A Clinical and Urodynamic Study on the Effects of Oral Tolterodine on Serial Alterations in Neurogenic Detrusor Overactivity vis-à-vis Oral Oxybutynin in Children (Existing Oxybutynin Users)

I. K. Singh, M. Bajpai

Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi-110029, India

Abstract. Objective: Tolterodine has proved effective for treating non-neurogenic overactive bladder in Paediatric patients but has been less well studied in children with neurogenic detrusor overactivity. The objective of the current study was to look for incremental benefits of tolterodine (if any) in patients who are already being treated with oxybutynin. Methods: Patients with neurogenic bladder who were on oxybutynin at least for a period of 6 months were retrospectively analysed. Oxybutynin was switched over to tolterodine and prospectively analysed. The clinical and the urodynamic parameters were compared after completion of 6 months of tolterodine therapy. Results: Thirty patients with neurogenic bladder were included in the study. There were significant improvement in MCC (Median = 199.5 ml), LPP (Median = 52.5 cm H2O), volume at detrusor pressure 40 cm H2O (157 ml) after oxybutynin and MCC (226.5 ml), LPP (46 cm H2O), volume at detrusor pressure 40 cm H2O (158 ml) after tolterodine against the basal value of 134 ml, 56 cm H2O, 93 ml respectively. There were incremental benefits of tolterodine over oxybutynin in all the symptoms and urodynamic parameters but the benefits were not statistically significant. The number of adverse events of oxybutynin was 9 whereas with tolterodine it was 4 which are statistically significant. Conclusion: There is significant improvement in all the urodynamic parameters and symptoms after the treatment with oxybutynin as well as tolterodine. There are incremental benefits of tolterodine over oxybutynin but the gain is not statistically significant.

Keywords: Neurogenic bladder, Overactive bladder, Oxybutynin, Tolterodine

Received: 26 January 2014 / Accepted: 28 January 2014

Introduction

Myelodysplasia (abnormal development of the spinal cord and canal) is the most common cause of neurogenic bladder (NB) in children. As the survival of spinal dysraphism patients has improved, upper urinary tract deterioration leading to renal failure represents the most significant source of urologic morbidity and mortality in this population.[1]

Clean intermittent catheterization (CIC) by Lapides[2] combined with anticholinergics if required has made "conservative" (medical) management a successful treatment option, and is the standard therapy for children with neurogenic bladder dysfunction with detrusor hyperactivity.[3-5] Although the intravesical formulation generally causes fewer adverse events, such as dry mouth, constipation and dizziness, than the oral formulation, some children cannot tolerate either of these routes.[6]

Tolterodine has proved effective for treating non-neurogenic overactive bladder in paediatric patients[7-11] but has been less well studied in children with neurogenic detrusor overactivity. There are published results indicating that tolterodine was effective in increasing volume to first detrusor contraction and decreasing the number of incontinence episodes. Tolterodine was generally well tolerated, with a low incidence of treatment-related adverse events.

The purpose of the current study is to compare the incremental benefits of tolterodine (if any) in patients who are already being treated with oxybutynin by studying the serial alteration...
in clinical behavior. Urodynamic changes (Bladder capacity, leak point pressure, bladder volume at 40 cm H2O of detrusor pressure, volume at first detrusor contraction) after switching over to tolterodine.

Materials and Methods

This was a retrospective and prospective study. Patients with neurogenic bladder secondary to spinal anomaly who were on oxybutynin at least for a period of 6 months were retrospectively analysed. Thirty patients who responded to the telephonic or letter communication were recruited. Detailed history and clinical examination of the patients were done by the investigator. The micturation diary maintained by the parents were analysed in every follow-up visit.

Patients were on oral oxybutynin (immediate released) at the dose of 0.4 - 0.6 mg/kg/day. Participants were switched to oral tolterodine (immediate released) in the dose of 0.12 mg/kg/day in 2 divided doses after a gap of two weeks for the wash out of oxybutynin effect. Before changing to tolterodine all the clinical and urodynamic parameters were recorded. The clinical assessment and urodynamics were evaluated after 6 months of tolterodine.

