, and neurogenic bladder. PVR volume was calculated by removing the amount of urine from the bladder capacity, those with PVR volume that was 20% or more of functional bladder capacity were also excluded. Informed consent was obtained from the parents. The side effects were recorded during the therapy, and efficacy was evaluated with voiding diary recorded by the parents at the beginning and end of therapy. The outcomes of the study were marked as: 0—completely healed, symptoms disappeared, no urinary incontinence and no social disorders at all; 1—significantly improved, very few symptoms left, occasionally once or twice urinary incontinence, social activity is almost unaffected; 2—symptoms alleviated, frequency of urinary incontinence decreased, but still with disability of social activity; 3—inefficacy, symptoms do not alleviate at all, no improvement in urinary incontinence, and still with serious social activity disability. The side effects of anticholinergic drugs were divided into peripheral nervous system (PNS) symptoms (dry mouth, dry skin, constipation, and so on) and central nervous system symptoms (mood changes, irritability, overexcitement, mental disorder, and so on). The side effects were recorded as: 0—no side effects; 1—light, observed by parents; 2—mild, observed by patients and parents; 3—severe, cannot be tolerated by patients and parents. After the treatment, all patients were followed for 3 months, and recurrence rate, quality of life, and side effects of drugs were measured and recorded.

Statistical analysis
SPSS V.16.0 software package was used for statistical analysis. χ² test was used to compare the means of the two groups. Values with p<0.05 were considered statistically significant.

RESULTS
A total of 668 cases were included in this study with 334 patients in each group (p=0.72). Patient subgroups were identified a priori using demographic characteristics (age, sex, course of disease) for exploratory analyses (table 1).

Table 1 Characteristics of tolterodine and belladonna mixture groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Course of disease (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>242</td>
<td>92</td>
<td>7.5 (5–10)</td>
</tr>
<tr>
<td>Belladonna mixture</td>
<td>254</td>
<td>80</td>
<td>7.7 (5–10)</td>
</tr>
</tbody>
</table>

*The rank-sum test was used to compare the means, p=0.072, with no statistical significance.

The results showed significant differences in side effects of PNS and central nervous system between the two groups (table 3). The tolterodine group showed very few side effects. Two cases stopped the treatment because of overexcitement in the night; six cases suffered from constipation. For the belladonna mixture group, the main side effects were insufferable dry mouth and

Table 2 Efficacy of tolterodine versus belladonna mixture

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cured</th>
<th>Significantly improved</th>
<th>Partially improved</th>
<th>No improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>142 (43%)*</td>
<td>122 (37%)*</td>
<td>64 (19%)*</td>
<td>6 (2%)*</td>
</tr>
<tr>
<td>Belladonna mixture</td>
<td>62 (19%)</td>
<td>58 (18%)</td>
<td>106 (32%)</td>
<td>108 (32%)</td>
</tr>
</tbody>
</table>

*P<0.001.
eyes, constipation, mood changes, irritability, and so on, which exhibited in 69% of total patients (p<0.001), but no patients abandoned belladonna mixture and turned to use tolterodine during the study.

The 3-month follow-up showed a significant treatment effect based on parental assessment of treatment benefit. Among parents of children who received tolterodine therapy, 89% reported a significant improvement of life quality, including social skills, self-confidence, better mood, and emotional stability, while only 35% in the belladonna mixture group reported such improvements.

**DISCUSSION**

Although the exact etiology of OAB is unknown to date, pharmacological therapy has been targeted to both the central nervous system and PNS. Acetylcholine is the primary excitatory neurotransmitter involved in bladder (detrusor) contraction and emptying. Therefore, muscarinic receptors, a kind of acetylcholine receptor, are potential PNS targets. Tolterodine is a bladder-selective muscarinic receptor antagonist. As competitive M choline receptor blocker, it is metabolized into a 5-hydroxymethyl derivative by the liver after oral administration. It competitively inhibits the binding of acetylcholine to its receptor, thereby inhibiting the involuntary contraction of the bladder, and can relieve urinary frequency, urinary urgency and urgency incontinence caused by excessive bladder activity. Tolterodine is widely used in adults with urinary incontinence and OAB. There are many reports on the tolerability, safety and efficacy of tolterodine in adult patients.

In 2000, Goessl et al. first reported the effects of tolterodine in children with reduced functional bladder capacity and/or detrusor hyperactivity, and there are also reports on the usage of tolterodine in children with OAB afterwards. In 2006, Kilic et al. reported treatment of children with detrusor instability with tolterodine that shows significantly better tolerability. In 2008, Reddy et al. found that tolterodine formulations were effective and well tolerated in children with neurogenic detrusor overactivity. Traditionally, detrusor hyperactivity was treated with anticholinergic drugs, such as propantheline, atropine, anisodamine, belladonna mixture, and so on, in China. Similar to other anticholinergic drugs, belladonna mixture mainly combines with cholinergic receptors (M receptor muscarinic cholinergic receptors, N receptor

<table>
<thead>
<tr>
<th>Grading</th>
<th>Tolterodine (n)</th>
<th>Belladonna mixture (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–none</td>
<td>280</td>
<td>31*</td>
</tr>
<tr>
<td>1–light</td>
<td>46</td>
<td>72*</td>
</tr>
<tr>
<td>2–mild</td>
<td>6</td>
<td>105*</td>
</tr>
<tr>
<td>3–severe</td>
<td>2</td>
<td>126*</td>
</tr>
</tbody>
</table>

*P<0.001.
The limitation of this study was that belladonna mixture had strong side effects, most patients had difficulty finishing the course of treatment, which influences the final efficacy.

In conclusion, tolterodine had better tolerability and efficacy than belladonna mixture in treating OAB in children.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Ethical Committee, Zhejiang University School of Medicine (No 2016-128).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES