Comparison of the Effects by Obybutynin and Tolterodine on Spina Bifida Patients: A Pilot Crossover Study

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Objectives: To compare the effects of obybutynin and tolterodine in neurogenic bladder patients with spina bifida in a crossover study.

Methods: Seven myelomeningocele and one spinal lipoma cases, maintained with obybutynin and clean intermittent catheterization for more than 60 months, were enrolled. Age ranged from 8 to 23 years (mean 12.0, male/female = 2/6). After 2 weeks of washout period, obybutynin (0.3 mg/kg, maximum 12 mg) or tolterodine (0.12 mg/kg, maximum 4 mg) was administered for 4 weeks, and then switched to the other drug for 4 weeks. At the end of the three periods, the patients and/or parents documented urinary storage status and adverse effects, and urodynamic study was performed.

Results: In seven cases undergoing sequential urodynamic study, the baseline compliance of the patients (6.81 ± 1.83) increased to 9.98 ± 4.97 by obybutynin and 10.16 ± 2.53 by tolterodine (P < 0.05 for each). Better compliance was noted in two cases with tolterodine and in two cases with obybutynin. Stronger adverse effects were reported in three out of eight patients (37.5%) by obybutynin and three out of eight patients (37.5%) by tolterodine. Although storage effect and side effects were equivalent for total patients, markedly diverse response was noted for each patient, with five choosing tolterodine and three choosing obybutynin.

Conclusions: Individualized evaluation is required for optimal choice of anticholinergics.

Key words neurogenic bladder, obybutynin, spina bifida, tolterodine

1. INTRODUCTION

Anticholinergic agents are first-line therapy for reduction of intravesical pressure in low-compliant neurogenic bladder (NGB) frequently seen in patients with spina bifida.1,2 The drugs play a central role in modern management of NGB due to spina bifida. High dosage of anticholinergic agent reduces the contraction and tonus of the bladder smooth muscle by blockade of muscarinic receptors and achieves reduction of intravesical pressure, which is vital for preventing damage to the upper urinary tract.2 The effect of the drug may not only be palliative, as early administration of anticholinergics reportedly improves the prognosis of bladder function itself, and may reduce the cases requiring bladder augmentation.1,3,4

Obybutynin chloride (obybutynin) has long been a standard drug used for this purpose. New anticholinergics, such as tolterodine,5 solifenacin6 and imidafenacin7 have been introduced for adult overactive bladder (OAB) and shown to have less adverse effects than obybutynin. However, their utility for severe congenital NGB is not established, as the application of the drug is mainly directed by physician’s initiative. For example, Ellsworth and colleagues have conducted a dose escalation study of tolterodine for pediatric NGB population, and reported reliable decrease of compliance in most of their patients, without significant side effects.8 However, no direct comparison has been reported between obybutynin and tolterodine, and there is as yet no consensus for choice of anticholinergic drug in spina bifida patients.

Herein, we conducted a pilot study of crossover comparison between obybutynin and tolterodine in patients with NGB due to spina bifida.

2. METHODS

Neurogenic bladder patients due to spina bifida maintained on clean intermittent catheterization and with obybutynin (0.3–0.4 mg/kg maximum 12 mg) for more than 60 months, and those who were able to document their urinary storage status and adverse effects, were enrolled.

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The patients having undergone any reconstructive surgery of the urinary tract were excluded. Out of 70 spina bifida patients followed at Shiga Medical Center for Children and at Kyoto University, 11 cases met the criteria, with eight patients and/or their guardians submitting written informed consent (Table 1). After 2 weeks of washout period, obybutynin (0.3 mg/kg, maximum 12 mg/day) or tolterodine (0.12 mg/kg, maximum 4 mg/day) was administered for 4 weeks, and then switched to the other drug for 4 weeks as open-label drugs.8,9 Each drug was administered in divided dosage twice a day. Four cases were administered obybutynin preceding tolterodine with the remaining four administered in reverse. The order of the drugs was alternately assigned to the enrolled patients. At the end of each point, the patient or guardian recorded frequency/void (catheterization)/leak chart (FVC) for 2 days simultaneously with the documentation of adverse effects. In seven patients, sequential urodynamic studies (UDS) were also performed at the same time. The first test was done as standard video urodynamics, and the other two tests were done with saline without fluoroscopy. The maximal volume infused in the initial urodynamics during washout period was defined either from sensation of fullness in the patients having bladder sensation, or from maximal catheterized urine volume in clean intermittent catheterization chart in the patients having no filling sensation. Maximal pressure was defined as the intravesical pressure at the Maximal Capacity. Under administration of either drug, the infusion was continued until the intravesical pressure reached the Maximal Pressure defined in the initial test. Evaluated parameters for storage effect were compliance in UDS, functional bladder capacity and maximal dry time, and a 40% or more increase compared to the other drug was considered superior. Statistical analysis was performed by Wilcoxon’s signed-rank test, with \( P < 0.05 \) considered significant.

### 3. RESULTS

The patients’ demographics are shown in Table 1. Mean age at the study was 12.0 years old.

According to FVC, one patient reported superior storage status with tolterodine and one patient with obybutynin (Table 2). In seven cases undergoing sequential UDS, both drugs increased bladder compliance significantly. The baseline compliance of the patients (6.81 ± 1.83 mL/cmH2O) increased to 9.98 ± 4.97 by obybutynin, and 10.16 ± 2.53 by tolterodine \( (P < 0.05) \) for each, but no significant difference between the two drugs. Although the effect in total patients was equivalent between the two drugs, a markedly diverse response was noted in cystometric curves of individual case (Fig. 1). Superior bladder compliance compared to the other drug was noted in two cases with tolterodine and in two cases with obybutynin.