The dry period was grouped into 1 i.e. < 3 hrs, 2 i.e. > 3 hrs. The frequency of micturation (self void or number of catheterization if the patient was on CIC) was categorized into 1 i.e. < 8/day, 2 i.e. 8/day or more. The urgency or the urge incontinence episodes were recorded as 0 ie absent, 1 i.e. 0-1 episode/week, 2 i.e. > 1 episode/day. The presence of nocturnal enuresis was recorded as 0 ie absent, 1 i.e. 1-3/week, 2 i.e. 4-6/week and 3 i.e. daily. Complete cure was defined as patients who became dry in between clean intermittent catheterizations or continent with self voiding. Patients less than 5 years of age at the time of initial evaluation of clinical symptoms were excluded from the statistical comparison of clinical symptoms as according to International Children's continence society, patient should be at least 5 years of age for assessing continence, frequency, urgency and nocturnal enuresis. Periods of dryness were considered for evaluation in this group.

Patients with urinary tract anomaly, grade IV or V VUR, management with indwelling catheter for more than 6 months or within the last 4 weeks of study initiation and clinically significant urinary tract infection (UTI) 4 weeks before study initiation were excluded from the study.

Urodynamic Study (UDS)

The urodynamic study is done by using the Urodynamics of Albyn Medical, Spain by using Phoenix plus software. The volume of bladder at first detrusor contraction occurs is recorded (defined by detrusor contraction pressure more than 10 cm of H2O from the baseline). Volume of bladder at resting detrusor pressure of 40 cm of H2O is recorded. The functional bladder capacity (Maximum cystometric capacity, MCC) is calculated when the continuous leakage of saline occurs. The pressure of detrusor when the leak occurs is recorded as the leak point pressure (LPP). The number of uninhibited detrusor contractions (UDC) are recorded defined by number of detrusor contractions at more than 10 cm of H2O. The expected capacity of the bladder (ECC) is calculated by the formula:

\[ \text{Capacity} = \left[ \text{Age (in years)} + 2 \right] \times 30 \text{ ml} \]

Statistical analysis was done by using Stata 9.0 (College Station, Texas, USA). Data are presented as number or mean or median (range) as appropriate. Changes in continuous variables (MCC, LPP, volume at detrusor 40, volume at first detrusor contraction, compliance) were compared using Wilcoxon signed rank test since the data were non-normal. The shift in the symptoms (such as dry period, frequency, urgency, nocturnal enuresis, number of incontinent episode, dryness of mouth, constipation, flushing, hyperpyrexia, visual or cognitive disturbance) from baseline was compared using McNemar’s test. The p value less than 0.05 was considered as statistically significant.

The study was conducted after taking the required ethical clearance from the ethical committee of the Institute. The necessary written informed consents were taken from the participants and parents.

Results

Thirty patients who responded to the telephonic or letter communication and satisfied the inclusion criteria were included. Twenty two were males and 8 were females. The age ranges from 2-16 years with the mean of 9.07 ± 4.06 (median= 8.5) years. Six patients were less than 5 years of age at the initial evaluation and were excluded from the statistical calculation of frequency, urgency, nocturnal enuresis and dry in between catheterization and self voiding, but were included in the comparison for urodynamic parameters. The primary pathology was meningomyelocele in 21 patients (70%), spina bifida in 6 patients (20%), and anorectal malformation with sacral anomaly in 2 patients (6.67%) and sacral agenesis in 1 patient (3.33%). All patients were on oral oxybutynin for a mean period of 31.93 ± 30.8 months (median=20) with the range of 6-120 months. They were on oral tolterodine for a range of 5-11 months with the mean of 6.78 ± 1.83 months (median= 6.4).

Twenty one patients were on clean intermittent catheterization 3-4 hourly and 9 were on self voiding. There was no catheterization related complication. During the study period only 2 patients had symptomatic culture proven urinary tract infection of 1 episode each, of which one patient was on CIC.
Singh I K, et al

and the other on self voiding. Both patients had grown E. coli in their urine culture.

Initially only 1 patient was having dry period more than 3 hrs. After treatment with oxybutynin 14 patients were having dry period more than 3 hrs (p < 0.05) and the number further increased to 16 after tolterodine (p < 0.05). However, this increase in dry period after tolterodine upon oxybutynin was not statistically significant (p = 0.48).

Of the 24 patients who were more than 5 years of age, 15 were dry in between the CIC or self voiding after oxybutynin which is highly significant (p < 0.05). Another 3 patients became dry after tolterodine (p < 0.05), this incremental benefit is not significant (p = 0.18).

Frequency of Urine

Initially all the patients were having frequency more than 8/day. After treatment with oxybutynin, the frequency of urine was reduced significantly in 16 of the 24 patients i.e. less than 8/day either self void or with CIC (p < 0.05) and 18 patients after tolterodine (p < 0.05). But the improvement in frequency after tolterodine over oxybutynin was not statistically significant (p = 0.32).

Urgency

All 24 patients were having urgency. Sixteen patients had no urgency or urge incontinence after oxybutynin (p < 0.05). After treatment with tolterodine, there was further decrease in urgency episode in another 2 patients (p < 0.05), but the incremental benefit over oxybutynin was not significant (p=0.32).

Nocturnal Enuresis

There was significant improvement in nocturnal enuresis after oxybutynin and 15 patients became dry at night (p < 0.05). Of the remaining patients, 5 had nocturnal enuresis episodes less than 50% of the time (i.e., 1-3/week) and another 4 patients had more than 50% of the time (>4 episodes/week) after oxybutynin. There was further improvement after tolterodine in 5 patients of whom 3 were dry at night (p < 0.05), but not significant as compared to oxybutynin (p = 0.26).

Urodynamic Parameters

The mean basal maximum cystometric bladder capacity (MCC) was 157.67 ± 105.73 ml (median of 134) with the range of 31-480 ml. The bladder capacity increased upto a mean of 253.97 ± 167.71 ml (median = 199.5) with the range of 50 - 649 ml after treatment with oxybutynin (p < 0.05) as compared to tolterodine treatment with mean of 257.57 ± 159.17 ml (median = 226.5) and range of 46 - 727 ml (p < 0.05). The incremental change was not significant (p = 0.14). (Fig. 1)

The basal leak point pressure ranged from 40-96 cm H2O with the mean of 58.6 ± 14.04 ml (median=56). The mean leak point pressure decreased to 48.8 ± 14.61 (median=52.5) cmH2O after treatment with oxybutynin, with the range of 21-75 cm H2O (p < 0.05). The mean leak point pressure after treatment with tolterodine was 48 ± 18.62 cm H2O (median = 46) with the range of 19 - 87 cm H2O (p < 0.05). But the additional decrease in the LPP after tolterodine over that of oxybutynin is not statistically significant (p = 0.37). (Fig. 2)

The mean volume of bladder at detrusor pressure of 40cm H2O improved from 132.41 ± 84.81 ml (median = 93 ml) to the mean of 184.22 ± 132.36 (median = 157 ml) (p < 0.05) after oxybutynin. The value further increased to a mean of 184.88 ± 107.31 ml (median = 158) after tolterodine (p = 0.13). As compared to the basal value improvement is statistically significant after tolterodine (p < 0.05).

The basal bladder volume at the first detrusor contraction increased from mean of 64.11 ± 65.74 (median = 38) to 63 ± 57.25 ml (median = 43.5) and 102.47 ± 87.46 ml (median = 84 ml) after treatment with oxybutynin (p = 0.36) and tolterodine (p = 0.41) respectively. The incremental change was not significant (p = 0.79)

The basal number of uninhibited detrusor contraction decreased from mean of 2.72 ± 2.84 (median = 2) to mean of 2.13 ± 3.2 (median = 1) after oxybutynin (p = 0.35). The value further decreased to a mean of 1.37 ± 2.04 (median = 0) after tolterodine therapy which is significant (p < 0.05).
The compliance significantly increased up to a mean of 6.2 ± 5.16 (median = 5) after oxybutynin therapy (p < 0.05) from a mean of 3.8 ± 2.67 (median = 3) and to 6.67 ± 7.18 (median=4.5) after tolterodine therapy (p < 0.05). But there was no incremental benefit of tolterodine over oxybutynin (p = 0.65).

Seven patients had adverse effects after administration of oxybutynin (9 adverse events, 5 dryness of mouth, 2 constipation, 2 hyperpyrexia) as compared to 4 patients (4 events) (2 dryness of mouth, 2 constipation) after tolterodine. Apart from the above 3 symptoms, there was no other adverse effects in the study group. The reduction in the complication events was statistically significant (p < 0.05).