Stronger adverse effects were reported in three out of eight patients (37.5%) by obybutynin (dry mouth, 3; flushing, 1), and three out of eight patients (37.5%) by tolterodine (dry mouth, 2; flushing, 1).

Finally, occurrence of the adverse effects did not always correlate with stronger storage effect (seen in cases 1, 5 and 6 [Table 2]). Based on these findings five patients chose tolterodine and three patients chose to continue obybutynin.

### 4. DISCUSSION

The present report focuses on the comparison of tolterodine and obybutynin for treating spina bifida patients, and reveals a remarkable individual variation in response to the drugs.

A group of new anticholinergic drugs recently introduced into the market have proven efficacy for the adult OAB population, with generally less adverse effects than obybutynin.3–7 However, for appropriate application of these new drugs for severe congenital spinal disorders like spina bifida, comparison should be made with obybutynin, the standard drug. The new anticholinergics are intended to be used for OAB but not for the most severe NGB, such as spina bifida, and pharmaceutical companies has not been enthusiastic for their usage in pediatric cases.10,11 In these patients, anticholinergics reduce intravesical pressure and improve bladder compliance, presumably by directly acting onto the muscarinic receptors of the bladder smooth muscle, with a dosage far above the standard dosage set for treatment of non-neurogenic OAB.8,9 Thus, usage of these new anticholinergics for low compliant NGB requires an independent investigation at higher dosage in comparison with obybutynin.

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**TABLE 1. Demographic and pre-study data**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age</th>
<th>Gender</th>
<th>Original disease</th>
<th>Pre-study obybutynin administration (months)</th>
<th>Baseline UDS data</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Max capa (mL)</td>
<td>Max pressure (cmH2O)</td>
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<td>Spinal lipoma</td>
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Capa, capacity (mL); LPP, leak point pressure (cmH2O); MMC, myelomeningocele; UDS, urodynamic studies.
The majority of the patients in this study were at high-risk for upper urinary tract damage and who might have required augmentation if anticholinergics failed. As their bladder function were maintained at stable status with high-dose obybutynin over long period, sequential comparison between tolterodine and obybutynin at high dosage was conducted in this study. Our study followed that of Ellsworth and colleagues, first reporting the efficacy of tolterodine for NGB due to spina bifida with escalated dosage. The report has reasonably established a standard dosage of tolterodine for low-compliant bladders.

The first finding in our study is that both tolterodine and obybutynin have significant and equivalent urinary storage effect overall according to UDS and FVC. However, the second, and the more important findings of this study, was that the effect of the drugs was not equivalent for each individual case. For example, superior bladder compliance in UDS compared to the other drug was noted in two cases with tolterodine and in two cases with oxybutynin (Fig. 1 and Table 2), and such differences were also reflected to clinical symptoms including functional bladder capacity and dry time.

Such individual variability has also been encountered for adverse effects. Dry mouth, one of the typical adverse effects of anticholinergic, occurred in three out of eight patients; it was stronger for three obybutynin patients and two tolterodine patients. Although fewer side effects were initially expected for tolterodine from the data in adult OAB cases, the difference between obybutynin was not as dramatic as expected at the higher dosage required for NGB. While some patients definitively refused to resume obybutynin, some patients made the reverse decision as dramatic as expected at the higher dosage required for NGB. While some patients definitively refused to resume obybutynin, some patients made the reverse decision and the number of choice was split for the two drugs (five for tolterodine and three for obybutynin). In these cases, the adverse effects may not simply imply elevated drug concentration, since stronger adverse effects were apparently uncorrelated with superior storage effect.

The individual variability has been keynote findings of this study, and may denote heterogeneous nature of individual response to anticholinergics. Each cholinergic agent is known to have different affinity to muscarinic receptors of different organs. A group reported that contraction of the bladder of spinal injury patients is different from normal bladder, in that the former was mediated by M2 muscarinic receptor, while the latter was mediated by M3 receptor. Precise roles of M2 and M3 receptors for the effect of anticholinergic agents in healthy and diseased bladder are not completely elucidated yet. The anticholinergics may not only be a palliative measure to reduce intravesical pressure, but also have a protective effect against abnormal muscle remodeling in spina bifida patients. As long as we do not fully understand the distinct role of cholinergics on bladder function, we may not be able to predict effects of each anticholinergic drug on each pediatric NGB. In addition, pharmacokinetics of each drug may further influence the effects. Consequently, each NGB patient responds differently to each anticholinergic drug, making an individualized approach mandatory for the choice of optimal drug. Further, we...
should note the mental disturbance caused by obybutynin due to the passage of the drug through the blood-brain barrier. In this study no marked difference in mental activity was noted in the enrolled patients.

As a limitation of the present study, the number of patients examined was too small to conclude the difference between the two drugs in the overall population, but rather the effect and adverse effect were just as equivalent between the two drugs. However, the response of individual cases in this report clearly indicates that, side-to-side comparison should be applied to any NGB case maintained with an anticholinergic drug, seeking for an alternative drug with less adverse effect or better storage effect. Accumulation of such experiences may further consolidate the findings of this pilot study.

In summary, both tolterodine and obybutynin are effective for spina bifida patients and have comparable side effects, although an individualized approach is required for the choice of optimal drug because of the variable response of each case.

Disclosure

We do not have any conflict of interests with any company or institutes.

REFERENCES