Discussion

Myelodysplasia is the most common cause of neurogenic bladder, of which meningomyelocele is the commonest. In the present study, meningomyelocele accounts for 70 % of the cases of neurogenic bladder. Clean intermittent catheterization (CIC) or self catheterization (CISC) in combination with anticholinergics (oxybutynin) is the standard therapy for children with neurogenic bladder dysfunction with detrusor hyperactivity. Oxybutynin is the time tested anticholinergic medicine of choice for long. A drawback to the use of oxybutynin in children is the frequent occurrence of side-effects, causing up to 10% of patients to stop treatment[12,13]. Therefore, newer anticholinergics have been tried in children recently, to see the effectiveness and tolerability of the newer drugs even though they are already proven efficacy in adults. There are few comparative studies of oxybutynin and tolterodine in children with non-neurogenic detrusor overactivity. But available literature of the comparative study between the two medicines in neurogenic overactive bladder is lacking apart from the study of Goessl.[9]

In a comparative study of children with detrusor instability, Kilic et al[14] found that improvements in urge incontinence episodes were similar for the children who received tolterodine or oxybutynin. Improvements in the urodynamic parameters were also the same in the two groups. In the present study, we found a significant improvement in the symptom score and all the urodynamic parameters after both the drugs i.e. bladder capacity from a median of 134 ml to 199.5 ml (oxybutynin) vs 226.5 ml (tolterodine) which is highly significant. But the gain in volume after tolterodine over oxybutynin is not statistically significant (p = 0.14). Similarly there was no significant incremental benefit of tolterodine over oxybutynin in any of the urodynamic parameters. Hjalmass et al[12] and Goessl et al[9] also found that the effects of both tolterodine and oxybutynin were equivalent.

Goessl et al[9] demonstrated significant improvements in maximum bladder capacity, bladder compliance and maximum detrusor pressure among children 3 months to 15 years old taking 0.1 mg/kg tolterodine daily in neurogenic bladder patients. In their comparative study between oxybutynin and tolterodine in children with myelomeningocele reported on 22 children, 10 of whom were crossed-over from oxybutynin to tolterodine because the side-effects were intolerable. The urodynamic effects were equivalent for both agents and only one patient had side-effects on tolterodine.

In the present study, there was improvement in almost all the urodynamic parameters and clinical symptoms after tolterodine over oxybutynin i.e. bladder capacity, leak point pressure, volume at detrusor 40, number of uninhibited detrusor contractions, but the incremental benefits are not statistically significant.

In our study, there was no intolerance or drop out to either of the drug. There were 9 complication events by 7 patients after oxybutynin and 4 complication events after tolterodine (p < 0.05). But, Killic et al[14] reported a significant increase in the complication events with oxybutynin leading to crossing over to tolterodine. Similar findings were achieved in the Bolduc et al[9] and Raes et al[15] studies. Bolduc reported the similar efficacy of both the drugs with lesser adverse effects with tolterodine in the study of overactive bladder in children when the patients could not tolerate oxybutynin; they were switched over to tolterodine. But Mahanta et al[16] reported no adverse effect in a group of 30 patients treated with tolterodine.

From the small sample size study like the present study, it is difficult to draw any conclusion regarding the incremental benefit of tolterodine over oxybutynin in the clinical efficacy. More study with larger sample size and randomization will be needed.

Conclusion

There is significant improvement in the bladder capacity, leak point pressure, volume at detrusor pressure 40 cm H2O after treatment either with oxybutynin or tolterodine, but the incremental benefit of tolterodine over oxybutynin is not statistically significant. There is incremental benefit of tolterodine over oxybutynin in all the symptoms i.e. continence, frequency, urgency, number of incontinence episodes, nocturnal enuresis, dry period, but the benefit is not statistically significant. The reduction in the adverse effects was statistically significant. It may be mentioned that the mean duration of follow up with oxybutynin was 31.93±30.8 months whereas with tolterodine this follow up was only 6.78±1.83 months. The number of patients in this study as well as the duration of treatment given were not sufficient enough to derive statistically valuable data. A longer follow up with a larger number of patients is required in future studies.

References


